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Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

**RE: RIN 0910-AF94; DOCKET NO. 2006P-0069**
**HEALTH CLAIM: SOLUBLE FIBER FROM CERTAIN FOODS AND RISK OF CORONARY HEART DISEASE. PROPOSED AMENDMENT TO EXEMPT CERTAIN FOODS FROM THE NUTRIENT CONTENT REQUIREMENT OF "LOW FAT"**

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## I. OVERVIEW AND SUMMARY OF NBFC POSITIONS

The National Barley Foods Council (NBFC) appreciates this opportunity to provide comments regarding the Food and Drug Administration's (FDA) February 6, 2007 proposal to amend the regulation authorizing a health claim on the relationship between soluble fiber from certain foods and the risk of coronary heart disease. The amendment proposes to exempt certain foods from the nutrient content requirement of "low fat." The exemption would apply if the food exceeds this requirement due to fat content derived from whole oat sources. The amendment would expand the use of this health claim to some whole oat products that are currently ineligible for this health claim.

FDA has requested comments on the proposed amendment as well as comments on whether or not whole oat food products that contain sources of fat other than from whole oat sources should be exempt from the "low fat" requirement and if so, how much and what types of fat contributed by these food sources would be acceptable.

The NBFC's position is summarized below:

A. NBFC agrees with the proposed rule to exempt certain foods from the nutrient requirement of "low fat" if the food exceeds this requirement due to the fat derived from whole oat sources.

B. NBFC proposes that FDA to expand this rule to include barley products that are currently ineligible for the soluble fiber-coronary heart disease (CHD) health claim due to the higher fat content of specific barley sources.

C. NBFC proposes that FDA to expand the rule to include all authorized soluble fiber-containing products that are ineligible for the CHD health claim because they are not "low fat" due to added fat sources. NBFC suggests that "moderate fat" foods should be eligible for the claim, where "moderate fat" is defined as an upper limit for total fat of 6.5 grams, 1g saturated fat, 0.5g *trans* fat, and 20mg cholesterol per RACC for all products covered by the rule.

Outlined in the following pages is the rationale and support for each of the NBFC positions.

## II. RATIONALE FOR NBFC POSITIONS

### A. Whole Oat Products Ineligible for the Oat Beta-Glucan CHD Health Claim Due to the Higher Fat Content of Specific Oat Sources Should be Exempt from the "Low Fat" Requirement

NBFC agrees with the FDA position to exempt foods that exceed the "low fat" criterion due to the fat contained in some whole oat sources for the reasons that were cited in the proposal. Most oat products authorized to make the heart health claim (i.e. oat bran, rolled oats, whole oat flour, and oatrim) meet the "low fat" requirement unless fat from other sources is added. However, some products, like flavored, reduced-sugar instant oatmeal, contain marginally higher amounts of fat from whole oats, and therefore do not meet the "low fat" requirement per recommended amount customarily consumed (RACC). The type of fat contained in oats is predominantly polyunsaturated and monounsaturated fatty acids. This is consistent with the recommendations of the 2005 Dietary Guidelines for Americans in that most of the fats in the diet should be obtained from polyunsaturated and monounsaturated fatty acid sources. Furthermore, the consumption of foods containing beta-glucan soluble fiber, such as oat products, is helpful in reducing the risk of CHD.

### B. Barley Products Ineligible for the Barley Beta-Glucan CHD Health Claim Due to the Higher Fat Content of Specific Barley Sources Should be Exempt from the "Low Fat" Requirement

NBFC proposes to FDA that expand this rule to include barley products that are currently ineligible for the coronary heart disease (CHD) health claim due to the higher fat content of specific barley sources. Similar to authorized oat sources, most of the authorized barley products (whole grain and milled barley products, such as dehulled or hull-less barley, pearl, flakes, grits, meal, flour, β-glucan enriched meal or flour fractions, and bran) meet the "low fat" requirement, but a few authorized barley sources do not meet this requirement (Appendix-Table 1). The fat contained in the higher fat barley sources is predominantly polyunsaturated fat, consistent with recommendations of the 2005 Dietary Guidelines for Americans (Appendix-Table 2). Typically, barley products contain significantly lower amounts of total fat and saturated fat than oat products; comparison of the fatty acid profile indicates that barley contains primarily polyunsaturated fatty acids, whereas oats have a more equal distribution of polyunsaturated and monounsaturated fatty acids (Appendix-Table 3). Like oat products, barley products are a source of beta-glucan soluble fiber known to be useful in reducing risk of CHD.

### C. All Authorized Soluble Fiber-Containing Foods Should Be Eligible for the CHD Health Claim If They Have A "Moderate Fat" Content

NBFC proposes that FDA expand the current rule so that soluble fiber-containing foods that have a moderate content of total fat can be eligible to make the CHD health claim. Although several of the current health claims for reduced CHD risk (reviewed in Section E) do not require that the "low fat" criterion be met, this criterion is currently required for the health claim for soluble fiber from certain foods and reduced risk of CHD. In addition to the "low fat" requirement, the soluble fiber containing food must also be "low in saturated fat" and "low cholesterol" in order to bear the claim.

FDA expressed concern in the proposed rule that relaxing the total fat requirement for fat from all fat sources may weaken the CHD claim. Under this scenario FDA points out that products carrying the CHD claim could contain up to 13g of fat per RACC or the disqualifying level of total fat to make a health claim. The agency indicates that consumers using these products could easily increase their fat intake to levels above those recommended by the 2005 Dietary Guidelines for Americans. Furthermore, FDA states that increased fat intake may also increase *trans* fat consumption because the current regulations have disqualifying levels only for saturated fat, cholesterol, and total fat. To prevent this situation from occurring, NBFC proposes the establishment of an upper limit for total fat of 6.5g (moderate fat), 1g saturated fat, 0.5g *trans* fat, 20mg cholesterol per RACC be applied for all products covered by the rule. These criteria are already being utilized by whole grain foods with moderate fat content using the health claim[1] and the diets low in saturated fat, *trans* fat, and cholesterol health claim[2], both based on authoritative statements (FDAMA) for the reduced risk of CHD. Use of these criteria would keep total fat intake at moderate levels, but keep saturated fat, *trans* fat, and cholesterol levels low, consistent with the dietary recommendations of the 2005 Dietary Guidelines for Americans.

