

APPENDIX C

**2003 Whole Grains Health Claim Notification
(Kraft Foods)**



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Dear Ms. Schrimpf:

On August 8th, Kraft Foods North America, Inc. (Kraft) notified the Food and Drug Administration (FDA) that the company plans to use the food label to educate consumers about the well-established relationship between the consumption of whole grain foods and reduced risk of coronary heart disease. As required by section 403(r)(3)(C) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 343(r)(3)(C), Kraft provided to FDA the authoritative statement of the Food and Nutrition Board of the National Research Council upon which the label claim will be based, along with additional detailed supporting scientific literature. FDA subsequently advised Kraft that the required notice was received on August 11th and the notification period would expire on December 9th. With this letter, we are including a petition revised to incorporate recent discussions with FDA, as confirmed in my letter dated November 3rd and in response to your subsequent request for a fully amended petition to facilitate display on the agency's web site.

The exact wording of the claim will be as follows: "Diets rich in whole grain foods and other plant foods, and low in saturated fat and cholesterol, may reduce the risk of heart disease." The claim will be used on foods that contain at least 51% whole grain (using dietary fiber as a marker); meet the regulatory definitions for "low saturated fat" and "low cholesterol"; bear quantitative trans fat labeling; contain less than 6.5 grams total fat and less than or equal to 0.5 grams trans fat per reference amount customarily consumed (following standard rounding rules); and meet all general requirements for health claims in 21 C.F.R. 101.14.

Respectfully submitted,

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**Notification for a Health Claim
Based on an Authoritative Statement:
Whole Grain Foods and Heart Disease**

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**Notification for a Health Claim
Based on an Authoritative Statement:**

Whole Grain Foods and Heart Disease

I. INTRODUCTION

Kraft Foods North America, Inc. (Kraft) is planning to use the food label to educate consumers about the well-established relationship between the consumption of whole grain foods and reduced risk of coronary heart disease (CHD). As required by section 403(r)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 343(r)(3)(C), Kraft is notifying the Food and Drug Administration (FDA) that the company intends to make a health claim based upon an authoritative statement of the Food and Nutrition Board (FNB) of the National Research Council (NRC), the working arm of the National Academy of Sciences (NAS). The exact wording of the proposed claim is as follows: “Diets rich in whole grain foods and other plant foods, and low in saturated fat and cholesterol, may help reduce the risk of heart disease.”

The claim will be used on foods that contain a minimum of 51% whole grains (using dietary fiber as a marker), meet the regulatory definitions for “low saturated fat” and “low cholesterol,” bear quantitative trans fat labeling in the Nutrition Facts box, contain less than 6.5 grams total fat and 0.5 grams or less trans fat per reference amount customarily consumed (RACC) (following standard rounding rules), and meet all general requirements for health claims in 21 C.F.R. § 101.14. In particular, the claim will appear on foods such as whole grain cereals, crackers, breads, and whole grain based snack mixes and bars.

The proposed claim is based upon the following authoritative statement made in the classic report *Diet and Health: Implications for Reducing Chronic Disease Risk*¹ (“*Diet and Health*”):

Diets high in plant foods – i.e., fruits, vegetables, legumes, and whole-grain cereals – are associated with a lower occurrence of coronary heart disease and cancers of the lung, colon, esophagus, and stomach.

(*Diet and Health*, at 8). Although this statement was published in 1989, the relationship between whole grain foods and reduced risk of CHD, in the context of a diet low in saturated fat and cholesterol, remains substantiated by a balanced review of the current scientific literature.

II. BACKGROUND—THE *DIET AND HEALTH* REPORT

The *Diet and Health* report reflects a comprehensive review and analysis of scientific literature addressing diet and the spectrum of major chronic diseases. The report presents the findings of the Committee on *Diet and Health* (the “Committee”), a 19-member interdisciplinary committee established by the FNB to explore the relationship between chronic disease risk and foods, food groups, food components, and dietary patterns. Widely considered a major work in the field of nutrition, the report remains respected and relevant today. It has been used as a basis for two authoritative statement health claims authorized pursuant to FDAMA notifications: in 1999, it was cited as a basis for a health claim concerning whole grain foods and reduced risk of CHD; in 2000, it provided a basis for a health claim addressing the relationship between potassium, blood pressure, and reduced risk of stroke.

¹ National Research Council, *Diet and Health: Implications for Reducing Chronic Disease Risk*, at 8 (National Academy Press 1989).

Kraft has carefully reviewed the conclusions set forth in the *Diet and Health* report concerning the beneficial relationship between whole grain foods and reduced risk of CHD. In addition to the information and findings set forth in the text of *Diet and Health*, our review considered the studies evaluated by the Committee on *Diet and Health* and cited in the report, more recent studies addressing whole grain foods and CHD, current recommendations concerning whole grain consumption, current recommendations and science concerning total fat intake, regulatory precedent including the currently authorized whole grain claim,² and other information relevant to the development of an authoritative statement health claim addressing whole grain foods and CHD.

