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OFFICE OF NUTRITIONAL PRODUCTS, LABELING AND
DIETARY SUPPLEMENTS (HFS-800)
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PETITION FOR HEALTH CLAIM:

**BARLEY BETAFIBER AND CORONARY HEART
DISEASE**

PETITIONER:

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I. INTRODUCTION

A. Overview and Rationale

Cargill, Incorporated ("Cargill") submits this health claim petition pursuant to Section 403 (r)(4) of the Federal Food, Drug, and Cosmetic Act regarding the relationship between the consumption of soluble fiber from certain foods and the reduced risk of coronary heart disease (CHD). This petition requests that the "Soluble fiber from certain foods and risk of coronary heart disease" health claim (21 CFR 101.81) be expanded to include "barley betafiber"¹ (as defined in Section V of this document) as an additional substance eligible for the health claim based on significant scientific agreement. Human and animal evidence detailed in this petition demonstrates that barley betafiber is efficacious in lowering serum cholesterol, and thus has the potential to reduce CHD risk.

Approximately 100 million Americans, about half of the US adult population, has elevated serum cholesterol levels (AHA, 2006). Public health campaigns emphasize cholesterol control as a means of reducing CHD risk. The National Cholesterol Education Program's (NCEP) Adult Treatment Panel (ATP) III recommends lifestyle changes, such as the reduction of dietary saturated fat and cholesterol, and inclusion of moderate physical activity to lower serum cholesterol (NCEP, 2002). To further help Americans meet their cholesterol goals, the NCEP ATP III encourages the use of viscous (soluble) fibers to enhance serum cholesterol lowering. The panel recommends that a cholesterol-lowering diet be enriched with foods that provide at least 5g to 10g viscous (soluble) fiber daily. Intakes of 10g to 25g soluble fiber per day can be additionally beneficial (NCEP, 2002).

The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, a nationally representative sample of US adults, reports a median intake of

¹ Barley Betafiber is an enzyme-processed barley beta-glucan concentrate, marketed by Cargill as BarlivTM.

2.4g soluble fiber per 1735 kcals (Bazzano et al., 2003). This level of soluble fiber intake is well below the NCEP ATP III recommendations. Barley betafiber is an excellent source of soluble fiber that can boost soluble fiber intake and, more importantly, has proven cholesterol-lowering properties.

Consumption of barley betafiber also contributes to total dietary fiber intake. The Institute of Medicine (IOM) of the National Academies has recommended that total dietary fiber be consumed at a rate of 14g total dietary fiber/1000 kcals per day to reduce the risk of chronic disease, particularly CHD (IOM, 2005).

Recommendations for adult men are 30g - 38g total dietary fiber/day and 21g - 25g total dietary fiber/day for adult women (IOM, 2005). Recent estimates indicate Americans consume only about 14g - 19g dietary fiber per day (USDA, 1997). The 2005 Dietary Guidelines for Americans also notes that most Americans need to increase their intake of dietary fiber (USDA/DHHS, 2005). The potential increase in dietary fiber from foods containing barley betafiber would help to increase dietary fiber intakes of the US population, consistent with the recommendations of the 2005 Dietary Guidelines for Americans (USDA/DHHS, 2005).

Barley food consumption (based on food disappearance data) in the US has declined to 0.7 lb/person/year since its peak consumption of 6.7 lb/person/year in 1947 (Economic Research Service, 2002). Hence, the current intake of barley-derived beta-glucan is relatively low in the US. Recent authorization of the health claim for whole grain barley and certain dry milled barley products and reduced risk of CHD will promote increased barley beta-glucan consumption (FDA, 2005). Food applications with barley betafiber will also assist in increasing barley beta-glucan consumption among a wider segment of the US population. Barley betafiber is a highly concentrated source of barley beta-glucan (with a minimum of 70% purity) that can be readily incorporated into a broad variety of foods, including beverages (especially juice and juice drinks), breakfast cereals, breads, cookies, crackers, muffins, pasta products, tortillas, soups, vegetarian patties/crumbles, extruded

snacks, cereal and granola bars, meal replacement and nutrition bars, sauces, and yogurt. The widespread availability of barley betafiber enriched foods can have important implications in both lowering total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) and reducing CHD risk in the US population.

There are other beta-glucan concentrates currently in the marketplace, but none, with the exception of oatrim (up to 10% beta-glucan), that has proven cholesterol-lowering ability in humans. Barley betafiber provides more beta-glucan soluble fiber on a gram per gram basis than any other beta-glucan soluble fiber source. Its lower viscosity compared to other beta-glucan concentrates enables barley betafiber to be utilized in a wide range of food applications. Furthermore, the high purity of this product enables the use of relatively small amounts of the product to provide 0.75g beta-glucan soluble fiber per serving.

In this petition, Cargill believes it has fulfilled the health claim requirements outlined in 21 CFR 101.14 to permit a health claim between barley betafiber and CHD. We propose that the soluble fiber health claim (21 CFR 101.81) be amended to include barley betafiber as an eligible source of beta-glucan soluble fiber to make the CHD health claim. Currently beta-glucan-containing foods eligible to bear the claim must contain at least 0.75g beta-glucan soluble fiber per reference amount customarily consumed (RACC). We are proposing that a barley betafiber-containing food bearing the health claim also contain a minimum of 0.75g beta-glucan soluble fiber from barley betafiber per RACC.

B. Background

In 1997, the Food and Drug Administration (FDA) authorized the health claim for the association of soluble fiber from whole oats in the form of rolled oats, oat bran, and whole oat flour and the reduced risk of CHD (FDA, 1997). A review of all the available data submitted by the Quaker Oats Company (petitioner) and additional data submitted by others convinced FDA that beta-glucan soluble fiber was the primary component in whole oats that affects serum lipids. The agency reached this conclusion on the basis of two main findings. One, there was evidence of a dose response relationship between the level of beta-glucan consumed and the level of reduction in blood TC and LDL-C. Secondly, a daily intake of 3g or more beta-glucan soluble fiber was more effective in lowering serum lipids than intake levels less than 3g beta-glucan soluble fiber per day.

On noting that beta-glucan soluble fiber is the component in whole oats responsible for their cholesterol-lowering effect, several comments to FDA suggested that beta-glucan soluble fiber from other sources, such as barley and oat gums also affect the risk of CHD in the same way as beta-glucan soluble fiber from whole oats (FDA, 1997). Although FDA acknowledged at that time that there is evidence that consumption of beta-glucan soluble fiber from a variety of food sources may help to lower serum cholesterol levels, the agency decided to limit eligibility to bear a claim to rolled oats, oat bran, and whole oat flour because FDA had only reviewed the totality of evidence for these products. However, FDA adopted a final rule that was structured so that it could be amended to accommodate claims for other sources and types of soluble fibers and the risk of CHD.

FDA also noted that there were no generally accepted or validated criteria for predicting which sources of processed forms of beta-glucan fiber are capable of reducing serum cholesterol (FDA, 1997). The agency expressed concern that certain types of processing may decrease the ability of the fiber to have the desired

effect for reasons that are unpredictable and that vary from source to source. However, FDA stated that human clinical trials can be used to resolve these issues. FDA also stated that it encourages manufacturers to petition for a claim for their soluble fiber product if there is evidence to demonstrate that the particular soluble fiber-containing product is effective in lowering serum lipids. The agency further noted that the effect of individual soluble fibers needs to be documented and evaluated on a case-by-case basis (FDA, 1997).

In 1998, FDA approved a health claim for psyllium seed husk and CHD in response to a health claim petition filed by the Kellogg Company (FDA, 1998). The authorization of psyllium seed husk led to the amendment of 21 CFR 101.81 for health claims from "Soluble fiber from whole oats and the risk of CHD" to "Soluble fiber from certain foods and the risk of CHD." This change laid the regulatory framework to include other eligible soluble fiber foods. The soluble fiber health claim regulation (21 CFR 101.81) was further amended in 2003 to include a specific class of oatrim, in response to a petition jointly submitted by the Quaker Oats Company and Rhodia Inc (FDA, 2002). Although the petitioners had requested the approval of oatrim with a beta-glucan content of 4% to 25% manufactured by two processes, an enzymatic method and an acid/base method, FDA only authorized oatrim with a beta-glucan content that did not exceed 10% and that had been manufactured by the acid/base process. The primary reason for this decision was that only the latter form of oatrim had been tested in a human trial and shown to be clinically efficacious.

Recently the National Barley Foods Council filed a petition to amend 21 CFR 101.81 to include barley as a source of beta-glucan soluble fiber associated with reduced risk of CHD. On December 23, 2005, FDA published an interim final rule in the Federal Register that amended the beta-glucan soluble fiber and reduced risk of CHD health claim to include barley as an additional source of beta-glucan soluble fiber (FDA, 2005). The agency concluded on the basis of the totality of scientific

evidence that, in addition to certain oat products, whole grain barley and certain dry milled barley grain products are appropriate sources of beta-glucan soluble fiber for the CHD health claim (FDA, 2005).

II. PRELIMINARY REQUIREMENTS

A. Barley Betafiber is a Food Ingredient that Provides Nutritive Value and Technical Function [21 CFR 101.14 (b)(3)(i)]

Barley betafiber has nutritive value on the basis that it is a concentrated source of beta-glucan soluble fiber. It contains at least 70% beta-glucan. Beta-glucan is defined as a “dietary fiber” by the standard AOAC method for fiber analysis (AOAC 991.43). Barley betafiber also provides calories and a small amount of protein (Table 1). The extraction process removes most of the lipid component, resulting in a product that is primarily carbohydrate due to its high soluble fiber content.

In addition to its primary use as a source of soluble fiber, barley betafiber also has functional benefits, including use in certain food applications as a thickener (e.g. soups), texturizer (e.g. snack foods), humectant (e.g. retain moisture in tortillas), or fat replacer (e.g. salad dressings).

Table 1. Macronutrient Composition of Barley Betafiber^a

Macronutrients	per 100g of Product
Calories	368
Total Fat (g)	0.07 (trace)
Total Carbohydrate (CHO) (g)	90
Dietary Fiber (g)	82.2
Soluble Fiber (g)	81.6
Beta-glucan (g)	73.2
Sugars (g)	0.8
Protein (g)	2.5
Moisture (g)	4.6
Ash (g)	2.7

^a Average based on analytical data of 5 samples

B. Barley Betafiber is Safe and Lawful [21 CFR 101.14 (b)(3)(ii)]

Barley betafiber, a food ingredient, is the substance that is the focus of this health claim petition. In 2003, an independent panel of experts qualified in evaluating the safety of food and food ingredients deemed barley betafiber to be Generally Recognized as Safe (GRAS) for use up to 3g per serving in specified foods as a nutritional supplement (source of fiber), as a thickening agent, a texturizing agent, a humectant and a fat replacer consistent with current Good Manufacturing Practice (Report of the Expert Panel on GRAS Status of Barley Betafiber, Appendix 1²). A GRAS notification for barley betafiber will be submitted to FDA subsequent to this health claim petition.

Barley is a traditional food with a long history of safe use. Archeological discoveries date barley consumption back to 8000 B.C. (Newman, 2005). It is one of the oldest cultivated crops and was an important dietary constituent until the end of the 19th century (Newman, 2005). Barley was used to make porridges, broths, flat breads and biscuits in every age (Newman, 2005). In modern times, barley lost favor with the growth of the wheat industry (Newman, 2005).

In Maghreb countries (Morocco, Algeria, Libya, Tunisia), barley is still used in a variety of traditional foods (bread, soup, porridge), resulting in an average intake of up to 172g/person/day (Morocco)³. With this intake of barley, about 6g/person/day of beta-glucan is consumed. Importantly, the preparation of the mentioned foods involves cooking for longer periods of time, which ensures extraction of beta-glucan from its natural context (cell walls, complexes with proteoglycans). The physiological

² Report of the Expert Panel on the GRAS Status of Barley Betafiber (GRAS Expert Panel).

³ Estimates between 1980 and 1990 indicate Morocco was the largest per capita food user of barley, with an annual per capita intake of 63kg (FAO, 2000). This level of intake corresponds to a daily intake of 172g barley or about 6g beta-glucan. Average beta-glucan content of barley consumed in Maghreb countries is about 3.5% (Ferrante et al., 2001)

properties of beta-glucan as a dietary fiber may therefore be found in these traditional foods, as is intended with the addition of barley betafiber to processed foods.

Beta-glucan is widely present in numerous grains and other plants (i.e. oats, barley, rye, mung beans) (Appendix 1). It is thus consumed not only with barley but also with other cereals and edible plants. Adverse effects due to the consumption of beta-glucans from such foods have not been reported. Particularly relevant to the discussion of processed beta-glucan is the safe use for more than 10 years of oat-derived beta-glucan concentrates (e.g., oatrim).

The subchronic toxicity of high molecular weight (HMW) (native) barley beta-glucan (a prototype of barley betafiber, produced by the method described in this petition) has been examined in 28-day toxicity studies in rats and mice (Appendix 1). In these studies, the highest dose level tested (10% in the diet, corresponding to an intake of about 21g and 8g barley beta-glucan/kg bw/day in mice and rats, respectively) was the No-Observed-Adverse-Effect-Level (NOAEL).