Allowing foods of moderate fat content to be eligible for the CHD health claim while enforcing criteria related to moderate fat, low saturated fat and cholesterol content, and keeping *trans* fat as low as possible would encourage more product development in this area and provide a greater availability of soluble fiber foods geared to CHD risk reduction.

In the following section, support from various sources for permitting soluble fiber foods with moderate-fat content is provided.

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[1] Health Claim Notification for Whole Grain Foods with Moderate Fat Content. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. Dec. 9, 2003.

[2] Health Claim Notification for Saturated Fat, Cholesterol, and *Trans* Fat, and Reduced Risk of Heart Disease. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. Nov. 15, 2006.

## III. SUPPORT FOR SOLUBLE FIBER-CONTAINING PRODUCTS WITH A MODERATE FAT CONTENT

### A. Dietary Recommendations Support a Moderate Fat Intake

#### 1. National Cholesterol Education Program (2002)

The National Cholesterol Education Program (NCEP) was launched by the National Heart, Lung, and Blood Institute (NHLBI) to provide leadership in reducing illness and death from CHD in the United States by reducing the percentage of Americans with high blood cholesterol. Since 1988 three expert panels have been convened to develop consensus guidelines for the management of blood cholesterol. The *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III* [3] is the most recent report to be developed after a systematic review of the scientific literature, followed by evidence statements summarizing current knowledge and recommendations based on the evidence statements.

ATP III findings note that of the fatty acids that make up the total fat in the diet, only saturated fatty acids and *trans* fatty acids raise LDL-cholesterol levels. Serum LDL-cholesterol levels are independent of intakes of total fat, *per se*. NCEP ATP II recommended limiting total fat in Step I and Step II diets to $\leq$ 30 percent of calories primarily as a means of lowering saturated fatty acid intakes. The dietary focus is to reduce fatty acids that raise LDL-cholesterol.

> ***Evidence Statement:*** *Unsaturated fatty acids do not raise LDL-cholesterol concentrations when substituted for carbohydrates in the diet.*
>
> ***Recommendation:*** *It is not necessary to restrict total fat for the express purpose of reducing LDL-cholesterol levels, provided saturated fatty acids are reduced to goal levels.*
> (NCEP-ATP III Report (2002) at V-11)
>
> ***Evidence Statement:*** *The percentage of total fat in the diet, independent of caloric intake, has not been documented to be related to body weight or risk for cancer in the general population. Short-term studies suggest that very high intakes (> 35 percent of calories from fat) modify metabolism in ways that promote obesity. On the other hand, very high-carbohydrate intakes (> 60 percent calories) aggravate some of the lipid and non-lipid risk factors common in metabolic syndrome.*
>
> ***Recommendation:*** *Dietary fat recommendations should emphasize reduction in saturated fatty acids. Further, for persons with lipid disorders*

[3] Report published in 2002 can be accessed at http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3 rpt.htm

*or the metabolic syndrome, extremes of total fat intake—either high or low—should be avoided. In such persons, total fat intakes should range from 25-35 percent of calories. For some persons with the metabolic syndrome, a total fat intake of 30-35 percent may reduce lipid and nonlipid risk factors.*
(NCEP-ATP III Report (2002) at V-12)

The ATP III recommends a diet low in saturated fat (< 7% of total calories), low in *trans* fat, low in cholesterol (< 200 mg/day) with a total fat intake of 25 to 35% of calories. The higher total fat range is a change from the low fat diet (< 30 percent of calories) suggested by ATP II. Higher fat intakes, particularly those including unsaturated fat can help to reduce triglycerides and raise HDL-cholesterol in persons with metabolic syndrome. Increased consumption of viscous (soluble) fiber (10-25 g/day) such as is also recommended by ATP III. Thus soluble fiber-containing foods that are low to moderate in fat content and eligible for the soluble fiber health claim are consistent with the therapeutic lifestyle change diet recommended by the NCEP ATP III to reduce CHD.

### 2. Institute of Medicine (2002/2005)

The Institute of Medicine (IOM), under the National Academy of Sciences convenes expert panels of scientists to develop dietary reference intake values for healthy U.S. and Canadian populations. Acceptable macronutrient intake ranges are outlined in the IOM report, *Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Micronutrients)* following a detailed and comprehensive review of the scientific literature. In summarizing acceptable total fat distribution ranges for adults, IOM[4] reports:

*When fat intakes are low and carbohydrate intakes are high, intervention studies, with the support of epidemiological studies, demonstrate a reduction in plasma HDLcholesterol concentration, an increase in the plasma total cholesterol:HDL cholesterol ratio, and an increase in plasma triacylglycerol concentration, which are consistent with an increased risk of CHD. Conversely, many interventional studies show that when fat intakes are high, many individuals consume additional energy, and therefore gain additional weight. Weight gain on high-fat diets can be detrimental to individuals already susceptible to obesity and will worsen the metabolic consequences of obesity, particularly the risk of CHD. Moreover, high-fat diets are usually accompanied by increased intakes of saturated fatty acids, which can raise plasma LDLcholesterol concentrations and further heighten CHD. Based on apparent risk for increased energy intake, and*

[4] Dietary Fats: Total Fat and Fatty Acids, Chap. 8. and Macronutrients and Healthful Diets, Chap. 11. In Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Macronutrient DRIs). The National Academy of Sciences. *[draft report, 2002; final report 2005]*

*therefore obesity with the consumption of high-fat diets, an AMDR for fat and carbohydrate is estimated to be 20 to 35 and 45 to 65 percent of energy, respectively, for all adults. By consuming fat and carbohydrate within these ranges, the risk for obesity, as well as risk for CHD and diabetes, can be kept to a minimum.*
(IOM (2002/2205) Report at 11-27)

IOM has determined that diets low in saturated fat, *trans* fat, and cholesterol with total fat intakes up to 35% of calories are acceptable for CHD risk reduction. Soluble fiber-containing foods with a moderate fat content are consistent with these diets.

### 3. 2005 Dietary Guidelines for Americans

The Dietary Guidelines for Americans provide authoritative advice on dietary habits that promote health and reduce the risk of major chronic diseases for the U.S. population. The Guidelines are jointly issued and updated every five years by the Departments of Agriculture and Health and Human Services. The *2005 Dietary Guidelines for Americans* was issued following the recommendations in the *2005 Dietary Guidelines Advisory Committee Report (2005)*[5]. In regard to fat intake, the Committee recommended low intakes of saturated fats (< 10 percent of calories), *trans* fats (as low as possible), cholesterol (< 300 mg/day) and total fat intake of 20 to 35 percent of calories for adults, 25 to 35 percent for children 4 to 18 years, and 30 to 35 percent of calories for children 2 to 3 years.