On the basis of this review, Kraft concluded that *Diet and Health* supports the use of a health claim communicating the relationship between whole grains and CHD on a wide variety of whole grain foods. In particular, a review of the report and supporting literature demonstrates that consistency with *Diet and Health* does not require that the proposed claim be restricted to whole grain foods that meet the definition of “low fat” in 21 C.F.R. § 101.62. The “low fat” constraint was incorporated into the 1999 notification, but is not required by the report or underlying scientific evidence. Moreover, consumption of the whole grain foods that are the subject of this notification is entirely compatible with a healthful diet consistent with the recommendations of public health experts. Additionally, the whole grain and saturated fat criteria specified in this notification, along with the quantitative restrictions on total fat and trans fat content, will restrict the total fat content of products bearing the claim, ensuring that products bearing the proposed claim will contain moderate levels of total fat considerably lower than the disqualifying level for total fat. When framed as proposed, the claim gives appropriate emphasis to the benefit of consuming whole grain foods that are low in saturated fat and cholesterol without unduly limiting communication focused on whole grains to foods that are “low” in total fat content.

² Whole Grain Foods Authoritative Statement Claim Notification, docket no. 99P-2209 (Mar. 10, 1999); Letter from S. Pape to C. Lewis (July 6, 1999).

III. AUTHORITATIVE STATEMENT

A. *Diet and Health*

The authoritative statement upon which the proposed whole grain health claim is based appears in the executive summary of the *Diet and Health* report. The executive summary, which reflects the Committee's major conclusions and their bases, contains the Committee's finding that—

Diets high in plant foods – i.e., fruits, vegetables, legumes, and whole-grain cereals – are associated with a lower occurrence of coronary heart disease and cancers of the lung, colon, esophagus, and stomach.

(*Diet and Health*, at 8). Immediately following this statement, the FNB offered possible explanations for the anticipated health benefits of plant-based foods, including whole grains:

Although the mechanisms underlying these effects are not fully understood, the inverse association with coronary heart disease may be largely explained by the usually low saturated fatty acid and cholesterol content of such diets. Such diets are also low in total fat, which is directly associated with the risk of certain cancers, but rich in complex carbohydrates (starches and fiber) and certain vitamins, minerals, trace elements, and nonnutritive constituents, and these factors probably also confer protection against certain cancers and coronary heart disease.

(*Diet and Health*, at 8). On the subject of total fat, the FNB stated (*Diet and Health*, at 7) that “[t]here is clear evidence that the total amounts and types of fats and other lipids in the diet influence the risk of atherosclerotic cardiovascular disease and, to a less well-established extent, certain forms of cancer and possibly obesity.” The FNB explained that a reduction in total fat consumption would be expected to promote health by facilitating concomitant reductions in intake of saturated fatty acids:

Intake of total fat *per se*, independent of the relative content of the 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.

(*Diet and Health*, at 7). The Committee on Diet and Health recommended that total fat intake be reduced to 30% or less of calories, with less than 10% of total calories derived from saturated fat. (*Diet and Health*, at 13). In offering this recommendation, the Committee again emphasized the need to limit saturated fat and cholesterol (*Diet and Health*, at 13):

A large and convincing body of evidence from studies in human and laboratory animals shows that diets low in saturated fatty acids and cholesterol are associated with low risks and rates of atherosclerotic cardiovascular diseases. High-fat diets are also linked to a high incidence of some types of cancer and, probably, obesity. Thus, reducing total fat and saturated fatty acid intake is likely to lower the rates of these chronic diseases. Fat intake should be reduced by curtailing the major sources of dietary fats rather than by eliminating whole categories of food. For example, by substituting fish, poultry without skin, lean meats, and low- or nonfat dairy products for high-fat foods, one can lower total fat and saturated fatty acid intake while ensuring an adequate intake of iron and calcium—two nutrients of special importance to women. Dietary fat can also be reduced by limiting intake of fried foods, baked goods containing high levels of fat, and spreads and dressings containing fats and oils.

B. Health Claims Based on *Diet and Health*

In 1999, the FNB's authoritative statement concerning whole grains was used to support the following health claim:

Diets rich in whole grain foods and other plant foods and low in total fat, saturated fat, and cholesterol, may help reduce the risk of heart disease and certain cancers.

The notification proposing this health claim (the "1999 whole grains notification") presented evidence that the proposed authoritative statement continued to be supported by the evolving body of science. The notification characterized the available science as reflecting significant scientific agreement regarding the ability of a low fat diet rich in whole grain foods to reduce the risk of CHD and

certain cancers. The notification has been interpreted to require that foods eligible to bear the notified claim must be “low” in fat, saturated fat, and cholesterol, as defined by FDA.