In human studies in which levels of up to 5g barley betafiber/day were consumed for a period of 12 weeks, no adverse effects were noted (Appendix 1). In only two studies were mild intestinal symptoms (flatulence, bloating) recorded upon daily ingestion of 39g - 42g barley-derived dietary fiber (Newman et al., 1989b; Pick et al., 1998; Appendix 1). These effects, which are often observed with rapid, significant increases in fiber intake, were reported to dissipate soon after the initiation of the studies.

Phytic acid is a natural component of cereal grains with a known inhibiting effect on the intestinal absorption of certain minerals (e.g., calcium). Analyses of barley beta-glucan have shown that phytic acid is not concentrated in the extraction and isolation

process of barley beta-glucan. Analysis of representative commercial lots of barley betafiber revealed a phytic acid content of less than 1% (Appendix 1).

C. Barley Betafiber is Associated with Reduced Risk of Coronary Heart Disease [21 CFR 101.14(b)(1)]

CHD remains the number one cause of death and disability in the US. According to the American Heart Association's latest statistics, every 26 seconds an American will suffer a coronary event, and about every minute someone will die of CHD complications (AHA, 2006). Individuals who have survived a heart attack have an increased probability of illness and death that is 1.5 to 15 times greater than that of the general population (AHA, 2006). These men and women are at a significantly higher risk for another heart attack, sudden death, angina pectoris, heart failure, and stroke. In 2006, the projected direct health care costs and indirect costs due to lost productivity are expected to exceed \$142 billion annually (AHA, 2006).

The leading modifiable risk factor for CHD is elevated serum cholesterol. Approximately 100 million or half of the US adult population has serum cholesterol levels that exceed 200 mg/dL (AHA, 2006). Several clinical studies have shown that lowering elevated TC, and specifically LDL-C, through dietary and drug intervention therapies significantly reduces the risk of CHD. Drug therapy is usually initiated only after dietary modification has proven to be inadequate in achieving desired goals in individuals with borderline high or moderately elevated serum cholesterol levels. Potential side effects and the cost of pharmaceutical agents are some of the reasons for delaying drug intervention.

As a first line approach in lowering serum cholesterol, the NCEP ATP III recommends lifestyle changes such as reducing dietary saturated fat and cholesterol, and including moderate physical activity (NCEP, 2002). However if serum cholesterol goals are not met, NCEP ATP III encourages the consumption of

viscous (soluble) fibers to enhance serum cholesterol lowering. NCEP ATP III noted that an increase in consumption of 5g to 10g soluble fiber is accompanied by an approximate 5% reduction in LDL-C (NCEP, 2002).

Barley betafiber is an excellent source of beta-glucan soluble fiber with documented effectiveness in lowering serum cholesterol. Therefore, consumption of barley betafiber is associated with reduced risk of CHD, a condition that is a major public health concern for the US population.

III. SUMMARY OF SCIENTIFIC EVIDENCE

A. Overview of Scientific Data

All published and unpublished studies that evaluated the effects of concentrated,⁴ processed sources of barley beta-glucan on serum lipids were reviewed. Relevant studies were identified from current Medline searches and from the National Barley Foods Council health claim petition, which contained a thorough review of the scientific literature relating to barley and serum lipids and barley and other health effects as of 2003.

The scientific data reviewed pertaining to barley betafiber and barley beta-glucan concentrates demonstrate that barley betafiber and barley beta-glucan concentrates were consumed as food ingredients. Therefore, barley betafiber, the substance that is the subject of this health claim petition conforms to the definition of the term "substance" in 21 CFR 101.14(a)(2).

A pilot study and a randomized, double-blind, placebo-controlled, parallel group clinical trial with hypercholesterolemic subjects demonstrated the efficacy of barley betafiber in lowering TC and LDL-C. As observed in oat and barley beta-glucan studies, 3g barley betafiber is an effective level of intake to significantly lower serum lipids. Results from animal studies that utilized barley betafiber and/or barley betafiber prototypes also showed significant reductions in plasma cholesterol, consistent with human clinical findings. The animal data also support the equivalency of barley and oat beta-glucan in lipid reduction, regardless of whether the beta-glucan is in its native state or processed to a concentrate using the enzymatic method outlined in this petition.

⁴ Concentrated source of beta-glucan is defined here as containing a significantly higher percent of beta-glucan than would be found in native barley or oats.

In addition to serum cholesterol lowering, barley betafiber was shown to reduce glycosylated hemoglobin (HbA_{1c}) levels. A recent body of evidence has shown that elevated HbA_{1c} concentrations are related to increased CHD risk in non-diabetics. Therefore individuals who consume barley betafiber have the opportunity to reduce CHD risk in multiple ways.

The clinical trial using barley betafiber did not report any significant side effects and the tolerance of food products (cereal and juice drink) containing this product was high, as demonstrated by the high compliance rate and the absence of subject drop-outs. No significant adverse effects are expected from the estimated increase in soluble fiber consumption. The expected increase, even at the 90th percentile of intake is at the lower end of the 10g - 25g viscous soluble fiber range that NCEP ATP III suggests is beneficial, and below the range of dietary fiber intakes recommended by the IOM (Appendix 1). The GRAS Expert Panel concurs with this assessment and has affirmed the GRAS status of barley betafiber (Appendix 1).

Review of human and animal studies of all highly concentrated barley beta-glucan extracts indicates that not all such products have cholesterol-lowering ability (Keogh et al., 2003; Biörklund et al., 2005; Maqueda de Guevara, 2000). Different processing and extraction methods can result in a beta-glucan product that has no impact on blood lipids. The data clearly shows that each processed beta-glucan product must be evaluated on a case-by-case basis, consistent with FDA's analysis (FDA, 1997).

Overall, the scientific evidence overwhelmingly supports the ability of barley betafiber to significantly reduce CHD risk without any significant adverse effects. Thus, the consumption of barley betafiber is expected to have a beneficial impact on the health of the US population.

B. Human Clinical Data

1) Pilot Study with Barley Betafiber as Serum Cholesterol Lowering Agent

A total of 12 men and women who were hypercholesterolemic and glucose intolerant (i.e. with elevated fasting blood glucose levels), but otherwise healthy, were recruited to participate in a pilot study at the University of Minnesota Medical School (Table 2, Pins et al., unpublished). The 6 men and 6 women were randomly allocated to receive 5g barley betafiber/day in either cereal or a juice drink. Body weight, lipid and glucose measurements were taken before intervention began. Subjects consumed the barley betafiber every day in cereal or juice drink for 21 days while maintaining a normal lifestyle. Body weight, lipid and glucose measurements were repeated at the end of the 21-day treatment period. Compared to baseline levels, blood LDL-C levels dropped 14.5% in the barley beta-glucan concentrate cereal group and 12.5% in the barley beta-glucan concentrate juice drink group. Fasting blood glucose levels also dropped during the intervention. Body weight did not change, nor were there any significant gastrointestinal or other side effects.

2) Clinical Trial with Barley Betafiber as Serum Cholesterol Lowering Agent

Pins et al. conducted a 10-week double-blind, randomized, placebo-controlled five-arm parallel group clinical trial of barley betafiber (Table 2; Pins et al., submitted to *J Fam Pract*). Although the clinical trial included a treatment group that consumed a HMW barley beta-glucan concentrate, only the data pertaining to the (LMW) barley betafiber is included in this petition. A complete description of the clinical trial and all accompanying data can be found in Appendix 2. Data from the clinical trial passed an external data quality audit that verified its accuracy (Appendix 3).

The study group of 155 subjects was composed of 75 men and 80 women, aged 20 to 70 years, who met the NCEP ATP III criteria for diet therapy due to elevated LDL-C (i.e. LDL-C > 130 mg/dL). Screening excluded individuals with diabetes, cancer, secondary hyperlipidemia, cardiovascular disease (CVD), triglycerides > 500 mg/dL, body mass index (BMI) \geq 40, large or unexplained weight loss within the previous 6 months, those who were smokers, and women who were pregnant or lactating. Individuals were also excluded if they were taking lipid-altering medications or lipid-altering dietary supplements, consumed more than 2 alcoholic drinks a day, or were allergic to aspirin, grain products, or artificial ingredients used in the treatment foods.

The study design consisted of a 4-week diet stabilization phase followed by a 6-week treatment phase. During the diet stabilization phase, subjects were instructed to consume a diet low in saturated fat and trans fats (< 10% kcals/day), which they were to follow throughout the course of the study. Subjects were then randomized to receive one of two doses per day (3g or 5g) barley betafiber or a control. Blood lipids, blood apolipoproteins, blood pressure and other CVD risk markers were measured at baseline and at the end of the treatment period. Dietary intake data were collected during the first and last week of treatment to monitor dietary compliance and consistency.

Table 2. Summary of Human Clinical Trials Utilizing Barley Betafiber as a Dietary Intervention to Reduce Risk of CHD.

Study	Study Design, Subjects (Ss), Initial Mean TC	Beta-Glucan (BG) Treatments	Methods	Results
Pilot Study Pins et al., unpublished pilot study	Uncontrolled pilot study N=12 (6 M, 6 F) Hypercholesterolemic, glucose intolerant	5g barley betafiber (BBF)‡ in ready-to-eat cereal or juice drink. ‡ Cargill Barliv™	Subjects (Ss) were randomized into 2 groups: one received 5g barley betafiber (BBF) in cereal and the other 5g barley betafiber (BBF), in juice drink. Treatment products were consumed daily for 3 weeks; subjects maintained their normal lifestyle.	Change from baseline: BBF Cereal group: LDL-C: - 23 mg/dL (- 14.5%) BBF Juice drink group: LDL-C: - 21 mg/dL (- 12.5%)

N: number; M: males; F: females

Table 2 (cont'd.)

Study	Study Design, Subjects (Ss), Initial Mean TC	Beta-Glucan (BG) Treatments	Methods	Results*
Clinical Trial Pins et al., submitted for publication. (Manuscript submitted to <i>J. Fam Pract.</i>)	Randomized, double-blind, placebo-controlled, 5-arm parallel group (10-week) N=155 (75 M, 80F) Hypercholesterolemic TC: 235 mg/dL	3g barley betafiber‡ (n=31) 5g barley betafiber (n=30) 0g barley BG (control, n=30) barley betafiber‡: 75% BG dwb avg MW=150 kDa ‡ Cargill Barliv™	4-week diet stabilization phase—diet low in saturated fat and trans fats (< 10% kcal/day). 6-week treatment period. Treatments were delivered to Ss as ready-to-eat cereal (1x/day) and juice drink (2x/day). Ss were instructed to continue on their low fat diet during the treatment phase.	BG Treatments vs. Control <u>TC:</u> 3g barley betafiber: - 14.4 mg/dL (- 6.0%)* 5g barley betafiber: - 23.7 mg/dL (- 9.9%)* <u>LDL-C:</u> 3g barley betafiber: - 11.6 mg/dL (- 7.5%)* 5g barley betafiber: - 18.5 mg/dL (- 11.9%)* <u>Apo B:</u> 3g barley betafiber: - 11.1mg/dL (- 8.0%)* 5g barley betafiber: - 17.5 mg/dL (- 12.7%)* <u>Apo-A1:</u> 3g barley betafiber: + 2.4 mg/dL (+ 1.9%) 5g barley betafiber: + 2.1 mg/dL (+ 1.7%) <u>HDL-C:</u> 3g barley betafiber: + 0.6 mg/dL (+ 3.6%) 5g barley betafiber: - 0.1 mg/dL (- 0.2%) <u>TG:</u> 3g barley betafiber: - 16.6 mg/dL (- 11.4%) 5g barley betafiber: - 7.0mg/dL (- 15.8%) <u>TC/HDL-C:</u> 3g barley betafiber: - 0.5 (- 6.9%)* 5g barley betafiber: - 0.6 (- 7.3%)* No significant changes in BW or diet.

* significance $p < 0.05$; BG: beta-glucan; dwb: dry weight basis; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; Apo B: apolipoprotein B; Apo A1: apolipoprotein A1; HDL-C: high density lipoprotein cholesterol; TG: triglycerides; TC/HDL-C: total cholesterol/ high density lipoprotein cholesterol

Barley betafiber was formulated into a ready-to-eat corn flakes breakfast cereal and a low-calorie tropical juice drink containing 5% fruit juice. Control products consisted of the corn flakes cereal and the low-calorie tropical juice drink without beta-glucan fortification. The nutritional profiles of the food products were consistent with heart health claim requirements. Subjects consumed two servings of fruit drink and one serving of cereal with meals each day to obtain the necessary doses of beta-glucan. The beta-glucan content and molecular weight of barley betafiber are specified in Table 3.

Table 3. Characteristics of Barley Betafiber Used In the Clinical Trial

	Barley Betafiber
Molecular weight ^a	150
Beta-glucan (%)	70 ^b
Total fat	0.1
Protein	2.2
Moisture	6.2
Ash	2.6

^a Weight-average molecular weight; ^b 75% beta-glucan on a dry weight basis.