> ***Know your fats**. Look for foods low in saturated fats, trans fats, and cholesterol to help reduce the risk of heart disease (5% DV or less is low, 20% DV or more is high). Most of the fats you eat should be polyunsaturated and monounsaturated fats. Keep total fat intake between 20% to 35% of calories.* (Consumer Brochure at http://www.health.gov/dietaryguidelines/dga2005/document/html/brochure.htm)

The ranges of total fat intake are largely based on the IOM's AMDR. Although the 2000 Dietary Guidelines for Americans recommended a moderate fat intake, the level of intake suggested was less than 30% of calories, similar to the guideline in the 1995 Dietary Guidelines for Americans. In a departure from previous guidelines, the 2005 Dietary Guidelines encompasses a broader range of fat intakes for the reduction of chronic disease:

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[5] 2005 Dietary Guidelines Advisory Committee Report; Nutrition and Your Health: Dietary Guidelines for Americans. Departments of Agriculture and Health and Human Services. http://www.health.gov/dietaryguidelines/dga2005/report/

*The lower limit for fat intake is set at 20 percent of calories because serum triacylglyerol concentrations increase and serum HDL-cholesterol concentrations decrease when fat intake is low and carbohydrate intake is high. This in turn, may increase the risk of CHD. Furthermore it is difficult to achieve recommended intakes of several nutrients when fat intake is below 20 percent of calories.*

*The upper limit on total fat intake is related to the saturated fat content of diets that provide more than 35 percent of calories from fat. Practical efforts to create heart-healthy menus that provide more than 35 percent of energy from total fat result in an unacceptably high content of saturated fatty acids. Because saturated fatty acids are present in all fats, higher intakes of total fat are associated with increased saturated fatty acid intakes. Increasing the saturated fatty acid content of the diet increases the LDL-cholesterol concentration, which, in turn increases the risk of CHD.*
(2005 Dietary Guidelines Advisory Committee Report, Section 4: Fats, pgs. 4-5)

Thus, a soluble fiber-containing food with moderate fat content is consistent with the diet recommended by the 2005 Dietary Guidelines for Americans.

### 4. American Heart Association (2006)

Diet and lifestyle recommendations are a critical component of the American Heart Association's (AHA's) strategy to prevent cardiovascular disease in the U.S. population. The AHA Nutrition Committee, an expert panel of scientists in the field of nutrition and cardiovascular disease has recently issued dietary guidelines: *Diet and Lifestyle Recommendations Revision 2006, A Scientific Statement from the American Heart Association Nutrition Committee*[6].

Recommendations appropriate for the general public regarding fat intake do not mention total fat, but emphasize reductions in saturated fat, *trans* fat, and cholesterol:

*Limit your intake of saturated fat to < 7% of energy, trans fat to < 1% of energy, and cholesterol to < 300 mg per day by*
*___ choosing lean meats and vegetable alternatives;*
*___ selecting fat-free (skim), 1% fat, and low-fat dairy products; and*
*___ minimizing intake of partially hydrogenated fats*
(AHA 2006; Circulation 114:83)

[6] American Heart Association Nutrition Committee, 2006. AHA Scientific Statement. Diet and Lifestyle Recommendations Revision 2006. Circulation 114:82-96.

The AHA Nutrition Committee does not discuss total fat intake in the *Diet and Lifestyle Recommendations Revision 2006* other than to state the following:

> *The AHA supports the recommendations of the Institute of Medicine and the National Cholesterol Education Program for total fat. A range of 25% to 35% for total fat is an appropriate level of intake in a healthy dietary pattern.*
> (AHA 2006; Circulation 114:88)

Whole grain, high-fiber food consumption is encouraged by the AHA Nutrition Committee as part of the diet to reduce cardiovascular risk. Therefore soluble-fiber containing foods that are moderate in fat content, but low in saturated fat, *trans* fat, and cholesterol are consistent with AHA guidelines.

## B. Low Fat Diets Do Not Consistently Lower CHD Risk; Moderate Fat Diets Also Lower CHD Risk

In the past, following a low-fat diet was believed to consistently reduce CHD risk, however, there is increasing evidence that this is no longer the case. Results of the Women's Health Initiative Dietary Modification Trial, one of the largest long-term randomized clinical trials ever conducted[7] are a demonstration of this. Over a period of 8.1 years of follow-up, a sample of 48,835 post-menopausal women of diverse backgrounds and ethnicities, did not significantly reduce the risk of CHD, stroke, or cardiovascular disease when a low-fat dietary pattern was consumed compared to the average American diet. There were trends toward greater reductions in CHD risk among those individuals with lower intakes of saturated fat or *trans* fat, or higher intakes of vegetables/fruits. Although the intervention was designed to lower total fat intake to 20% of calories, and saturated fat to 7% of calories by virtue of lowering total fat content, the results indicate that this goal was not achieved.

Fat Intakes at Baseline, Year One and Year Six of follow-up for Intervention and Comparison Groups:

| Daily Fat Intakes, % of Energy | Baseline, Mean (SD) | | Year 1, Mean (SD) | | Year 6, Mean (SD) | |
|---|---|---|---|---|---|---|
| | Intervention | Comparison | Intervention | Comparison | Intervention | Comparison |
| Total fat | 37.8 (5.1) | 37.8 (5.0) | 24.3 (7.5) | 35.1 (6.9) | 28.8 (8.4) | 37.0 (7.3) |
| Saturated Fat | 12.7 (2.5) | 12.7 (2.5) | 8.1 (2.8) | 11.8 (2.9) | 9.5 (3.2) | 12.4 (3.1) |
| Monounsaturated Fat | 14.4 (2.3) | 14.4 (2.3) | 8.9 (3.1) | 13.3 (2.9) | 10.8 (3.5) | 14.2 (3.1) |
| Polyunsaturated Fat | 7.8 (2.0) | 7.8 (2.0) | 5.2 (1.8) | 7.2 (2.1) | 6.1 (2.1) | 7.5 (2.1) |
| *Trans* Fat | 2.7 (1.1) | 2.8 (1.1) | 1.6 (0.8) | 2.5 (1.1) | 1.8 (0.9) | 2.4 (1.1) |

[7] Howard BV, Van Horn L, Hsia J et al, 2006. Low-fat dietary pattern and risk of cardiovascular disease. The Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 295:655-666.