The 1999 whole grain notification also included a specification for whole grain content, defining “whole grain foods” for purposes of the proposed health claim as foods with 51% or more whole grain ingredient(s) by weight per Reference Amount Customarily Consumed (RACC). Such foods provide a minimum of 16 grams of whole grain, which is the equivalent whole grain food serving under the Food Guide Pyramid.

It was proposed that dietary fiber be used as a marker to identify whole grain foods for the purpose of assessing compliance with the claim. A formula³ based on the fiber content of whole wheat (the most prevalent grain in the U.S. diet) was proposed to calculate the minimum amount of fiber necessary for foods with different RACCs to qualify for the claim. The result of this calculation for different RACCs is provided in Table 1.

Table 1
Minimum Fiber Content to Qualify for the Whole Grain Health Claim
for Different Reference Amounts Customarily Consumed

RACC (g)	Minimum fiber content (g)
30	1.7
45	2.5
50	2.8
55	3.0

³Dietary fiber necessary to qualify for the claim = (11 grams dietary fiber per 100 grams whole wheat x 51% x RACC)/100.

C. Total fat intake as addressed in *Diet and Health*

Although the claim proposed in the 1999 notification expressly referenced low fat diets, and the notification required foods bearing the claim to be “low fat” as defined by FDA, neither the *Diet and Health* report nor more recent science mandates such an approach. The *Diet and Health* report reflects significant scientific agreement that diets low in saturated fat and cholesterol are associated with a reduced risk of CHD. The Committee on Diet and Health did suggest that diets high in total fat may increase CHD risk, primarily because such diets may also be high in saturated fat. The emphasis placed in *Diet and Health* on saturated fat and cholesterol supports a similar emphasis and approach in claims pertaining to CHD risk. The continued relevance of this approach is confirmed by recent literature and dietary recommendations, which are discussed in detail in Parts VII and VIII below.

Although saturated fat and cholesterol are predominant concerns identified in *Diet and Health*, it is appropriate to consider total fat intake in fashioning a claim addressing CHD risk. There should be some assurance that foods bearing such claims do not promote excessive or otherwise unreasonable consumption of fat. There is, however, no basis for concluding that a food that does not meet the technical definition of “low fat” in 21 C.F.R. 101.62(b)(2) cannot be part of a diet that contains an appropriate amount of total fat. The Committee on Diet and Health suggested that high fat foods should be limited, but did not recommend the elimination of foods that may contain moderate levels of fat.

A flexible approach to total fat content is particularly warranted in the case of whole grains, for which a beneficial effect has been demonstrated. The beneficial effect of whole grains independent of fat intake was evident in studies considered in the preparation of *Diet and Health* and is corroborated by more recent science. The available literature supports a conclusion that the total fat content, *per se*, of diets rich in fiber or whole grain foods is unrelated to CHD, and provides no

persuasive evidence that whole grain foods that are low in saturated fat and cholesterol, but not necessarily low in total fat, are any less effective in reducing the risk of CHD than their low-fat counterparts. A balanced review of 40 studies with original data on the effect of whole grain foods or dietary fiber (a marker for whole grains) on the risk or incidence of CHD is provided below in Part VII.

IV. EXACT WORDING OF THE PROPOSED CLAIM

Kraft intends to make the following authoritative statement claim on the label and/or labeling of certain whole grain food products:

Diets rich in whole grain foods and other plant foods, and low in saturated fat and cholesterol, may help reduce the risk of heart disease.

This claim is similar to the currently authorized whole grains health claim except that the claim is succinctly worded to focus upon the relationship between heart disease and diets rich in whole grains and low in saturated fat and cholesterol. As noted previously, this focus is fully consistent with *Diet and Health* and is further supported by substantial amounts of additional data and recommendations that have become available since *Diet and Health* was published. The supportive data and other information are discussed in detail in Parts VII and VIII of this notification.

V. STATUTORY BASIS FOR THE CLAIM

Section 303 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (21 U.S.C. § 343(r)(3)) authorizes food manufacturers to make health claims without prior FDA approval provided certain conditions are met. In enacting the FDAMA notification scheme for health and nutrient content claims, Congress intended to provide “streamlined procedures” for the dissemination of scientifically sound nutrition information to the public (H.R. Rep. No. 105-399, at

98 (1997)). The ultimate legislative goal, well-served by the present notification, was to ensure a flexible regulatory mechanism by which well-established diet and health information reaches consumers. This objective is in line with FDA's recently announced Consumer Health Information for Better Nutrition initiative.