Baseline characteristics of the subjects indicated a moderately overweight (BMI = 28.8 kg/m²) group, with 29% indicating a family history of CHD. Mean blood lipid and lipoprotein levels were as follows: LDL-C: 154 mg/dL, HDL-C: 50 mg/dL, triglycerides: 160 mg/dL, apolipoprotein B: 139 mg/dL, and apolipoprotein A-1: 121 mg/dL. All study subjects were healthy with no history of CHD (Appendix 2).

Approximately 40% of the group was identified as having metabolic syndrome,⁵ a condition of increasing concern in the US. On the basis of 2000 census data, about 47 million residents in the US have metabolic syndrome (Ford et al., 2002). It is well

⁵ NCEP ATP III indicates a diagnosis of metabolic syndrome is made when 3 or more risk factors are present. Risk factors include a waist circumference of ≥ 102 cm in men or ≥ 88 cm in women; triglyceride levels ≥ 150 mg/dL; HDL-C of < 40 mg/dL in men or < 50 mg/dL in women; blood pressure $\geq 130/85$ mmHg; and fasting plasma glucose of ≥ 110 mg/dL (NCEP, 2002).

accepted that metabolic syndrome is an unequivocal risk factor for type 2 diabetes (Grundy et al., 2005). Furthermore, many investigators consider metabolic syndrome a risk factor for atherosclerotic CVD, but when type 2 diabetes emerges, cardiovascular risk increases significantly more (Grundy et al., 2005). Thus, the American Heart Association and the National, Heart, Lung, and Blood Institute have identified metabolic syndrome as a secondary target for reducing cardiovascular events (Grundy et al., 2005). The study was stratified for subjects with metabolic syndrome.

Compliance was greater than 95% in all treatment and control groups and there were no study dropouts. The treatments were well tolerated and there were no differences in the frequency of side effects at baseline and during any of the treatment periods or compared to the control group (Appendix 2). Diet and lipid changes were stabilized during the 4-week stabilization period, prior to the beginning of the treatment phase. Diet and body weight did not significantly change throughout the treatment phase (Appendix 2).

Table 2 shows the lipid changes in the barley betafiber treatment and control groups. At the end of the 6-week intervention period, 3g barley betafiber significantly lowered TC by 6.0% ($p < 0.05$) and 5g barley betafiber lowered cholesterol by 9.9% ($p < 0.05$) compared to the control. Consumption of 3g and 5g barley betafiber significantly reduced LDL-C by 7.5% ($p < 0.05$) and 11.9% ($p < 0.05$) respectively, compared to the control group. HDL-C levels were not significantly affected by either the 3g or 5g barley betafiber doses (Table 2). Consumption of 5g barley betafiber significantly decreased apolipoprotein B (apo B) by 12.7% ($p < 0.05$) compared to the control. Although the 3g barley betafiber dose lowered apo B by 8.0%, this was not significant ($p < 0.05$). Barley betafiber (3g or 5g) did not significantly impact apolipoprotein A-1 (apo A-1) levels at either dose. The ratio of TC/HDL-C was significantly reduced by both 3g and 5g barley betafiber doses

($p < 0.05$ for both) in relation to the control group. Compared to the control group, both barley betafiber groups experienced a drop in fasting triglyceride levels, but this was not significant ($p < 0.05$).

Percent lipid changes noted with barley betafiber treatments were also assessed compared to baseline (Appendix 2). TC was significantly reduced from baseline by 7.2% ($p < 0.05$) and 11.1% ($p < 0.05$) in the 3g and 5g barley betafiber groups respectively. Compared to baseline, 3g barley betafiber significantly lowered LDL-C by 8.7% ($p < 0.05$) and 5g barley betafiber reduced LDL-C by 13.1% ($p < 0.05$). No significant changes in HDL-C levels were observed compared to baseline. Apo B significantly dropped from baseline levels by 14.8% ($p < 0.05$) in the 5g barley betafiber group and 10.1% ($p < 0.05$) in the 3g group. Doses of either 3g or 5g barley betafiber did not significantly impact apo A-1. Barley betafiber significantly lowered the ratio of TC/HDL-C from baseline at both 3g and 5g barley betafiber doses ($p < 0.05$ for both). Fasting triglyceride levels were significantly reduced from baseline levels for both doses of barley betafiber ($p < 0.05$ for both).

The NCEP ATP III has developed guidelines that specify different LDL-C goals for individuals based on the number of CHD risk factors present (NCEP, 2002). Risk factors, exclusive of LDL-C, include cigarette smoking, hypertension, low HDL-C, family history of premature CHD, and older age. The LDL-C goal for individuals with 0 to 1 CHD risk factors is < 160 mg/dL, whereas the LDL-C goal for individuals with 2 or more CHD risk factors is < 130 mg/dL. Each of the study participants was assessed in relation to their own LDL-C goal, following the interventions. In the barley betafiber group, 82% and 95% of the subjects with 0 to 1 CHD risk factors who had consumed 3g and 5g barley betafiber doses, respectively, reached their LDL-C goals (Appendix 2). In contrast, only 74% of the control group with the same number of risk factors attained their LDL-C goals. Among subjects with 2 or more CHD risk factors, 14% of those receiving 3g barley betafiber and 44% of those

receiving 5g barley betafiber reached their LDL-C goal, compared to 0% in the control group.

3) Review of Clinical Trials with Other Highly Concentrated Barley Beta-Glucan Extracts as Serum Cholesterol Lowering Agents

The ability of beta-glucan soluble fiber contained in barley foods to lower serum cholesterol has been affirmed in the recent interim final rule that authorizes whole grain barley and certain dry milled barley grain products as appropriate sources of beta-glucan soluble fiber for the beta-glucan soluble fiber and reduced risk of CHD health claim (FDA, 2005). Clinical studies such as that conducted by Behall et al. (2004a, 2004b) and McIntosh et al. (1991) clearly demonstrate the ability of barley beta-glucan to reduce risk of CHD. Hence, we limited our current review to studies of concentrated sources of barley beta-glucan soluble fiber. A search of the scientific literature identified two such studies (Table 4), one conducted by researchers in New Zealand (Keogh et al., 2003), and another conducted in the Netherlands and Sweden (Biörklund et al., 2005).

In the Keogh et al. (2003) study, a beta-glucan extract (Glucagel™)⁶ with a beta-glucan content of 75% beta-glucan by weight, similar to the beta-glucan content of barley betafiber, was evaluated. However, Glucagel™ was manufactured by a different processing method than barley betafiber. Glucagel™ was “produced from high beta-glucan content barley that was milled and sieved to separate the starch and cell-wall material. A two-step extraction process was carried out to produce the beta-glucan-enriched product: 1) water extraction at 50-60°C and 2) a freeze-and-thaw extraction from which the beta-glucan was recovered.” The details of the process are outlined by Morgan and Ofman (1998).

⁶ Glucagel™ is manufactured by GraceLinc Ltd., New Zealand; Typical MW: 130 kDa
<http://www.glucagel.com/product.htm>

Table 4. Summary of Human Clinical Trials Utilizing Other Barley Beta-Glucan Concentrates as a Dietary Intervention to Reduce Risk of CHD.

Study	Study Design, Subjects (Ss), Initial Mean TC	Beta-Glucan (BG) Treatments	Methods	Results
Keogh et al., 2003	<p>Randomized, single-blind, controlled cross-over (2 x 4-week treatment with 4 week washout)</p> <p>N=18 hypercholesterolemic men TC: 228 mg/dL</p>	<p>9.9g barley BG* (N=18) 0g BG (glucose, control, N=18)</p> <p>*barley BG (GlucageTM): 75% BG, MW 130kDa</p>	<p>BG level was the only nutrient that differed in the background diet. The diet provided 38% E from fat, 13% E from protein, 49% E from carbohydrate.</p> <p>BG and control treatments were incorporated into snacks and meals consumed throughout the day (i.e. bread, waffles, muffins, savory dishes, desserts, cakes, cookies).</p>	<p>BG Treatment Phase vs. Control Phase</p> <p><u>TC</u>: - 0.08 mmol/L = - 3.1 mg/dL (- 1.3%)</p> <p><u>LDL-C</u>: - 0.15 mmol/L = - 5.8 mg/dL (- 3.8%)</p> <p><u>HDL-C</u>: 0 mmol/L = 0 mg/dL</p> <p><u>TG</u>: + 0.18 mmol/L = + 6.9 mg/dL</p>

Table 4. Summary of Human Clinical Trials Utilizing Other Barley Beta-Glucan Concentrates as a Dietary Intervention to Reduce Risk of CHD.
(cont'd.)

Study	Study Design, Subjects (Ss), Initial Mean TC	Beta-Glucan (BG) Treatments	Methods	Results*
Biörklund et al., 2005	Randomized, single-blind, controlled, 5-arm parallel group (8-week) N=89 (44M, 45F) Hypercholesterolemic TC: 242 mg/dL	<p>*5g barley BG (n=19) 10g barley BG (n=16) **5g oat BG (n=19) 10g oat BG (n=15) 0g BG (rice starch, control, n=20)</p> <p>*barley preparation: 36% BG, MW 40kDa</p> <p>**oat preparation: 18% BG, MW 200kDa</p>	<p>Treatments were delivered as beverages made by mixing the fiber preparations with water, fruit concentrate, sucrose, rapeseed oil and glucose syrup powder. The beverages were equal in calories and fat content. Control beverage was made in a similar manner with rice starch.</p> <p>During a 3-week run-in period, Ss consumed the control beverage and their usual diet. Ss were then randomized to each of the 4 treatment groups and the control group for a 5 week period while Ss consumed their usual diets.</p>	<p>BG Treatments vs. Control</p> <p><u>TC:</u> † oat-5: - 0.49 mmol/L = -18.9 mg/dL (- 7.4%)* oat-10: - 0.29 mmol/L = -11.2 mg/dL (- 4.5%) barley-5: - 0.20 mmol/L = - 7.2 mg/dL (- 3.1%) barley-10: - 0.27 mmol/L = -10.4 mg/dL (- 4.2%)</p> <p><u>LDL-C:</u> † oat-5: - 0.29 mmol/L = - 11.2 mg/dL (- 6.7%) oat-10: - 0.16 mmol/L = - 6.2 mg/dL (- 3.9%) barley-5: - 0.08 mmol/L = - 3.1 mg/dL (- 1.8%) barley-10: - 0.17 mmol/L = - 6.6 mg/dL (- 1.4%)</p> <p><u>HDL-C:</u> † oat-5: - 0.08 mmol/L = - 3.1 mg/dL (- 5.6%) oat-10: - 0.01 mmol/L = - 0.4 mg/dL (- 0.8%) barley-5: - 0.04 mmol/L = - 1.5 mg/dL (- 2.8%) barley-10: - 0.05 mmol/L = -1.9 mg/dL (- 3.6%)</p> <p><u>TG:</u> † oat-5: - 0.24 mmol/L = - 9.3 mg/dL (- 15.3%) oat-10: - 0.24 mmol/L = - 9.3 mg/dL (- 14.0%) barley-5: - 0.08 mmol/L = - 3.1 mg/dL (-10.7%) barley-10: - 0.10 mmol/L = - 3.9 mg/dL (- 6.5%)</p> <p>(cont'd.)</p>

Table 4. Summary of Human Clinical Trials Utilizing Other Barley Beta-Glucan Concentrates as a Dietary Intervention to Reduce Risk of CHD.
(cont'd.)

Study	Study Design, Subjects (Ss), Initial Mean TC	Beta-Glucan (BG) Treatments	Methods	Results
Biörklund et al., 2005 (cont'd.)				<p><u>Apo-A:</u> † oat-5: - 0.06 mmol/L = - 2.3 mg/dL (- 3.6%) oat-10: + 0.04 mmol/L = + 1.5 mg/dL (+ 2.5%) barley-5: - 0.03 mmol/L = - 1.2 mg/dL (- 1.9%) barley-10: - 0.04 mmol/L = - 1.5 mg/dL (- 1.5%)</p> <p><u>Apo-B:</u> † oat-5: - 0.04 mmol/L = -1.5 mg/dL (- 3.4%) oat-10 - 0.03 mmol/L = -1.2 mg/dL (- 2.6%) barley-5: + 0.01 mmol/L = + 0.4 mg/dL (+ 0.9%) barley-10:- 0.02 mmol/L = - 0.08 mg/dL (- 1.7%)</p> <p>No significant changes in BW or diet.</p>

†: % treatment changes compared to control were computed from data in paper. BG: beta-glucan; E: energy; M: male; F: female; MW: molecular weight; N: number;; Apo: Apolipoprotein; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides

The clinical trial with Glucagel™ utilized a randomized, single-blind, 4-week crossover design in which 18 hypercholesterolemic men consumed 8.1g to 11.9g beta-glucan or 6.5g to 9.2g glucose (control) per day on the basis of total caloric intake scaled to body weight. Subjects consumed 10g beta-glucan per day (on average) as part of a typical 38% fat diet. Results, however, indicated no significant difference ($p > 0.05$) between treatment and control arms in TC, LDL-C, HDL-C, or triglycerides.