The researchers suggest that the lack of effect on cardiovascular disease in this study was due to the small decrease in saturated fat and reduced intakes of monounsaturated and polyunsaturated fat that yielded only minimal changes in LDL-cholesterol levels. Furthermore, the researchers indicate that because the current saturated fat intake in the United States is in the range of 11% of calories compared to 18% to 20% of calories in the 1970s, very targeted and aggressive dietary interventions are necessary to achieve substantial LDL-cholesterol lowering.

Since the late 1980s, dietary recommendations have emphasized lowering saturated fat (i.e. $\leq$ 10% of calories) and total fat to 30% or less of calories, typically resulting in the dietary substitution of fat with carbohydrate. When carbohydrate is substituted for saturated fatty acids, LDL-cholesterol levels fall, and reduced LDL-cholesterol levels are associated with reduced CHD risk (NCEP-ATP III, 2002). However, numerous clinical trials have demonstrated that changes in fat and carbohydrate intake not only impact LDL-cholesterol, but also affect other independent lipid risk factors such as HDL-cholesterol and triglyceride levels. Very low fat intakes coupled with very high carbohydrate intakes are associated with a reduction in HDL-cholesterol and a rise in triglycerides (NCEP-ATP III, 2002). The NCEP-ATP III Report states that these responses are sometimes attenuated when carbohydrate is consumed with viscous fiber, but "*it has not been demonstrated convincingly that viscous fiber can fully negate the triglyceride raising or HDL lowering actions of very high intakes of carbohydrates*." (NCEP-ATP III at V-13).

The IOM (2002/2005) made similar observations regarding lipid profiles, noting that low fat, high carbohydrate diets, compared to higher fat intakes, can induce a lipoprotein pattern called the "atherogenic lipoprotein phenotype," known to be associated with increased CHD risk. This phenotype is characterized by increased triglyceride and decreased HDL-cholesterol levels and increased small LDL particles. In physically active and lean populations, the atherogenic lipoprotein phenotype is minimally expressed, but in overweight, sedentary populations as seen in the U.S., very low-fat, high-carbohydrate diets promote the development of this phenotype. The IOM (2002/2005) points out that other abnormalities could also occur with low-fat, high-carbohydrate intakes, including chronically elevated postprandial plasma glucose and insulin concentrations. These types of changes could also be potentially related to the development of type 2 diabetes and CHD.

Moderate fat diets, particularly those diets that have replaced saturated fat with monounsaturated and polyunsaturated fats are cardioprotective and reduce CHD risk. The NCEP-ATP III Report (2002) provides the following evidence statements and recommendations regarding the substitution of cis-monounsaturated fat for saturated fat:

***Evidence Statements:*** *Monounsaturated fatty acids lower LDL cholesterol relative to saturated fatty acids. Monounsaturated fatty acids do not lower HDL cholesterol nor raise triglycerides.*

***Recommendations:*** *Monounsaturated fatty acids are one form of unsaturated fatty acid that can replace saturated fatty acids. Intake of monounsaturated fatty acids can range up to 20 percent of total calories. Most monounsaturated fatty acids should be derived from vegetable sources, including plant oils and nuts.*
(NCEP-ATP III (2002) at V-10)

Replacement of carbohydrate with monounsaturated fat (which implicitly increases total fat intake), reduces LDL cholesterol and increases HDL cholesterol[8]. Therefore, according to an American Heart Association Advisory, substitution of monounsaturated fat instead of carbohydrate for saturated fat may favorably impact cardiovascular risk[9].

The IOM (2002/2005) noted that eighteen well-controlled clinical studies compared the effects of substituting monounsaturated fatty acids versus carbohydrates for saturated fat. In these studies, diets high in monounsaturated fatty acids provided 17–33% of energy from monounsaturated fat and contained 33-50% of energy from total fat compared to low-fat, high-carbohydrate diets that contained 18-30% of energy from total fat. Saturated fatty acids contributed 4-12% of energy and cholesterol varied from 100-410 mg/day in both types of diets. Compared to baseline levels, total cholesterol levels changed from -17 to +3% on the low-fat, high-carbohydrate diets, whereas the change ranged from -20 to -3% on the monounsaturated fatty acid diets. LDL-cholesterol reductions were similar among the two diets. Change in triglyceride concentrations ranged from -23 to +37% on the low-fat, high-carbohydrate diets compared to a change of -43 to +12% for diets high in monounsaturated fatty acids. Change in HDL-cholesterol levels ranged from -25 to +2% for those on the low-fat, high-carbohydrate diets compared to a change of -9 to +6% for those on the high monounsaturated fatty acid diets. Overall, these data indicate that in weight-stable individuals, low saturated fatty acid, high monounsaturated fatty acid diets produce a more favorable lipid profile than low fat, high carbohydrate diets.

When substituted for saturated fatty acids, polyunsaturated fatty acids, consisting mainly of n-6 linoleic acid, reduce LDL-cholesterol (NCEP-ATP III, 2002). At high intakes of linoleic acid, small reductions in HDL-cholesterol and triglycerides may also be observed (NCEP-ATP III, 2002). The NCEP-ATP III Report (2002)

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[8] Mozaffarian D, 2005. Effects of dietary fats versus carbohydrates on coronary heart disease: A review of the evidence. Curr Atherosclerosis Reports 7:435-445.

[9] Kris-Etherton PM, 1999. Monounsaturated fatty acids and risk of cardiovascular disease. AHA Science Advisory. Circulation. 100:1253-1258.

provides the following evidence statements and recommendations regarding the substitution of polyunsaturated fat for saturated fat:

> **Evidence Statements**: Linoleic acid, a polyunsaturated fatty acid, reduces LDL- cholesterol levels when substituted for saturated fatty acids in the diet. Polyunsaturated fatty acids can also cause small reductions in HDL cholesterol when compared with monounsaturated fatty acids. Controlled clinical trials indicate that substitution of polyunsaturated fatty acids for saturated fatty acids reduces risk for CHD.
>
> **Recommendations**: Polyunsaturated fatty acids are one form of unsaturated fatty acids that can replace saturated fat. Most polyunsaturated fatty acids should be derived from liquid vegetable oils, semi-liquid margarines, and other margarines low in *trans* fatty acids. Intakes of polyunsaturated fat can range up to 10 percent of total calories. (NCEP-ATP III (2002) at V-11)

### C. Fat Intake Must Be Individualized to Positively Impact CHD Risk

It is becoming increasingly clear that dietary fat recommendations must be individualized based on each unique individual's CHD risk profile. A lower fat diet may be appropriate to lower CHD risk for some individuals, whereas a moderate fat diet may be preferable for others. The traditional low fat-CHD paradigm was initially emphasized as a means of lowering total and LDL-cholesterol, but research continues to demonstrate that HDL-cholesterol, triglycerides, and other lipid and nonlipid factors are also important contributors to cardiovascular health.