Keogh and co-workers (2003) provided several possible reasons for the lack of efficacy of the beta-glucan extract, Glucagel™. They suggest that unfavorable structural changes may have occurred during commercial purification, such as depolymerization of the linear structure that could result in decreased molecular weight and reduced viscosity in the gastrointestinal tract. The mild extraction conditions (50-60°C) may not have deactivated endogenous beta-glucanases and may have also lead to increased depolymerization. In addition, the freezing and thawing processes may have contributed to the lack of effect as similar processes have been shown to reduce the extractability of oat beta-glucan in the intestine. Therefore a combination of processing factors may have been responsible for the poor response observed in this trial. The researchers note that the quantity of beta-glucan ingested is only part of the equation in observing hypocholesterolemic effects. Viscosity and the molecular weight of the beta-glucan soluble fiber also appear to be critical factors in ensuring efficacy.

In the second study of concentrated beta-glucan, Björklund et al. (2005) tested the cholesterol-lowering effects of beverages enriched with 5g and 10g barley beta-glucan compared to beverages enriched with 5g and 10g oat beta-glucan (Table 4). Polished grains of Swedish barley and oat bran from Swedish oats were used to produce fiber preparations with high beta-glucan content. Milled barley or oats was treated with enzymes, followed by the removal of the insoluble fiber and freeze drying the remaining fractions into powders that contained a beta-glucan content of

36% for the barley preparation and 18% for the oat preparation. The mean molecular weights of the barley fiber and oat fiber preparations were 40 kDa and 200 kDa, respectively. Each of the barley and oat fiber preparations was mixed with water, fruit concentrate, and sucrose, followed by the addition of glucose syrup powder, and rapeseed oil in differing concentrations to produce isocaloric beverages with equal fat content. Rice starch was used in place of the fiber preparations in the control beverage.

The study was an 8-week, single-blind, controlled study with five parallel groups carried out in two centers. A total of 100 hypercholesterolemic subjects were recruited and 89 completed the study. During a 3-week stabilization period, subjects consumed the control beverage. For the next 5-week period, the subjects were randomized into five groups, with four groups receiving a beverage containing 5g or 10g beta-glucan from oats or barley and one group receiving the control beverage.

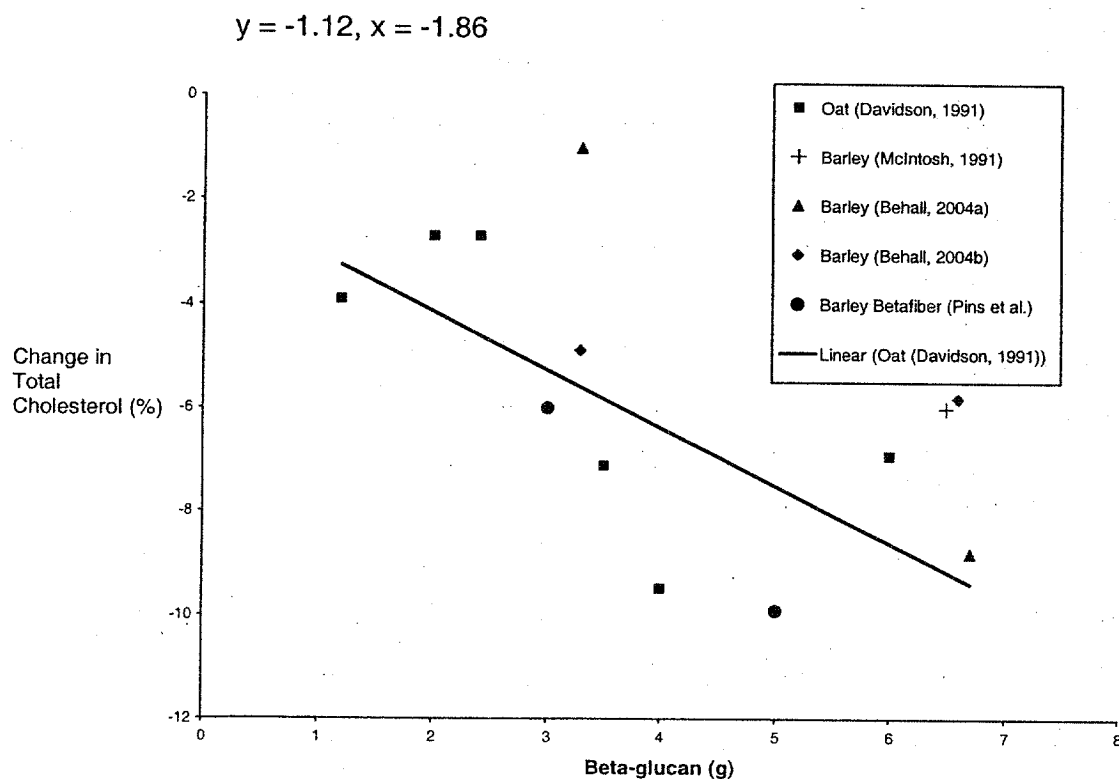
Among the oat and barley beta-glucan doses evaluated, only the 5g oat beta-glucan dose significantly lowered TC by 7.4% ($p < 0.01$) compared to the control. However, LDL-C levels were not significantly different between the 5g oat beta-glucan group and the control group. Serum lipid changes for the higher dose of oat beta-glucan (10g) and both the 5g and 10g barley beta-glucan dose levels were also not significantly different compared to the control. The reasons for the lack of effect in the group receiving 10g oat beta-glucan and in those receiving 5g and 10g barley beta-glucan are not clear. The researchers indicated that the viscosity in the intestine is dependent not just on the amount of beta-glucan, but also on the solubility, structure, and molecular weight of the beta-glucan. In this study, decreasing the molecular weight of the beta-glucan appears to reduce the viscosity and the cholesterol lowering effect. Biörklund et al. speculate that the potency of the barley extract may have been hampered by its low molecular weight; the molecular weight of the beta-glucan in the barley beverages (40 kDa) was almost half of the beta-glucan in the oat beverages (70 kDa). However, this does not explain the lack

of a dose-response relationship. The solubility of the beta-glucan products used in this study was not tested, but the researchers indicated that they anticipated it would be high because the process to isolate the beta-glucan powder filters away insoluble dietary fiber components. It is possible, however, that the solubility of beta-glucan in the 10g beverages may have been reduced during storage as they were in a more concentrated solution.

4) Effective Dose

The health claim final rule (21 CFR 101.81) has established 3g oat beta-glucan soluble fiber as the effective minimum daily intake to significantly lower cholesterol. The National Barley Foods Council has outlined in their health claim petition the equivalency of barley beta-glucan to oat beta-glucan, and FDA supported this conclusion in the recent interim final rule for whole grain barley and certain dry milled barley grain products (FDA, 2005). All of the barley clinical trials that have measured beta-glucan have utilized a dose of 3g barley beta-glucan per day or more to demonstrate significant serum cholesterol lowering. When data from barley clinical trials (Behall et al., 2004a, 2004b; McIntosh et al., 1991) were plotted using data from the oat beta-glucan dose response study by Davidson et al. (1991), it became evident that the regression equation relationship between beta-glucan consumption and the corresponding change in serum cholesterol was applicable to both oat and barley beta-glucan. Figure 1 suggests that the dose response for barley beta-glucan is similar to the dose response for oat beta-glucan and that 3g barley beta-glucan will reduce TC by about 5% on average. Data from the Pins et al. study also supports this finding, where it was demonstrated that 3g and 5g barley beta-fiber lowered TC by 6.0% and 9.9% respectively (Table 2). The regression equation relationship appears to be valid for barley beta-fiber as it is for native barley and oat beta-glucan.

Figure 1. Change in Total Cholesterol in Subjects Consuming Six Levels of Oat Beta-Glucan, Two Levels of Barley Beta-Glucan, and Two Levels of Barley Betafiber.



5) Summary of Clinical Data

The clinical trial with barley betafiber by Pins et al. (Table 2, Appendix 2) successfully demonstrates the efficacy of barley betafiber in lowering TC and LDL-C. Results of this study are consistent with the observation that 3g beta-glucan is an effective level of intake to lower serum cholesterol, regardless of whether the source is oats or barley, or whether the product contains native beta-glucan or a concentrated source of beta-glucan, as in barley betafiber. However, not all highly concentrated barley beta-glucan extracts are clinically efficacious, as demonstrated by the findings of Keogh et al. (2003) and Biörklund et al. (2005). It is for this very reason that FDA has indicated that each soluble fiber product should be evaluated on a case-by-case basis. Different processing and extraction methods can render a

beta-glucan soluble fiber product ineffective in lowering cholesterol. On the other hand, both doses (3g and 5g) of barley betafiber were shown to be clinically effective (Table 2, Appendix 2).

C. Animal Data

1) Animal Studies with Barley Betafiber Prototypes as a Cholesterol-Lowering Agent

Animal studies conducted by Delaney et al. (2003) and Wilson et al. (2004) demonstrate that barley betafiber is consistent with human studies in lowering cholesterol in an animal model (Table 5). Delaney et al. (2003) used a hamster model to compare the antiatherogenic properties of a barley betafiber prototype (78% beta-glucan) with a beta-glucan concentrate from oats (65% beta-glucan). This barley betafiber prototype had a molecular weight of 1000 kDa, similar to native barley beta-glucan, and was prepared by an extraction process comparable to the method described by Aman and Hesselman (1985), with minor modifications. Ground whole barley flour was mixed with boiling water and bacterial α -amylases to hydrolyze starch, solubilize beta-glucan and inactivate beta-glucanase. Solubilized beta-glucan was precipitated, washed with ethanol, and dried. The oat beta-glucan concentrate was prepared in a similar manner. The processing method used for the barley betafiber prototype in this study is similar to the processing used in production of the barley betafiber that is the subject of this petition, except that its molecular weight was not reduced as with barley betafiber.

In Delaney et al. (2003), Syrian golden F₁B hamsters were acclimated to a hypercholesterolemic diet for 2 weeks before they were fed 2g, 4g, or 8g beta-glucan/100g diet by the addition of beta-glucan concentrate prepared from oats or barley. Control animals consumed 15g cellulose/100g diet. Compared to control hamsters, the dose-dependent decreases in plasma TC and LDL-C at 9 weeks were

similar in magnitude to those noted in hamsters fed oat or barley beta-glucan. Both barley and oat beta-glucan significantly reduced TC and LDL-C compared to controls at doses of 4g beta-glucan ($p < 0.05$ for both) and 8g beta-glucan ($p < 0.05$ for both). Liver total, free and esterified cholesterol concentrations were significantly reduced for both sources at the 8g beta-glucan/100g diet dose ($p < 0.05$ for both). Similarly, aortic total and esterified cholesterol were significantly reduced in the 8g beta-glucan/100g diet in barley or oat beta-glucan groups ($p < 0.05$ for both). In addition, consumption of 8g beta-glucan/100g diet from barley or oats significantly increased total fecal neutral sterol excretion ($p < 0.05$) and in particular, cholesterol excretion. The researchers concluded that the cholesterol-lowering potency of beta-glucan from barley and oats was almost identical.

In the study by Wilson et al. (2004), the cholesterol-lowering properties of a LMW beta-glucan concentrate (barley betafiber) was compared to a HMW (1000 kDa) beta-glucan concentrate in Syrian golden F₁B hamsters fed a hypercholesterolemic diet (Table 5). Concentrated HMW beta-glucan was prepared from milled waxy hulless barley flour, using a modification of the extraction method of Aman and Hesselman (1985), as described in Delaney et al. (2003). The LMW beta-glucan concentrate (barley betafiber) was prepared from the same barley flour under conditions similar to those used for the HMW beta-glucan extraction, with addition of a beta-glucanase preparation from *Bacillus amyloliquefaciens*.

Following a 2-week diet stabilization period, the hamsters were fed diets that contained the HMW or LMW beta-glucan concentrates at a dose of 8g beta-glucan/100g diet or an 8g cellulose control. Significant decreases in TC and non-HDL cholesterol were observed in the animals fed barley betafiber (-36% and -50%, respectively, $p < 0.05$ for both) and HMW beta-glucan (-32% and -43% respectively, $p < 0.05$ for both). Liver cholesterol was not significantly impacted, but total and esterified cholesterol in aortic tissue were significantly reduced among both barley betafiber and HMW beta-glucan fed animals compared to controls ($p < 0.05$ for

both). An unexplained increase in free aortic cholesterol was observed in the group receiving the barley betafiber. Total fecal neutral sterol excretion increased significantly for both the barley betafiber (107%, $p < 0.05$) and HMW (93%, $p < 0.05$) groups, but fecal cholesterol excretion increased only in the hamsters fed the barley betafiber (331%, $p < 0.05$) compared to hamsters fed the control diet.