The NCEP-ATP III Report (2002) identifies low HDL-cholesterol (< 40 mg/dL), elevated triglycerides (< 150 mg/dL), and the metabolic syndrome as factors that also increase the risk of cardiovascular disease. Recent statistics suggest that 44.1 million adult Americans or 26.4% of the U.S. population have low HDL cholesterol levels[10]. Epidemiological data indicate that a 1% decrease in HDL-cholesterol is associated with a 2-3% increase in CHD risk (NCEP-ATP III, 2002). Variability in HDL-cholesterol levels in the general population are due to genetic factors (about 50%), but acquired factors such as elevated serum triglycerides, overweight and obesity, physical inactivity, cigarette smoking, very high carbohydrate diets (> 60 percent of energy; i.e. very low-fat diets), type 2 diabetes, or drugs also contribute (NCEP-ATP III, 2002). A low HDL-cholesterol level is often correlated with the presence of other atherogenic factors, including elevated serum triglycerides, remnant lipoproteins, and small, dense LDL particles (NCEP-ATP III, 2002). Low HDL cholesterol can also be a marker for insulin resistance and metabolic syndrome (NCEP-ATP III, 2002).

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[10] American Heart Association (AHA), 2007. Heart Disease and Stroke Statistics. 2007 Update-At-A-Glance. http://www.americanheart.org/downloadable/heart/1166712318459HS_StatsInsideText.pdf

Like low HDL-cholesterol levels, elevated triglycerides are associated with increased risk for CHD and are frequently associated with other lipid and nonlipid risk factors (NCEP-ATP III, 2002). Borderline high triglyceride levels (150-199 mg/dL) are primarily determined by acquired factors such as overweight, obesity, physical inactivity, excess alcohol intake, and in some instances, high carbohydrate diets (NCEP-ATP III, 2002). Genetics play a more prominent role in persons with high and very high levels of serum triglycerides. Therapeutic lifestyle changes are recommended as first line therapy for elevated triglycerides, including the avoidance of high carbohydrate or very low-fat diets (NCEP-ATP III, 2002). Elevated triglycerides, small LDL particles, and reduced HDL-cholesterol is a common form of atherogenic dyslipidemia associated with the metabolic syndrome (NCEP-ATP III, 2002). In addition to atherogenic dyslipidemia, the metabolic syndrome is characterized by abdominal obesity, hypertension, insulin resistance with or without glucose intolerance, and prothrombotic and proinflammatory states (NCEP-ATP III, 2002). An estimated 47 million Americans have metabolic syndrome[11]. The age-adjusted prevalence of metabolic syndrome for U.S. adults is about 23.7%[12].

The NCEP-ATP III Panel (2002) has indicated that vigorous lifestyle intervention is required in the treatment of symptoms of the metabolic syndrome. Weight loss, increased exercise, and dietary changes are recommended as first line approaches. There is no single diet that is recommended for persons with metabolic syndrome and physicians are encouraged to provide dietary advice based on each patient specific metabolic aberrations.[13,14] There is increasing support for moderate-fat diets rich in monounsaturated fatty acids in the treatment of metabolic syndrome because monounsaturated fats do not negatively impact HDL cholesterol and triglyceride levels, and may even improve blood glucose levels and insulin sensitivity.[15,16]

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[11] Ford ES, Giles WH, Dietz WH, 2002. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 287:356-9.

[12] American Heart Association (AHA), 2007. Heart Disease and Stroke Statistics. 2007 Update-At-A-Glance. http://www.americanheart.org/downloadable/heart/1166712318459HS_StatsInsideText.pdf

[13] Szapary PO, Hark LA, Burke FM, 2002. The metabolic syndrome: a new focus for lifestyle modification. Patient Care 36:75-88.

[14] Deen D, 2004. Metabolic syndrome: Time for action. Am Fam Physician 69:2875-82, 2887-8.

[15] Riccardi G, Rivellese AA, 2000. Dietary treatment of the metabolic syndrome—the optimal diet. Br. J Nutr. 83(Supp 1): S143-S148.

[16] Volek JS, Feinman RD, 2005. Carbohydrate restriction improves the features of metabolic syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction. Nutr Metabol 2:31.

Soluble fiber-containing foods that provide moderate levels of fat, particularly monounsaturated fat, permit individuals with low HDL levels, elevated triglycerides, or the metabolic syndrome to consume these types of carbohydrate foods without undue worry that their lipid profiles will be adversely affected.

### D. Clinical Data Demonstrating that Soluble-Fiber Containing Products Can Lower CHD Risk Within the Context of a Diet Moderate in Total Fat Intake

Most of the clinical trials of soluble-fiber containing products (whole oat products, whole barley products, psyllium) eligible for the CHD health claim were conducted within the context of a low-fat diet (i.e. low in total fat and saturated fat). A few of the oat clinical trials reviewed by FDA for the oat health claim had been carried out in the context of the typical American diet, however, these background diets were high in both total and saturated fat intake. To the best of our knowledge, none of the clinical trials evaluating soluble-fiber containing products utilized a moderate fat, low saturated, low *trans* fat, low cholesterol diet, with the exception of one.