Table 5. Animal Studies of Highly Concentrated Barley Beta-Glucan and Cholesterol Lowering

Study	Animals, Duration	Study Design	Barley Beta-Glucan (BG) Concentrates—Proximate Composition, MW	Barley Beta-Glucan Concentrate Processing Methods	Results
Studies with Barley Betafiber and/or Barley Betafiber Prototype					
Delaney et al., 2003	Syrian golden F ₁ B hamsters, 9 weeks treatment	<p>Hypercholesterolemic background diet</p> <p><u>Treatment groups:</u> -2g BG‡/ 100g diet -4g BG‡/ 100g diet -8g BG‡/100g diet ‡Barley betafiber prototype</p> <p>-2g oat BG ∞/ 100g diet -4g oat BG ∞/ 100g diet -8g oat BG ∞/100g</p> <p>∞ oat beta-glucan concentrate</p> <p>-cellulose (control)</p> <p>The barley betafiber prototype was blended into the hypercholesterolemic hamster feed at different levels to meet treatment BG requirements. Identical procedures were followed for oat beta-glucan concentrate and the cellulose control.</p>	Barley betafiber prototype: 78% BG, 1% fat, 7.8% protein, 5.2% moisture, 1.8% ash, avg MW= 1000 kDa	Ground barley flour was mixed with boiling water and bacterial α-amylases to hydrolyze starch, solubilize beta-glucan and inactivate beta-glucanase activities. Solubilized beta-glucan was precipitated, washed with ethanol, and dried.	<p>Treatment vs. Control TC: barley, 2g BG: ns. barley, 4g BG: -14.1%* barley, 8g BG: -26.6%*</p> <p>oat, 2g BG: ns. oat, 4g BG: -16.7%* oat, 8g BG: -32.2%*</p> <p><u>LDL-C:</u> barley, 2g BG: ns. barley, 4g BG: -19.5%* barley, 8g BG: -30.4%*</p> <p>oat, 2g BG: ns. oat, 4g BG: -26.0%* oat, 8g BG: -40.6%*</p> <p><u>HDL-C:</u> barley, 2g BG: ns. barley, 4g BG: ns barley, 8g BG: -18.9%*</p> <p>oat, 2g BG: +22.1%* oat, 4g BG: ns oat, 8g BG: -15.4%*</p>

* significantly different from control p < 0.05; BG: beta-glucan; MW: molecular weight; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol

Table 5. Animal Studies of Highly Concentrated Barley Beta-Glucan and Cholesterol Lowering (cont'd.)

Study	Animals, Duration	Study Design	Barley Beta-Glucan (BG) Concentrates—Proximate Composition, MW	Barley Beta-Glucan Concentrate Processing Methods	Results
Studies with Barley Betafiber and/or Barley Betafiber Prototype					
Wilson et al., 2004	Syrian golden F ₁ B hamsters 6 weeks treatment	Hypercholesterolemic background diet <u>Treatment groups:</u> -HMW barley BG concentrate : 8g BG/100g diet -LMW barley BG concentrate: 8g BG‡/100g diet -cellulose (control) ‡ Barley betafiber LMW (barley betafiber) was blended into the hypercholesterolemic hamster feed to meet treatment BG requirements. Identical procedures were followed for HMW and the cellulose control.	LMW: 75% BG, 0.2% fat, 2% protein, 7.5% moisture, 2.5% ash 2.5% MW: 175 kDa; barley betafiber consistent with the subject of this petition. HMW: 70% BG, 2.7% fat, 8.3% protein, 3.4% moisture, 2.4% ash; MW: 1000 kDa	HMW: As described in Delaney et al., 2003. LMW: A reduced MW/viscosity variant was prepared by extraction from the same barley flour with a beta-glucanase preparation from <i>Bacillus amyloliquefaciens</i> under conditions similar to those used for the HMW extraction.	Treatment vs. Control <u>TC:</u> HMW: - 32.1%* LMW: - 35.6%* <u>non-HDL-C:</u> HMW: - 42.6%* LMW: - 49.5%*

Table 5. Animal Studies of Highly Concentrated Barley Beta-Glucan and Cholesterol Lowering (cont'd.)

Study	Animals, Duration	Study Design	Barley Beta-Glucan (BG) Concentrates—Proximate Composition, MW	Barley Beta-Glucan Concentrate Processing Methods	Results
Studies with Other Highly Concentrated Barley Beta-Glucan					
Klopfenstein and Hosney, 1987	Rats 35 days treatment	Hypercholesterolemic diet <u>Treatment groups</u> -7%barley extract -7% oat extract -13% oat extract -7% wheat extract -7% sorghum extract Extracts replaced 7% of the flour in the experimental breads, except for the second oat bread that replaced 13% of the flour.	Barley beta-glucan extract: 68% non-cellulose, non-starch polysaccharides, 0.5% fat, 6.9% protein, 10.4% moisture, 13.6% ash.	Barley was hulled by pearling and milled and sieved to a fine flour. Ethanol is added to the flour and the mixture is boiled and centrifuged. Chloroform: methanol is added to the residue and it is centrifuged again. Water is added to the residue and the mixture is boiled and cooled. Alpha-amylase is added and the mixture is centrifuged. The residue is extracted with NaOH under N ₂ atmosphere and centrifuged. The supernatant is cooled to 5° C to which ethanol is added and the mixture is centrifuged. The residue is washed 3x with ethanol and dissolved in water. The product is dialyzed in distilled water and freeze-dried.	Treatment vs. control <u>TC:</u> 7%barley BG: - 18%* 7% oat BG: ns 13% oat BG: -15%* 7% wheat BG: -12%* 7% sorghum BG: -14%* (18 d)
Oda et al., 1994	Male Sprague Dawley rats 14 days treatment	Hypertriglyceridemic diet <u>Treatment groups:</u> -barley gum -oat gum -guar gum -cellulose (control)	Barley gum: 65.5% TDF, 0.6% fat, 13.8% protein, 9.5% moisture, 3.3 % ash	Barley flour was defatted with n-hexane, air-dried, milled, and sieved. Soluble gum preparations were isolated according to the procedure of Wood et al. (1976) by replacing isopropanol with ethanol.	Treatment vs. Control <u>TC:</u> barley gum: - 20%* oat gum: -17%* guar gum: - 48%*

Table 5. Animal Studies of Highly Concentrated Barley Beta-Glucan and Cholesterol Lowering (cont'd.)

Study	Animals, Duration	Study Design	Barley Beta-Glucan (BG) Concentrates—Proximate Composition, MW	Barley Beta-Glucan Concentrate Processing Methods	Results
Studies with Other Highly Concentrated Barley Beta-Glucan					
Hecker et al., 1998	Rats 25 days treatment	Hypercholesterolemic background diet <u>Treatment groups:</u> -barley BG concentrate incorporated into flour tortillas -cellulose (control)	Barley BG concentrate: 55-60% BG, 0.1% fat, 3.6% protein, 7-11% moisture, 0.95% ash; MW: unavailable.	Not available.	Treatment vs. Control <u>TC:</u> barley BG: ns <u>LDL-C:</u> barley BG: -40%*
Maqueda de Guevara et al., 2000	Male Sprague Dawley rats 28 days treatment	Hypercholesterolemic background diet <u>Treatment groups:</u> -barley BG≈ + flax oil -flax oil -barley BG≈ + coconut oil -coconut oil -corn (control) ≈Glucagel™-100g/kg	Glucagel™: 70% BG, proximate info. unavailable, typical MW 130kDa	Barley pollard flour was extracted with water at 25-55°C for 0.5 – 6 hour. The spent flour from each fraction was centrifuged for 10 min. and the supernatant was frozen for 24 hours. The frozen solution was thawed in a water bath at room temperature. The gelatinous material in the thawed solution was recovered through filtration and washed with water and ethanol before being dried at 50°C. The resulting product, Glucagel™ was purified by re-dissolving in water at 80°C and repeating the filtration, freeze-thaw, and washing steps (Morgan and Ofman, 1998).	Treatment vs. Control <u>TC:</u> barley BG: ns (-10% trend, p=0.07) <u>TG:</u> barley BG + flax oil: -13%* barley BG + coconut oil: -40%*

BG: beta-glucan; HMW: high molecular weight; LMW: low molecular weight; MW: molecular weight; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides; TDF: total dietary fiber

2) Review of Animal Studies with Other Highly Concentrated Barley Beta-Glucan Extracts as Cholesterol-Lowering Agents

The National Barley Foods Council health claim petition has summarized the data from a variety of animal models, including chicks, rats, hamsters, and swine, which support the cholesterol-lowering properties of beta-glucan contained in whole barley fractions (Fadel et al., 1987; Newman et al., 1991; Martinez et al., 1992; Sundberg et al., 1995, 1998; Wang et al., 1997; Ranhotra et al., 1998; Kalra and Jood, 2000, Li et al., 2003) and extracted barley beta-glucan preparations (Klopfenstein and Hosney, 1987; Oakenfull et al., 1991; Oda et al., 1994; Hecker et al., 1999; Maqueda de Guevara et al., 2000; Yang et al., 2003).

Among the studies that tested extracted barley beta-glucan preparations, four studies, Klopfenstein and Hosney (1987), Oda et al. (1994), Hecker et al. (1998) and Maqueda de Guevara et al. (2000) provided data indicating the use of a highly concentrated barley fiber source (Table 5). Klopfenstein and Hosney (1987) fed hypercholesterolemic rats experimental breads enriched with 68% non-cellulose, non-starch polysaccharide fractions⁷ from barley, oats, wheat, and sorghum for 35 days. The grain extracts replaced 7% of the flour in the bread. In the case of the oat beta-glucan extract, two test products were evaluated, one with 7% flour replacement with grain extracts and another with 13% flour replacement. TC was significantly reduced ($p < 0.05$) by the barley, oat (13% flour replacement), and wheat replaced flour at the end of the 35-day treatment phase compared to the cellulose control. Animals fed the sorghum extract were not followed for 35 days.

Oda et al. (1994) stabilized rats on a hypertriglyceridemic diet with 5% cellulose for 14 days. After this period, 2% cellulose was replaced by barley gum, oat gum, or

⁷ Studies conducted in the 1980s and early 1990s did not have a method for specifically isolating beta-glucan. A significant portion of the non-cellulose, non-starch polysaccharides contained in barley and oats would be beta-glucan.

guar gum in some of the animals for another 14 days. Methods to determine the beta-glucan content of the barley and oat gums were not available at this time, but both the barley and oat gums contained approximately 65% dietary fiber. Barley gum significantly reduced TC ($p < 0.05$) compared to the cellulose control. Oat and guar gum also significantly reduced TC levels. Barley gum did not impact liver cholesterol, but significantly suppressed the elevation of serum and liver triglyceride concentrations ($p < 0.05$ for both).

Hecker et al. (1998) incorporated a 55.6% barley beta-glucan concentrate (Centennial Foods Inc., Dillon, MT, USA) into flour tortillas to yield 2g soluble fiber per serving (one tortilla). The cholesterol-lowering properties of the beta-glucan-containing flour tortillas were evaluated in rats, where two groups of rats consumed either beta-glucan tortillas or control tortillas containing cellulose in place of beta-glucan for 25 days. Rats fed the beta-glucan tortillas had significantly lower LDL-C than controls ($p < 0.05$). However, there were no differences in TC, HDL-C, or triglycerides between the two groups. The beta-glucan tortilla fed rats consumed less feed and gained less weight ($p < 0.05$) and had higher fecal fat excretion ($p < 0.05$) than controls. Lower liver total lipid and cholesterol concentrations were also observed in beta-glucan fed rats ($p < 0.05$ for both).

Maqueda de Guevara et al. (2000) fed rats a beta-glucan extract (GlucagelTM; 70% beta-glucan) made from New Zealand barley, in conjunction with flax oil or coconut oil, for a period of 28 days. The beta-glucan product used in this study was the same as the one clinically tested by Keogh et al. (2003). Control animals consumed similar diets without GlucagelTM. Results indicated the type of oil had no significant effect on plasma cholesterol levels. Rats fed GlucagelTM had a 10% decrease in TC, an effect that was significant only at ($p < 0.07$). Plasma triglyceride levels however were lowered by 40% ($p < 0.01$) in rats fed GlucagelTM plus coconut oil.

3) Summary of Animal Data

The cholesterol-lowering effects observed in the animal studies with barley betafiber and/or a prototype of barley betafiber are consistent with the demonstrated clinical efficacy of this product in hypercholesterolemic human subjects. Results of the study by Delaney et al. (2003) show that beta-glucan concentrates from barley and oats modify plasma cholesterol and other atherogenic parameters with approximately identical potency. Native beta-glucan from barley or oats has a HMW (≥ 1000 kDa), which contributes to high viscosity and diminished sensory properties that limit its use in a number of food applications. A reduced molecular weight beta-glucan, such as barley betafiber, is better suited to wider food uses. Wilson et al. (2004) found that a LMW barley beta-glucan concentrate (barley betafiber) maintains its cholesterol-lowering activity similar to a native barley beta-glucan concentrate with HMW. Animal studies of other concentrated sources of barley beta-glucan indicate that some maintain their cholesterol-lowering ability (Hecker et al., 1998; Oda et al., 1994), while others do not (Maqueda de Guevara et al., 2000).