One study (in press; Appendix 4) carried out within the context of a moderate fat diet is a randomized clinical trial of two barley beta-glucan concentrates (BBG), one of reduced or low molecular weight (LMW) and one of native or high molecular weight (HMW). The study was designed to test whether the consumption of these products at two dose levels would lower LDL-cholesterol and other CHD risk factors. Mildly hypercholesterolemic subjects (LDL-cholesterol 140 -190 mg/dL) were stabilized for 4 weeks on an AHA diet, which was low in saturated fat and *trans* fat. Subjects were instructed to discontinue any lipid altering dietary supplements prior to the start of the 6-week intervention. Subjects were randomized to receive one of 5 treatments: 3g LMW BBG, 5g LMW BBG, 3g HMW BBG, 5g HMW BBG, or a control, while still continuing on the low saturated and low *trans* fat diet. Total fat intake typically ranged from 32-35% of calories among the different groups, with one group increasing intakes to 38% of calories (3g LMW BBG, week 5). Saturated fat intake ranged from 9.6-11.7% of calories and polyunsaturated fat intake was less than 10% of calories. Monounsaturated fat was the primary fat consumed. Cholesterol intakes were low with the exception of one group. Within the context of this moderate fat diet, LMW or HMW BBG, when added at either 3g or 5g per day, significantly reduced total cholesterol and LDL cholesterol without negatively impacting HDL-cholesterol or triglyceride concentrations.

Results of this BBG study demonstrate that soluble-fiber containing products can lower CHD risk within the context of a moderate-fat diet.

## E. Several Authorized Heart Health Claims Do Not Have A "Low Fat" Criterion

Coronary heart disease has been the subject of twelve authorized health claims. Of those, FDA has waived the "low fat" criterion for nine health claims, either in its entirety or for a certain class of foods:

- Saturated fat and cholesterol--CHD health claim (21CFR 101.75): All eligible foods making the claim must be "low in saturated fat," "low cholesterol," and "low fat." However, applying this criterion to meats, fish and poultry would preclude any of these foods from making the health claims. Therefore an exception was made for fish and game meat; instead of the "low fat" criterion, fish and game meat are required to meet the "extra lean" requirements for saturated fat, cholesterol, and total fat.

- Soy protein--CHD health claim (21CFR 101.82): Eligible foods using the claim must be "low in saturated fat" and "low cholesterol." The food must also be "low fat," unless it is derived from whole soybeans and contains no additional fat other than the fat inherently present in whole soybeans.

- Plant Sterol and Stanol Esters--CHD health claim (21 CFR 101.83): Eligible foods using the claim must be "low in saturated fat," and "low cholesterol." The "low fat" criterion does not have to be met, but the total fat level of foods must not exceed the total fat disqualifying level, with an exception for spread and salad dressing on a per 50g basis. The "low fat" requirement was waived because fats are necessary food vehicles for plant sterol and stanol esters formulations and the evidence supporting the cholesterol-lowering effects plant sterol and stanol esters was strong. Furthermore, the 2000 Dietary Guidelines for Americans recommended choosing a diet low in saturated fat and cholesterol and moderate in total fat based on the current scientific evidence. FDA not imposing a "low fat" requirement for this health claim was consistent with the recommendations of the 2000 Dietary Guidelines for Americans.

- Nuts –Qualified CHD health claim (July 14, 2003): Nuts which are inherently high in fat content do not meet the "low fat" criterion and in fact exceed the total fat disqualifying level for health claims. Despite this, FDA believed that a qualified claim for most nuts would help consumers, provided the label contained a disclosure statement. However, nuts bearing the claim must comply with the saturated fat disqualifying level of 4g saturated fat per 50g nuts. Products containing nuts, however, must not exceed the total disqualifying level

for health claims and must be “low in saturated fat,” and “low cholesterol.”

- Omega-3 Fatty Acids—Qualified CHD health claim (September 8, 2004): FDA concurs with the 2000 Dietary Guidelines that state that consuming diets low in saturated fat and cholesterol is more important in reducing CHD risk than consuming diets low in total fat. Therefore, FDA has concluded that foods that bear an omega-3 fatty acid qualified health claim do not have to meet the "low fat" criterion because the consumption of omega-3 fatty acids is associated with reduced CHD risk. Products must still comply with the total disqualifying level for health claims and must be “low in saturated fat,” and “low cholesterol.” The exception is fish which do not have to meet the “extra lean” criterion for saturated fat, but have to meet the “extra lean” criterion for cholesterol, because fatty fish are a source of omega-3 fatty acids.

- Monounsaturated Fatty Acids from Olive Oil—Qualified CHD health claim (November 1, 2004): Olive oil does not meet the “low fat” criterion and in fact exceeds the disqualifying level for total fat because it is essentially entirely fat. Olive oil also exceeds the disqualifying level for saturated fat (4g per 50g), but FDA is not requiring compliance with this or the disqualifying level for total fat because it would prevent olive oil and olive oil containing spreads from making the qualified claim and prevent consumers from making healthy food choices. However olive oil salad dressings and olive oil containing food products do have to comply with the disqualifying level for saturated fat, because these products can be formulated with varying amounts of fat. The “low cholesterol” criterion has to be met by all products.

- Unsaturated Fatty Acids from Canola Oil—Qualified CHD health claim (October 6, 2006): Canola oil exceeds the “low fat” criterion and the total fat disqualifying level because it is essentially entirely fat. FDA does not intend to enforce compliance of these criteria because then canola oil would not be able to make the qualified claim and consumers would be prevented from making healthy food choices. However, the “low in saturated fat,” and the “low cholesterol” criteria must be met. FDA concurs with current 2005 Dietary Guidelines for Americans, that consuming diets low in saturated fat and cholesterol is more important in reducing CHD risk than consuming diets low in total fat.

- CHD Health Claim Notification for Whole Grain Foods with Moderate Fat Content (December 9, 2003): This notification cites statements from the National Academy of Sciences Report, Diet and Health: Implications for Reducing Chronic Disease Risk such as “*Intake of total*

*fat per se, independent of the relative content of different types of fatty acids is not associated with high blood cholesterol levels and coronary heart disease. A reduction in total fat consumption, however, facilitates reduction of saturated fatty acid intake; hence, in addition to reducing the risk of certain cancers, and possibly obesity, it is a rational part of a program aimed at reducing the risk of coronary heart disease.*" In order for foods to qualify for the claim, they must be "low in saturated fat," "low cholesterol," and contain less than 6.5g total fat and 0.5g or less *trans* fat per RACC. The notifier states that the restriction on total fat content to less than 6.5g per RACC is intended as a quantitative reflection of the amount of fat on an individual food basis that is consistent with moderate intakes of total fat in the overall diet.