D. Other Potential Health Effects of Concentrated Barley Beta-Glucan

1) Beneficial Effects on Blood Glucose Metabolism

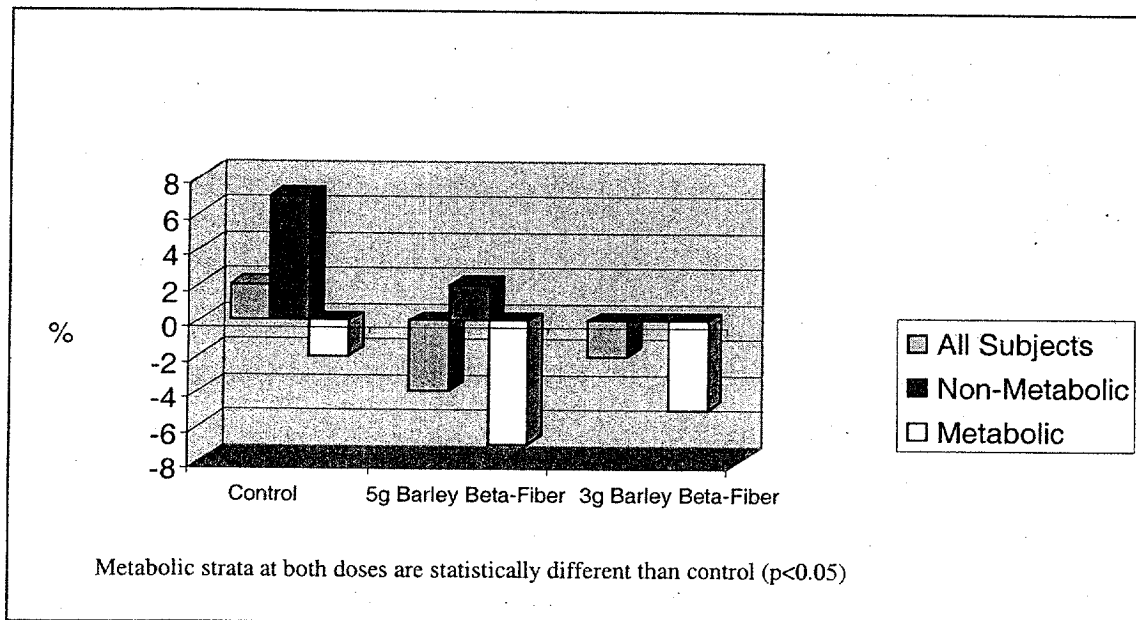
There is increasing evidence that chronic hyperglycemia is associated with increased CHD risk in both diabetics and non-diabetics. Glycosylated hemoglobin (HbA_{1c}), a measure of long-term glycemic control, has long been used as a predictor in the development of microvascular disease in persons with diabetes (Shichiri et al., 2000; UK Prospective Diabetes Study Group, 1998; Diabetes Control and Complications Trial Research Group, 1993). A body of information now available suggests that HbA_{1c} may also predict macrovascular disease risk in diabetics (Selven et al., 2005; Stevens et al., 2004; Alder et al., 2002, 1999; Stratton et al., 2000), and even more importantly, in individuals without diabetes or with normal glucose tolerance (Selven et al., 2005; Blake et al., 2004; Jorgensen et al., 2004; Sasso et al., 2004; Khaw et al., 2001; Vitelli et al., 1997; Park et al., 1996). There appears to be a linear relationship between HbA_{1c} levels and severity of CHD, even among persons with glucose values within the normal range (Sasso et al., 2004). Thus HbA_{1c} may be linked to CHD risk in a continuous relationship, similar to serum cholesterol and blood pressure (Sasso et al., 2004). Attempts to lower population mean HbA_{1c} levels may have important public health implications in reducing CHD risk.

Barley Betafiber Related Effects on HbA_{1c}

The 10-week double-blind, randomized controlled five-arm parallel group clinical trial conducted by Pins et al. (see Section III B2) also evaluated the effects of 3g and 5g barley betafiber on glucose metabolism. Preliminary findings (Pins et al., 2005a) indicate HbA_{1c} was significantly reduced in both barley betafiber treatment groups when compared to the control group (ANOVA F-test, $p < 0.05$; Figure 2). The effect was more pronounced in subjects identified with metabolic syndrome. No study of barley or oat beta-glucan has previously reported this HbA_{1c} lowering benefit among

non-diabetic subjects. (A more complete analysis of these results and other parameters relating to blood glucose metabolism will be completed in the near future). Individuals who consume barley betafiber may have the added benefit of reducing CHD risk by lowering HbA_{1c} levels in addition to reductions in serum cholesterol.

Figure 2. HbA_{1c}% Change from Baseline by Treatment Group and Metabolic Stratification



Glycemic Effects of Other Barley Beta-Glucan Concentrates

The National Barley Foods Council health claim petition has provided evidence that beta-glucan containing barley foods derived from typical or high fiber barley genotypes have the potential to lower postprandial blood glucose and insulin levels. Studies summarized in that petition also demonstrate that products containing extracted barley beta-glucan fractions have a similar effect. A Medline search was conducted and all studies that utilized concentrated barley beta-glucan products are reported here.

In the study by Yokoyama et al. (1997), a beta-glucan-enriched flour (20% beta-glucan) was prepared by repeatedly milling and sieving Waxbar barley to remove starch particles. This flour was used with durum wheat flour to produce a high barley beta-glucan pasta that was used in test meals to provide 12g beta-glucan and 30g total dietary fiber. Control meals contained 100% durum wheat pasta that provided no beta-glucan and 5g total dietary fiber. Glycemic and insulinemic responses were measured in five non-diabetic, fasted subjects who consumed the test or control meals. The maximum increment in plasma glucose ($p < 0.001$) and the total area under the plasma glucose curve (AUC) ($p < 0.05$) were lower with the barley beta-glucan pasta than with the wheat pasta. Similarly, the maximum increment in plasma insulin was significantly lower for the barley beta-glucan pasta than for the wheat pasta ($p < 0.05$). Although the average and total incremental insulin responses were lower for the barley beta-glucan pasta than for wheat pasta, the differences only approached significance ($p < 0.08$).

Eight healthy, non-diabetic subjects consumed 50g available carbohydrate from four different breads made from 100% wheat flour or wheat flour combined with three different barley fractions: a water-extracted fraction of whole grain barley flour (33% beta-glucan), a sieved fraction of whole grain barley flour (8.5% beta-glucan), and whole grain barley flour (4.6% beta-glucan) (Cavallero et al., 2002). Postprandial blood glucose responses indicated a linear decrease in glycemic index as the dose of beta-glucan increased. The concentrated water-extracted barley beta-glucan-containing bread had a 28% lower glycemic index than the 100% wheat flour bread ($p < 0.05$). This bread was also given the best score for sensory qualities.

Hallfrisch and coworkers (2003) compared the acute postprandial glucose and insulin responses of solubilized barley and oat extracts to oat bran and barley. The extracts known as Nu-trimX were produced by extracting solubilized beta-glucans from oats or barley endosperm while reducing its cellulose components in a wet extraction process. Oat bran was used to derive the oat extract and the barley

extract was obtained from the Prowashonupana cultivar, a barley genotype that contains twice the soluble fiber of oat bran. The beta-glucan concentrations of the extracts were not reported. In the study, 20 healthy non-diabetic subjects consumed 1g carbohydrate/kg bw as glucose (control) or 0.66g/kg bw as pudding, plus 0.33g/kg bw of either oat bran, barley flour, oat extract, or barley extract, in a randomized Latin square design (Hallfrisch et al., 2003). Area under the plasma glucose curve (AUC) was lower for all test meals compared to glucose ($p < 0.0003$). Similarly, plasma insulin responses were lower after all the oat and barley meals compared to glucose ($p < 0.002$). The barley extract with the highest concentration of beta-glucan elicited the lowest plasma glucose and insulin response compared to oat bran, barley flour, or oat extract; however the differences between groups were not statistically significant. Glycemic indices for oat bran, barley flour, oat extract and barley extract were 64, 65, 69, and 57, respectively.

The clinical trial that tested the cholesterol-lowering efficacy of Glucagel™ (75% beta-glucan) also evaluated fasting glucose and postprandial glucose responses in 18 mildly hypercholesterolemic subjects (Keogh et al., 2003). Subjects on average consumed 10g beta-glucan per day or a glucose control for 4 weeks. Fasting plasma glucose tended to decrease over the 4 week period for both treatment and control phases but there were no significant differences at the end of the intervention period. Postprandial plasma glucose responses were also not significantly different between treatment and control phases when a glucose tolerance test was administered. The lack of glycemic responses with Glucagel™ consumption paralleled the lack of response observed in blood cholesterol lowering.

2) No Significant Adverse Effects on the Gastrointestinal System and on Mineral and Vitamin Bioavailability

Tolerance of Barley Betafiber

Subjects consumed food products containing 3g and 5g barley betafiber over the course of 6 weeks (Pins et al., Appendix 2). Compliance was greater than 95% in treatment groups, suggesting that barley betafiber is well tolerated. Tolerance of this product was further demonstrated by the fact that there were no study dropouts. Study-related side effects were measured by a 13-question side effect questionnaire that subjects were required to complete at baseline and at each treatment visit. There were no significant changes in the frequency of side effects from baseline, mid-study visit, or the last study visit in any of the treatment groups compared to the control group.

Tolerance of Other Highly Concentrated Sources of Barley Beta-Glucan

In addition to the clinical trial by Pins et al., two other clinical trials have been conducted with highly concentrated sources of barley beta-glucan (Keogh et al., 2003; Biörklund et al., 2005). In their study of Glucagel™ (75% beta-glucan), Keogh et al. (2003) fed hypercholesterolemic men a daily dose of 9.9g barley beta-glucan for 4 weeks. No side effect information was reported, but the researchers indicated there were no subject dropouts or withdrawals due to lack of compliance. Biörklund et al. (2005) evaluated the daily consumption of 5g and 10g barley (36% beta-glucan) and oat (18% beta-glucan) preparations in hypercholesterolemic subjects for 5 weeks. A level of 99% compliance was achieved in both the barley and oat periods. Some subjects reported gastrointestinal discomfort. Major complaints included bloating, flatulence, and diarrhea, but these symptoms were reported in both the control group with the starch-fortified beverage as well as in the group consuming beta-glucan fortified beverages. The gastrointestinal symptoms were somewhat more frequent in the 10g oat group compared to the other groups, but the symptoms decreased gradually for all subjects after 1 to 2 weeks of consumption.

No Significant Impact of High Beta-Glucan or High Soluble Fiber Intake on the Gastrointestinal System and Vitamin and Mineral Bioavailability

No studies to date have provided any evidence of significant adverse effects such as gastrointestinal disturbances, choking, or mineral or vitamin malabsorption related to the intake of beta-glucan soluble fiber. In their reviews of the data, the National Barley Foods Council health claim petition, the Quaker Oats health claim petition, and Quaker Oats and Rhodia health claim petition each reported no evidence of serious side effects with the increased consumption of beta-glucan from either barley or oats.

The Dietary Reference Intakes Report on Dietary, Functional and Total Fiber has indicated that the potential adverse health effects of functional fibers (including beta-glucan soluble fiber) are not completely known and should be evaluated on a case-by-case basis (IOM, 2005). The most potential deleterious effects suggested are the interaction of functional fibers with other nutrients in the gastrointestinal tract.

Very few studies have examined the effect of barley fiber on mineral bioavailability. Wisker et al. (1991) evaluated calcium, magnesium, zinc, and iron balances in young women who consumed 15g low-phytate barley fiber concentrate for 22 days. The increased barley fiber intake had no significant effect on mineral balance. However, these findings are not relevant to increased beta-glucan soluble fiber intake because the barley fiber concentrate used in the Wisker et al. (1991) study was 97% insoluble fiber.

Sandstrom et al. (1987) compared the absorption of zinc from bread or porridge made from 60g barley, rye, oatmeal, triticale or whole wheat in healthy subjects. The results indicated that phytic acid rather than fiber influenced zinc absorption. Rye bread with the lowest phytic acid content was associated with the highest absorption of zinc, whereas oatmeal porridge with the highest phytic acid content

had the lowest zinc absorption. Analyses of barley betafiber indicate phytic acid levels are always below 1%, and more frequently below 0.5%. Therefore it is unlikely that the minimal amount of phytic acid associated with barley betafiber would significantly impact zinc absorption.

Soluble fiber fractions isolated from barley flour, whole grain rye flour and oat bran were analyzed for their ability to bind copper, cadmium, and zinc *in vitro* (Persson et al., 1991). In determining which components in soluble fiber are responsible for mineral binding, it was observed that beta-glucans from either barley or oats do not bind copper, cadmium, or zinc to a significant extent. The researchers note that beta-glucan soluble fiber is largely fermented *in vivo*, and the chelating capacity of fermented fiber is less than that found *in vitro*, thus more mineral would be available for absorption.

Although mineral balance experiments with extracted beta-glucan soluble fiber have not been conducted, there is evidence that highly soluble fibers do not have a negative impact on mineral absorption. Coudray et al. (1997) evaluated the effect of feeding a soluble fiber (inulin) and a partly soluble fiber (sugar beet fiber) on the absorption and balance of calcium, magnesium, iron, and zinc in healthy young men. Subjects consumed up to a maximum of 40g soluble fiber/day for a 28-day period. The absorption and balance of magnesium, iron, and zinc were not significantly altered by the consumption of either soluble fiber source. On the other hand, both soluble fiber sources increased calcium absorption and balance.