- CHD Health Claim Notification for Saturated Fat, Cholesterol, and *Trans* Fat (November 15, 2006): This notification cites statements from the 2005 Dietary Guidelines for Americans as authoritative statements for the claim: *"Consume less than 10 percent of calories from saturated fatty acids and less than 300 mg/day of cholesterol, and keep trans fatty acid consumption as low as possible."* In order for foods to qualify for the claim, they must be "low in saturated fat," "low cholesterol," and contain less than 6.5g total fat and 0.5g or less *trans* fat per RACC.

It is important to point out that FDA permitted the whole grain foods with moderate fat content and reduced CHD risk notification despite the fact that a previous notification of whole grain foods and the reduced risk of CHD was already authorized. This scenario is identical to the one that NBFC is currently requesting. FDA has already authorized a CHD health claim for soluble fiber-containing foods that are "low fat," and the NBFC is requesting that FDA also authorize a CHD health claim for soluble fiber-containing foods that are moderate in fat content, or modify the currently authorized health claim to allow foods of moderate total fat content to be eligible for the claim.

The regulatory decisions made by FDA in authorizing health claims without meeting the "low fat" criterion initially established for CHD claims, clearly demonstrates FDA's precedent in permitting claims consistent with the current scientific evidence and current 2005 Dietary Guidelines for Americans. In this manner, FDA is providing consumers valuable information to make food choices consistent with dietary patterns that have been associated with reduced CHD risk.

## F. Recommendation for Type and Amount of Fat

Information provided in Sections A-E of this document states that monounsaturated fats and/or polyunsaturated fats are suitable fats to be added to soluble fiber-containing products eligible for the CHD health claim. The NCEP-ATP III Report (2002) suggests dietary monounsaturated fat intake can range up to 20% of calories and polyunsaturated fat intake can range up to 10% of calories. Translation of this recommendation to individual foods suggests a higher monounsaturated to polyunsaturated fat ratio. The scientific evidence especially supports the use of monounsaturated fats and omega-3 fatty acids in enhancing CHD risk reduction. The 2005 Dietary Guidelines for Americans, the NCEP-ATP III Report (2002), and the 2006 AHA Diet and Lifestyle Recommendations support low to moderate intakes of total fat, therefore it is reasonable to permit products bearing CHD health claims a similar fat range—i.e. low-fat to moderate-fat content.

An upper limit in total fat of 6.5g per RACC is suggested, as it is half of the total fat disqualifying limit of 13g per RACC for health claims. This upper limit is also consistent with the upper limits in other authorized health claims, such as the health claim notification for whole grain foods with moderate fat content and the reduced risk of CHD and the health claim notification for saturated fat, cholesterol, and *trans* fat and the reduced risk of CHD.

Current Dietary Guidelines and public health recommendations suggest limiting the intake of saturated fat, *trans* fat, and cholesterol. Therefore soluble fiber-containing products eligible for the CHD health claim must be “low in saturated fat,” and “low cholesterol” and as low as possible in t*rans* fat. FDA has not yet established a “low *trans* fat” definition, therefore an upper limit of 0.5g per RACC is suggested, consistent with the health claim notification for whole-grain foods with moderate fat content and the reduced risk of CHD and the health claim notification for saturated fat, cholesterol, and *trans* fat and the reduced risk of CHD.

In summary, monounsaturated and polyunsaturated fats may be added, with a greater emphasis on monounsaturated fats and the omega-3 fats of the polyunsaturated fatty acid category. Qualifying soluble-fiber foods must contain 1g or less of saturated fat, 0.5g or less of *trans* fat, 20mg or less of cholesterol, and 6.5g or less of total fat per RACC.

## IV. BENEFITS OF SOLUBLE FIBER-CONTAINING PRODUCTS WITH A MODERATE FAT CONTENT

The prevailing scientific consensus is that it is no longer mandatory to follow low-fat diets for CHD prevention, but that a wider range of fat intakes are permissible to accommodate different CHD risk profiles and different eating patterns, as long as these diets are low in saturated fat, cholesterol, and *trans* fats. Sacks and Katan (2002) recently noted in their review that it is likely that many diets could be designed that could reduce cardiovascular disease risk, and this potential diversity is crucial for engaging the diverse cultures and tastes of people worldwide in reducing the risk of cardiovascular disease.

In summary, relaxing the "low fat" criterion for CHD health claims will provide the following benefits:

- In the case of barley products, it will provide consumers with "low fat" and "moderate fat" barley sources and hence greater flexibility in achieving dietary goals.

- Increase the number of soluble-fiber containing foods that lower CHD risk, thereby reaching a wider segment of the population.

- Encourage product formulations with soluble fiber and fats associated with reduced CHD risk such as monounsaturated fats, omega-3 fatty acids, nuts, and soy protein.

- Increase the number of foods for individuals for whom low-fat, high carbohydrate diets are contraindicated (i.e. those prone to hypertriglyceridemia and low HDL; those with metabolic syndrome, diabetes).

- Help to educate the consumer that moderate fat eating patterns can also reduce CHD risk.

APPENDIX Table 1. Fat Content of Whole Grain and Milled Barley Products

| Barley Products Currently Authorized for the CHD Health Claim | RACC (g) | Fat (g) per RACC* |
|---|---|---|
| Dehulled/hulless barley | 45 | 1.0 - 1.4 |
| Pearl barley | 45 | 0.5 |
| Barley flakes, plain dry cereal | 40 | 0.9 - 1.2 |
| Barley flakes, flavored sweetened dry cereal | 55 | 1.3- 1.7 |
| Barley grits, plain dry cereal | 40 | 0.9 – 1.2 |
| Barley grits, flavored sweetened dry cereal | 55 | 1.3- 1.7 |
| Barley flour | 30 | 0.7 - 0.9 |
| Beta-glucan barley enriched meal/flour | 30 | 0.7 – 0.9 |
| Barley bran | 15 | 1.0 - 2.0 |
| Barley flakes, very high β-glucan varieties, plain dry cereal | 40 | 2.6 |
| Barley grits, very high β-glucan varieties, plain dry cereal | 40 | 2.6 |
| Higher Fat Barley Products Currently Not Authorized for the CHD Health Claim When the RACC is 55g | | |
| Barley flakes, very high β-glucan varieties, flavored sweetened dry cereal | 55 | 3.6 |
| Barley grits, very high β-glucan varieties, flavored sweetened dry cereal | 55 | 3.6 |

*Low Fat: ≤ 3 g/RACC

Sources:

Dehulled barley, Pearl Barley, Barley flour:
USDA-ARS (2006). USDA National Nutrient Database for Standard Reference, Release 19, http://www.nal.usda.gov/fnic/foodcomp/search/.