Behall (1990) conducted two human studies and also observed no significant alteration of mineral balance with soluble fiber consumption. In the first study, the 4-week consumption of 19.5g fiber from cellulose, an insoluble fiber, was compared to the 4-week consumption of 19.5g soluble fiber from carboxymethylcellulose gum, karaya gum, or locust bean gum. None of the fibers influenced the mineral balance of calcium, magnesium, manganese, iron, copper, or zinc, with the exception of a

negative manganese balance after carboxymethylcellulose consumption. In the second study, diabetic subjects consumed 31.7g highly soluble fiber (guar gum) for 6 months. Mineral balance was not affected by the long-term consumption of guar gum.

There is currently no available data on the effect of beta-glucan soluble fiber, if any, on vitamin bioavailability. In general, the data for soluble fiber and total dietary fiber is sparse. A limited number of single meal studies show a potential reduction in the absorption of some vitamins. Roe et al. (1988) observed that the 24-hour absorption of riboflavin from a load test that was given after consuming 7.5g fiber from psyllium reduced riboflavin absorption by 32% ($p < 0.01$). Similarly, Riedl et al. (1999) found that the soluble fibers—pectin, guar, or alginate reduced beta-carotene absorption by 33% to 43% when a standard meal with an antioxidant mixture was consumed with these fibers ($p < 0.05$). All of the soluble fibers (pectin, guar, alginate) and insoluble fibers (cellulose, wheat bran) tested decreased the absorption of lycopene and lutein by 40% to 74% ($p < 0.05$) respectively. Alpha-tocopherol absorption, however, was not affected by any of the dietary fibers. It is important to note that these are single meal studies and do not take into account the gastrointestinal adaptation that takes place over the course of extended high fiber consumption.

In contrast to the single-meal studies above, Sierra et al. (2002) observed no effect on vitamin A, vitamin E, iron, magnesium, potassium, and phosphorus levels among diabetics who daily consumed 14g fiber from psyllium for 6 weeks. Similarly, Anderson and coworkers (1980) evaluated the mineral and vitamin status of diabetics who were consuming high fiber diets for an average of 21 months. Serum calcium, phosphorus, iron-binding capacity, magnesium, and hemoglobin values were normal in this subject group. Normal serum levels of vitamin B₁₂ and folic acid were also detected. Indirect assessments also suggested that intakes of vitamins A, D, and K were also adequate.

Overall, the data suggest that the increased consumption of barley beta-glucan soluble fiber will have no significant adverse effects on the US population. In reviewing the data for establishing a dietary reference intake for dietary fiber, the IOM concluded, "...as part of an overall healthy diet, a high intake of dietary fiber will not produce significant deleterious effects in healthy people," therefore, a Tolerable Upper Intake Level is not set for dietary fiber (IOM, 2005).

3) No Significant Adverse Effects from an Estimated Increase in Soluble Fiber Consumption

Barley betafiber is intended for use as an ingredient in foods. The majority of foods containing barley betafiber will provide 0.75g beta-glucan soluble fiber per serving, the same amount of beta-glucan soluble fiber that FDA has already approved for whole oat products, specified oatrim, and recently for whole grain barley and certain dry milled barley grain products. If an individual were to consume a barley betafiber-containing food with 0.75g beta-glucan soluble fiber per serving at four eating occasions per day, the total amount of beta-glucan soluble fiber consumed would be 3g daily. This level of intake is the amount of beta-glucan soluble fiber recommended to achieve meaningful serum cholesterol reduction.

In Cargill's self-determined GRAS assessment for barley betafiber, it was assumed that if each food with barley betafiber (among foods for intended use) contained the maximum proposed level of 3g beta-glucan soluble fiber, the estimated average intake would be 7.3g barley beta-glucan/person/day from all proposed food categories combined. Consumers in the 90th percentile would consume 13.9g barley beta-glucan/person/day (Table 6). This 13.9g soluble fiber intake is within the 10g - 25g soluble fiber range suggested by the NCEP ATP III (NCEP, 2002). The GRAS Expert Panel (Appendix 1) reviewed the data and affirmed the GRAS status of barley betafiber. Studies with intakes as high as 30g - 40g soluble fiber/day do not show deleterious effects on mineral absorption (Coudray et al., 1997; Behall, 1990).

The beta-glucan soluble fiber contained in barley has a long history of safe use. In Maghreb countries (Morocco, Algeria, Libya, Tunisia), barley is used in a variety of traditional foods (bread, soup, porridge), resulting in an average intake of up to 172g barley/person/day (Morocco). With this intake of barley, about 6g beta-glucan/person/day is consumed. Importantly, the preparation of these traditional foods involves cooking the barley grain for long periods of time, which ensures extraction of beta-glucan from its natural cell wall context.

Currently, the IOM recommends an intake of 30g - 38g dietary fiber/day for adult men and 21g - 25g dietary fiber/day for adult women (IOM, 2005). In the US, the range of fiber intake is just 14g -19g dietary fiber/day, which is well below recommended levels (USDA, 1997). The potential increase in dietary fiber from consumption of barley betafiber would only help to increase dietary fiber intakes of the US population, consistent with the recommendations of the 2005 Dietary Guidelines for Americans (USDA/DHHS, 2005).

**Table 6. Estimated 2-Day Average Intake of Barley Beta-Glucan and Barley Betafiber
by Consumers of Proposed Food Uses**
**Total Population
(2 years and older)**

Population group and Food category	Users		2-Day Average Intake per User							
			Barley Beta-Glucan				Barley Betafiber			
	Number	% Population	g/day		g/kg bw/day		g/day		g/kg bw/day	
			Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile	Mean	90th Percentile
Bars	748	4	2.0	3.5	0.04	0.08	2.9	4.9	0.06	0.12
Beverages	11819	57	4.0	7.9	0.09	0.19	5.7	11.3	0.12	0.28
Breads, whole grain and specialty	5384	32	2.5	4.6	0.04	0.08	3.5	6.5	0.06	0.12
Breakfast cereals	10342	47	3.3	6.0	0.07	0.15	4.7	8.6	0.10	0.22
Cookies, lite	365	2	2.6	4.8	0.04	0.08	3.6	6.8	0.06	0.12
Crackers, reduced fat	331	2	2.2	4.3	0.04	0.08	3.1	6.1	0.05	0.11
Instant rice	446	2	1.8	3.5	0.03	0.06	2.6	5.0	0.05	0.09
Macaroni products	6525	33	2.0	4.5	0.04	0.08	2.9	6.4	0.06	0.11
Muffins, reduced fat	53	< 0.5	2.2	3.3	0.03	0.04	3.2	4.8	0.05	0.06
Salad dressings, lite	1818	12	2.2	4.5	0.03	0.07	3.1	6.4	0.05	0.10
Snack chips, reduced fat	350	2	1.7	3.0	0.03	0.06	2.5	4.3	0.04	0.08
Soups	3089	17	2.5	4.5	0.04	0.08	3.5	6.5	0.06	0.12
Tortillas and taco shells	2882	16	2.5	5.2	0.04	0.09	3.6	7.4	0.06	0.13
Vegetarian patties/crumbles	92	< 0.5	1.4	2.5	0.03	0.05	2.0	3.5	0.04	0.07
Yogurt, reduced fat	1193	6	1.5	2.9	0.03	0.06	2.2	4.1	0.04	0.08
All categories combined	17010	92	7.3	13.9	0.14	0.32	10.5	19.9	0.21	0.45

Data source: U.S. Department of Agriculture, 1994-96, 1998 Continuing Survey of Food Intakes by Individuals (CSFII).

Notes: Estimates represent 2-Day average intakes per user generated using USDA sampling weights. Breastfeeding children and individuals who provided only one 24-hour dietary recall were excluded from the analysis. Results based on a small sample size may not be statistically reliable.

IV. CHEMISTRY AND ANALYSES

A. Processing and Isolation Procedures for Barley Betafiber

The enzymatic production process for barley betafiber is outlined in Appendix 4. The starting material is cleaned, dehulled whole grain barley, which is milled to flour, followed by a two-stage enzyme treatment with water at 62-67°C. The mixture is then heated to 95-100°C to extract and hydrolyze the desired polysaccharides. The solids are removed by centrifugation; the resultant supernatant is treated with ethanol and precipitated to isolate beta-glucan gum. The barley beta-glucan gum that is recovered is washed with ethanol, dried, milled, and sifted to meet desired specifications (Table 7). The process is controlled to achieve an end product with a minimum purity of 70% beta-glucan.

Table 7. Specifications for Barley Betafiber

Analyte	Specifications
Beta-glucan	≥ 70 ^a
Moisture	< 12%
Ethanol	< 2000 ppm
Lead	< 0.5 ppm
Appearance/Color	White to light tan powder
Total Mesophilic Bacteria	< 10,000 CFU/g
Salmonella sp.	Negative in 100g

^a Dry weight basis

B. Chemical and Physical Properties of Barley Betafiber

Barley betafiber is a concentrated source of barley beta-glucan. Beta-glucans are polysaccharides of unbranched, mixed linkage (1→3), and (1→4)- β-D-glucans. Barley and oat derived beta-glucans contain about 70% (1→4) and 30% (1→3) linkages. Table 8 summarizes the physiochemical properties of barley betafiber.

Table 8. Chemical and Physical Properties of Barley Betafiber

Characteristic	Barley Betafiber
Molecular Weight ^a	150 kDa
Solubility in Water	Soluble
Viscosity	1.0% – 1.3% of guar gum
Chemical Stability	pH 3 – 10 (aqueous solutions)
Thermal Stability	Stable during normal processing and storage conditions
Physical Form	White to light tan powder

^a Weight-average molecular weight

V. FOODS ELIGIBLE TO BEAR THE CLAIM

A. Qualifying Definition of Barley Betafiber

Cargill requests FDA to amend 21 CFR 101.81 to include barley betafiber as a qualifying source of beta-glucan soluble fiber. The qualifying definition for barley betafiber is a product that is produced from cleaned, dehulled whole grain barley, processed by the enzymatic method specified in Appendix 4. It provides at least 70% beta-glucan soluble fiber on a dry weight basis, and has an average molecular weight of 150 kDa \pm 20%. This definition for barley betafiber includes the product that was shown to have cholesterol-lowering efficacy in both humans and animals (see Sections III B1, B2; III C1). Total mixed-linkage beta-glucan levels of barley betafiber may be determined by AOAC 995.16 or an equivalent method. There is no standard method for determining molecular weight (weight-average molecular weight). However, a method for determining molecular weight of barley beta-glucan concentrate was developed and described in the study by Wilson et al. (2004). This method has been used to determine the molecular weight (weight-average molecular weight) of barley betafiber and its prototypes.

FDA approved oatrim, a soluble fraction of alpha-amylase hydrolyzed oat bran or whole oat flour as an eligible oat source of beta-glucan soluble fiber for the CHD health claim on the basis of a single human clinical trial which demonstrated the clinical efficacy of an alpha-amylase oatrim that contained up to 10% beta-glucan (FDA, 2002). Oatrim, processed by an acid/base method and containing beta-glucan levels greater than 10% was not considered an eligible source by the FDA, because there were no human clinical data to support cholesterol-lowering efficacy (FDA, 2002). Thus, FDA provided the following definition of oatrim as an eligible source for the CHD health claim (FDA, 2002):

Oatrim. The soluble fraction of alpha-amylase hydrolyzed oat bran or whole oat flour, also known as oatrim. Oatrim is produced from either oat bran as defined in paragraph (c)(2)(A)(1) of this section, or whole oat flour as defined in paragraph (c)(2)(ii)(A)(3) of this section by solubilization of the starch in the starting material with an alpha-amylase hydrolysis process, and then removal by centrifugation of the insoluble components consisting of a high portion of protein, lipid, insoluble dietary fiber, and the majority of the flavor and color components of the starting material. Oatrim shall have a beta-glucan soluble fiber content of up to 10% (dwb) and not less than that of the starting material (dwb).

Cargill is proposing a comparable definition for barley betafiber, based on the fact that this product has been shown to be efficacious in humans in lowering elevated serum cholesterol:

Barley betafiber. The concentrated soluble fraction of alpha-amylase hydrolyzed whole grain barley, also known as barley betafiber. Barley betafiber is produced from dehulled or hulless whole grain barley as defined in 21 CFR 101.81 (c)(2)(ii)(A)(5) by a two-stage alpha-amylase process, heating and removal of insoluble components by centrifugation, followed by treatment with ethanol and precipitation. Barley betafiber shall have a minimum beta-glucan soluble fiber content of 70% (dwb) and a molecular weight (weight-average molecular weight) of 150 kDa \pm 20%.

B. Qualifying Level of Barley Betafiber

21 CFR 101.81 has established 3g beta-glucan as the minimum effective daily intake to significantly reduce serum cholesterol. In the interim final rule for whole grain barley and certain dry milled barley products, FDA stated that it agreed that the cholesterol lowering efficacy of whole grain oat and dry milled barley sources of beta-glucan soluble fiber appears equivalent (FDA, 2005). FDA also indicated that

the scientific evidence supports a minimum daily effective intake of beta-glucan soluble fiber from dry milled barley products to be the same as that which was previously found for beta-glucan soluble fiber from whole oat sources, i.e. 3g per day (FDA, 2005).

Section III B4 of this petition concurs with the finding that 3g beta-glucan soluble fiber from barley betafiber is equivalent in cholesterol lowering efficacy to 3g beta-glucan from whole grain oats, whole grain barley, and certain dry milled barley products. On the basis of four eating occasions, as specified for other eligible sources of beta-glucan (oat bran, rolled oats, oat flour, specified oatrim, whole grain barley, certain dry milled barley products), we also propose that barley betafiber-containing foods bearing the health claim contain at least 0.75g beta-glucan per reference amount customarily consumed (RACC).

C. Representative Foods that May Bear the Claim

Cargill proposes that all eligible barley betafiber-containing foods that contain a minimum of 0.75g beta-glucan per reference amount customarily consumed should be eligible to bear the health claim. Other eligibility requirements include that the food be low in fat, saturated fat, and cholesterol. Table 9, although not an all-inclusive list, provides examples of food types that may incorporate barley betafiber as an ingredient.

Table 9. Potential Food Uses of Barley Betafiber

Food Category	Serving Size	Beta-Glucan Soluble Fiber from Barley Betafiber^a (per serving)
Bars	40g	0.75g – 3g
Beverages	240 ml	0.75g – 3g
Bread (whole grain and specialty)	50g or 55g	0.75g – 3g
RTE Breakfast cereal	15g, 30g or 55g	0.75g – 3g
Cooked Breakfast cereal	1 cup	0.75g – 3g
Cookies, lite	30g	0.75g – 3g
Crackers, reduced fat	15g or 30g	0.75g – 3g
Instant rice	140g	0.75g – 3g
Macaroni products	140g	0.75g – 3g
Muffins, reduced fat	55g	0.75g – 3g
Salad dressings, lite	15g or 30g	0.75g – 3g
Extruded snacks, reduced fat	30g	0.75g – 3g
Sauces	2 oz. to 4 oz.	0.75g – 3g
Soups	245g	0.75g – 3g
Tortillas and taco shells	30g or 55g	0.75g – 3g
Vegetarian patties/crumbles	55g or 85g	0.75g – 3g
Yogurt, reduced fat	225g	0.75g – 3g

^a 1.1g – 4.3g of barley betafiber (70% purity) provides 0.75g – 3g of beta-glucan soluble fiber.

D. Projected Impact on Food Consumption

Barley betafiber is a food ingredient that is primarily a source of soluble fiber. Typical usage is expected to be approximately 1.1g barley betafiber to provide 0.75g beta-glucan per RACC. This level of intake will contribute only trace amounts of protein, fat and calories. Therefore the inclusion of barley betafiber in foods proposed in Table 9 will not have a significant impact on the nutrient profile of Americans other than to potentially boost soluble fiber intake, and as a consequence, total dietary fiber intake. No significant shifts in food intake patterns are anticipated. We anticipate that consumers of the product types that could

potentially contain barley betafiber will substitute a barley betafiber-containing food for a similar food without barley betafiber.

The majority of food manufacturers will be incorporating barley betafiber at a level that will provide 0.75g beta-glucan per serving. Using a conservative approach and assuming a maximum intake from all proposed food sources, the mean increase in beta-glucan intake would be 7.3g beta-glucan/person/day and 13.9g beta-glucan/person/day for the 90th percentile of consumption (Table 6). Dietary fiber intakes of Americans are currently estimated to be 14g -19g dietary fiber/day, which is well below the recommended levels of 30g - 38g dietary fiber/day for adult men and 21g - 25g dietary fiber/day for adult women (IOM, 2005). Even with the unlikely scenario that the maximum amount of barley beta-glucan from barley betafiber is consumed from all potential sources, the total increase in dietary fiber is still within the range of recommended intakes.

VI. PROPOSED MODEL HEALTH CLAIMS

Consistent with 21 CFR 101.81 (c)(2)(e), Cargill is proposing the use of the following model health claims in food labeling:

- Soluble fiber from barley betafiber, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of (name of food) provides _____ grams beta-glucan soluble fiber of the 3 grams beta-glucan soluble fiber necessary per day to have this effect.
- Diets low in saturated fat and cholesterol that include 3 grams beta-glucan soluble fiber from barley betafiber may reduce the risk of heart disease. One serving of (name of food) provides _____ grams of this soluble fiber.

VII. ENVIRONMENTAL IMPACT

Cargill claims a categorical exclusion under 21 CFR 25.32(p) for an environmental assessment and environmental impact statement. Under the environmental impact consideration regulations, actions involving the issuance of a health claim petition do not individually or cumulatively have a significant effect on the human environment and therefore do not require the preparation of an environmental assessment and environmental impact statement.

VIII. CONCLUSION

FDA has encouraged manufacturers to petition for a health claim if there is evidence to demonstrate that a particular soluble fiber-containing product is effective in lowering serum lipids. The agency has expressed concern that certain types of processing may decrease the cholesterol-lowering ability of a fiber source, but that human clinical trials can be used to resolve this issue. The human and animal studies of barley betafiber provide clear evidence of the cholesterol-lowering efficacy of the beta-glucan soluble fiber contained in barley betafiber. An independent third party audit has ensured the accuracy of the clinical trial data (Appendix 3).

Results of the clinical trial utilizing barley betafiber have been presented at the First International Congress on Pre-Diabetic and Metabolic Syndrome (Berlin, Germany, April 13-16, 2005), the American College of Nutrition (Charleston, SC, Sept. 22-25, 2005), the American Heart Association Scientific Sessions (Dallas, TX, Nov.13-16, 2005), and the 3rd World Congress on the Insulin Resistance Syndrome (San Francisco, CA, Nov.17-19, 2005). Abstracts and/or posters submitted to each of these meetings were peer-reviewed. The GRAS Expert Panel Report (Appendix 1) and the GRAS notification (submitted subsequent to this health claim petition) document the safety of barley betafiber.

The totality of the scientific evidence detailed in this petition demonstrates there is significant scientific agreement to authorize a health claim for barley betafiber. Approval of barley betafiber as an eligible source of beta-glucan soluble fiber will provide the American consumer with a variety of food choices from which to consume beta-glucan soluble fiber. Increased consumption of beta-glucan soluble fiber is consistent with the NCEP ATP III guidelines as a means of enhancing serum cholesterol reduction. CHD is a major public health concern in the US and early management of risk factors for CHD is a national public health goal. Consumption of

barley betafiber-containing foods, in conjunction with a heart healthy, low fat diet, can help to reduce the risk of CHD among US consumers.

We request FDA to issue an interim final rule effective upon publication of the barley betafiber health claim as we believe this health claim meets the statutory criteria cited in Section 403(r)(7) of the Federal Food, Drug and Cosmetic Act. Making the rule effective upon publication would:

(i) *enable consumers to develop and maintain healthy dietary practices.*

Consumption of barley betafiber containing foods, in conjunction with a diet low in saturated fat and cholesterol (as the suggested model claims indicate) has multiple health-promoting benefits for consumers. Soluble fiber will be increased with the consumption of barley betafiber containing foods. The NCEP ATP III recommends that a cholesterol-lowering diet be enriched with foods that provide at least 5g -10g viscous (soluble) fiber daily. Intakes of 10g - 25g viscous (soluble) fiber per day can be beneficial (NCEP, 2002). A nationally representative sample of US adults from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study had a median intake of 2.4g soluble fiber per 1735 kcals (Bazzano et al, 2003). This level of soluble fiber intake is well below the NCEP ATP III recommendations. Therefore, consumption of barley betafiber containing foods will help boost soluble fiber intake.

Consumption of barley betafiber also contributes to total dietary fiber intake. The IOM has recommended intakes of 30g - 38g total dietary fiber/day for adult men and 21g - 25g total dietary fiber/day for adult women (IOM, 2005). Recent estimates indicate Americans consume only about 14g - 19g dietary fiber per day (USDA, 1997). The 2005 Dietary Guidelines for Americans also report that most Americans need to increase their intake of dietary fiber (USDA/DHHS, 2005). The potential increase in dietary fiber from foods containing barley betafiber would help to increase dietary fiber intakes of the US population, consistent with the

recommendations of the 2005 Dietary Guidelines for Americans (USDA/DHHS, 2005).

(ii) enable consumers to be informed promptly and effectively of important new knowledge regarding nutritional and health benefits of food.

Authorization of the barley betafiber health claim as an interim final rule will promptly inform consumers that barley betafiber is a scientifically substantiated source of barley beta-glucan soluble fiber for reducing CHD risk. This is consistent with the recent interim final rule that specified whole grain barley and certain dry milled barley products as eligible sources of barley beta-glucan soluble fiber for the health claim between barley beta-glucan soluble fiber and the reduced risk of CHD (FDA, 2005).

Whole grain barley and dry milled barley products approved for the CHD health claim do not have the range of application and flexibility of barley betafiber in food applications. The nature of barley betafiber allows it to be readily incorporated into a broad variety of foods, including beverages (especially juice and juice drinks), breakfast cereals, breads, cookies, crackers, muffins, pasta products, tortillas, soups, vegetarian patties/crumbles, extruded snacks, cereal and granola bars, meal replacement and nutrition bars, sauces, and yogurt. The widespread availability of barley betafiber enriched foods will assist in increasing barley beta-glucan soluble fiber consumption among a wider segment of the US population and, more importantly, have broader implications for lowering both TC and LDL-C, and reducing CHD risk among US consumers.

(iii) ensure that scientifically sound nutritional and health information is provided to consumers as soon as possible.

Authorization of an interim final rule for barley betafiber and the reduced risk of CHD will provide consumers prompt information that is scientifically sound. The promotion of scientifically valid sources of soluble fiber in a timely manner will further assist Americans in identifying eligible sources of soluble fiber for lowering CHD risk.

CHD remains the number one public health concern for the US population and the availability of a larger spectrum of foods identified with the ability to reduce CHD risk will only serve to enhance public health.

IX. PROPOSED REGULATION AMENDMENT

Cargill requests the following change to 21 CFR 101.81 to include the use of barley betafiber as a source of beta-glucan soluble fiber eligible to bear the health claim.

We request that 21 CFR 101.81 (c)(2)(i)(G)(1) be revised, as follows:

- (1) 3g or more per day of beta-glucan soluble fiber from whole oats, barley or barley betafiber, or a combination of whole oats, barley or barley betafiber.

We request that 21 CFR 101.81 (c)(2)(ii)(A) be revised, as follows:

- (A) Beta-glucan soluble fiber from whole oat, barley, and barley betafiber sources.

We request that 21 CFR 101.81 (c)(2)(ii)(A) be revised by adding a new subparagraph (6) as follows:

Barley betafiber. The concentrated soluble fraction of alpha-amylase hydrolyzed whole grain barley, also known as barley betafiber. Barley betafiber is produced from dehulled or hullless whole grain barley as defined by 21 CFR 101.81 (c)(2)(ii)(A)(5) by a two-stage alpha-amylase process, heating and removal of insoluble components by centrifugation, followed by treatment with ethanol and precipitation. Barley betafiber shall have a minimum beta-glucan soluble fiber content of 70% (dwb) and a molecular weight (weight-average molecular weight) of 150 kDa \pm 20%.

We request that 21 CFR 101.81 (c)(2)(iii)(A)(1) be revised as follows:

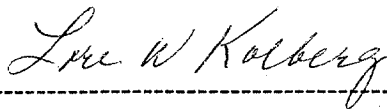
(A)(1) One or more of the whole oat, barley or barley betafiber foods from paragraphs (c)(2)(ii)(A)(1),(2),(3),(5), and (6) of this section and whole oat, barley and barley betafiber foods shall contain at least 0.75 gram (g) soluble fiber per reference amount customarily consumed of the food product;

X. CERTIFICATION

Attached herewith are copies of the scientific studies and other information referenced in, and constituting the basis for, this petition. To the best of the petitioner's knowledge, the clinical trials included in this petition were conducted in compliance with the requirements for informed consent set forth in 21 CFR Part 50. To the best of the petitioner's knowledge, all clinical investigations included in this petition were either conducted in compliance with the requirements of institutional review set forth at 21 CFR Part 56 or were not subject to such requirements in accordance of 21 CFR 56.104 or 56.105. To the best of the petitioner's knowledge, all non-clinical studies included in this petition were conducted in compliance with FDA's good laboratory practices regulations (21 CFR Part 58).

Lore Kolberg (Manager, Regulatory & Scientific Affairs, Cargill, Incorporated) and Rebecca Mathews (Consultant, R Mathews & Associates) on behalf of the petitioner certify that, to the best of our knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information, known by us to be pertinent to evaluation of the proposed health claim.

Respectfully submitted by,
Cargill, Incorporated

A handwritten signature in cursive script, reading "Lore W. Kolberg", is written over a horizontal dashed line.

Lore Kolberg
Manager, Regulatory and Scientific Affairs