Barley Flakes and grits :-same as above because they are made from dehulled barley and pearl barley.

Beta-glucan barley enriched meal/flour: Barley Balance specification sheet and
Dudgeon-Bollinger, A.L., Fastnaught, C.E., and Berglund, P.T. 1997. Extruded snack products from waxy hull-less barley. Cereal Foods World 42:762-766.

Barley Bran :
Dudgeon-Bollinger, A.L., Fastnaught, C.E., and Berglund, P.T. 1997. Extruded snack products from waxy hull-less barley. Cereal Foods World 42:762-766.
Wang, L., Xue, Q., Newman, R. K., Newman, C. W. (1993). Enrichment of tocopherols, tocotrienols and oil in barley fractions by milling and pearling. Cereal Chem 70:499-501.

Very high beta-glucan varieties :
Conagra Sustagrain Specification sheet and,
Wang, L., Newman, R. K., Newman, C. W., Jackson, L. L. & Hofer, P. J. (1993). Tocotrienol and fatty acid composition of barley oil and their effects on lipid metabolism. Plant Foods Hum Nutr 43:9-17.

APPENDIX Table 2. Fat Distribution of Higher Fat Barley Products Currently Not Authorized for the CHD Health Claim When the RACC is 55g (Per 100g)

| Barley Product | Total Fat | Saturated Fat | Monounsaturated Fat | Polyunsaturated Fat |
|---|---|---|---|---|
| Barley, very high β-glucan varieties | 6.5 | 1.8 | 1.2 | 3.5 |

Sources:

Conagra Sustagrain Specification sheet and

Wang, L., Newman, R. K., Newman, C. W., Jackson, L. L. & Hofer, P. J. (1993). Tocotrienol and fatty acid composition of barley oil and their effects on lipid metabolism. Plant Foods Hum Nutr 43:9-17.

APPENDIX Table 3. Comparison of the Fat Distribution of Oats and Barley Products (Per 100g)

| | Total Fat (g) | Saturated Fat (g) | Monounsaturated Fat (g) | Polyunsaturated Fat (g) |
|---|---|---|---|---|
| Oats, regular/quick/instant, dry | 6.3 | 1.11 | 1.98 | 2.3 |
| Hulled barley, dry | 2.3 | 0.48 | 0.295 | 1.108 |
| Pearled barley | 1.16 | 0.244 | 0.149 | 0.56 |
| Barley flour | 1.6 | 0.335 | 0.205 | 0.771 |

Source: USDA-ARS (2006). USDA National Nutrient Database for Standard Reference, Release 19, http://www.nal.usda.gov/fnic/foodcomp/search/.

APPENDIX 4

Randomized clinical trial shows extracted barley-beta-glucan concentrate improves cardiovascular disease risk biomarkers in hypercholesterolemic adults after 6-weeks of treatment.

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Abstract presented at American Heart Association Scientific Sessions, Dallas TX, Nov. 13-16, 2005

**Whole barley foods rich in soluble fiber (β-glucan) positively impact blood lipids; but these foods are not commonly consumed and require large quantities for therapeutic effect. This study investigates the effects of food products enriched with an extracted barley beta-glucan in hypercholesterolemic adults. We conducted a double-blind, placebo-controlled, 5-group parallel study to test the hypothesis that extracted barley β-glucan at modified molecular weights beneficially impacts CVD risk biomarkers. Treatment groups were low (LMW) and high (HMW) molecular weight β-glucan at 3 and 5 grams daily. Treatment delivery was a customized ready-to-eat individually packaged corn cereal and fruit juice with or without β-glucan given in divided doses for 6-weeks. Hypercholesterolemic (LDL-C 130-190 mg/dL) women (80) and men (75) aged 25-73 years who completed a 4-week modified fat diet were randomized to one of five groups. Treatment groups were stratified by metabolic syndrome status (79 non-metabolic, 76 metabolic subjects) using the ATP III guidelines and/or elevated fasting insulin levels ≥ 10 μU/L. Subjects were counseled to maintain low saturated fat diet and other lifestyle habits during the study. Mean body mass index was 29 ± 5.3 kg/m$^2$ and remained constant. Average**

**treatment compliance was 96% determined by collecting all treatment containers. Diet was assessed with food records and did not affect treatment outcomes.**

**Conclusion: Purified barely β-glucan improved outcomes with linear dose response effect. No significant change in HDL-C or Apolipoprotein A-1 was observed. Treatment effect did not vary by MW except for LDL number and hs-CRP where greater reduction was seen in 5g HMW compared to 5g LMW. Enriched functional food products may be a viable option to increase therapeutic consumption of barley β-glucan to improve cardiovascular disease risk biomarkers.**

*Pairwise Comparison of Biomarker Change Scores from baseline by ß-Glucan Treatment (n=155)*

***Values given as mean ± SE. Different letters within rows indicate statistical differences between groups at p =0.05.***

| | Control n = 30 | 5g HMW n= 32 | 5 g LMW n=30 | 3g HMW n=32 | 3g LMW n=31 |
|---|---|---|---|---|---|
| **LDL-C, mg/dL** | **-2 ± 3.5** *a* | **-23 ± 2.5** *c* | **-20 ± 2.9** *c* | **-14 ± 3.4** *b* | **-13 ± 2.7** *b* |
| **Apolipoprotein B, mg/dL** | **-3 ± 4.0** *a* | **-26 ± 3.0** *b* | **-20 ± 3.1** *b* | **-14 ± 3.5** *b* | **-14 ± 2.5** *b* |
| **LDL size, nm** | **-0.13 ± 0.18** *a* | **0.36 ± 0.18** *c* | **0.30 ± 0.18** *c* | **-0.07 ± 0.16** *a* | **0.14 ± 0.16** *b* |
| **LDL number** | **-8 ± 15.2** *a* | **-122 ± 17.5** *c* | **-69 ± 15.7** *b* | **-34 ± 15.0** *b* | **-47 ± 14.4** *b* |
| **Triglycerides, mg/dL** | **5 ± 12.8** *a* | **-25 ± 11.1** *b* | **-21 ± 14.1** *b* | **-12 ± 12.7** *b* | **-13 ± 10.1** *b* |