A. Requirements for health claims based on authoritative statements

The FFDCA, as amended by FDAMA, specifically authorizes the use of health claims based on authoritative statements when the following criteria are met:

(i) a scientific body of the United States Government with official responsibility for public health protection or research directly relating to human nutrition (such as the National Institutes of Health or the Centers for Disease Control and Prevention) or the National Academy of Sciences or any of its subdivisions, has published an authoritative statement, which is currently in effect, about the relationship between a nutrient and a disease or health-related condition to which the claim refers;

(ii) a person has submitted to the Secretary, at least 120 days (during which the Secretary may notify any person who is making a claim as authorized by clause (C) that such person has not submitted all the information required by such clause) before the first introduction into interstate commerce of the food with a label containing the claim, (I) a notice of the claim, which shall include the exact words used in the claim and shall include a concise description of the basis upon which such person relied for determining that the requirements of subclause (i) have been satisfied, (II) a copy of the statement referred to in subclause (i) upon which such person relied in making the claim, and (III) a balanced representation of the scientific literature relating to the relationship between a nutrient and a disease or health-related condition to which the claim refers;

(iii) the claim and the food for which the claim is made are in compliance with clause (A)(ii) and are otherwise in compliance with paragraph (a) and section 201(n); and

(iv) the claim is stated in a manner so that the claim is an accurate representation of the authoritative statement referred to in

subclause (i) and so that the claim enables the public to comprehend the information provided in the claim and to understand the relative significance of such information in the context of a total daily diet.

(FFDCA § 403(r)(3)(C)). The FFDCA further provides that the statement “shall not include a statement of an employee of the scientific body made in the individual capacity of the employee.”

In 1998, FDA issued a document providing guidance on the types of claims that qualify as FDAMA authoritative statements and the procedures that should be followed for submitting a health claim notification (Guidance for Industry (June 11, 1998)). In this guidance document, FDA identified six criteria for FDAMA claims, four of which are based on the plain language of the statute and the last two of which are based on FDA’s interpretation of the statute and its legislative history. According to the FDA guidance document, an authoritative statement:

- 1) is about the relationship between a nutrient and a disease or health-related condition;
- 2) is “published by the scientific body”;
- 3) is “currently in effect”;
- 4) “shall not include a statement of an employee of the scientific body made in the individual capacity of the employee”;
- 5) should reflect a consensus within the identified scientific body if published by a subdivision of one of the federal scientific bodies; and
- 6) should be based on a deliberative review by the scientific body of the scientific evidence.

The FDA guidance document further stated that the agency interprets FDAMA as requiring health claims to be supported by significant scientific agreement—the

same standard that is required for health claim regulations.⁴ Separately, FDA has also advised that a health claim based on an authoritative statement must not be equivalent to a health claim that is the subject of an authorizing regulation issued by the agency pursuant to section 403(r)(3)(B) of the FFDCa. (63 Fed. Reg. 34101, 34102 (June 22, 1998)).

B. Authoritative status of the *Diet and Health* statement

The *Diet and Health* statement upon which the proposed whole grains health claim is based qualifies as an “authoritative statement” under section 403(r)(3)(C) of the FFDCa, as amended by FDAMA. The statement concerns the relationship between whole grain foods and CHD, a serious and chronic disease that is associated with dietary habits over a lifetime. It is based upon a deliberative review of the literature by an expert Committee established by the FNB and the NRC, which in turn are affiliated with the NAS, an agency that is identified in FDAMA as an authoritative body that may be the source of authoritative statements. Because the statement appears in the executive summary of a major report of the NRC (the working arm of the NAS), it is reasonably characterized as reflecting consensus within an authoritative body. Indeed, in its review of the 1999 whole grains notification, FDA determined this precise statement to be an authoritative statement upon which a health claim may be based.

⁴ The 1998 guidance represented FDA’s current thinking, as of the date of its issuance, on the procedures to be followed for notifying the agency of a health claim or nutrient content claim based on an authoritative statement of a scientific body. As posted on the internet (<http://www.cfsan.fda.gov/~dms/hclmguid.html#foot1>), the guidance contains a link that references more recent information on food labeling. Among the significant developments in recent years are judicial decisions concerning the role of the First Amendment in shaping government regulation of commercial speech, including health-related claims, and completion of the report of the agency’s Task Force on Consumer Health Information for Better Nutrition, along with the associated guidance documents. See, e.g., *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999); 68 Fed. Reg. 41387 (July 11, 2003).

The statement also is “currently in effect,” as required by FDAMA. Since the 1999 whole grains notification, multiple papers, studies, and dietary recommendations have corroborated the conclusions set forth in *Diet and Health* concerning the relationship between CHD and diets rich in whole grains and low in saturated fat and cholesterol. These papers, studies, and recommendations are discussed fully in Parts VII and VIII of this notification.

C. Form and Content of Claim

In addition to establishing criteria for authoritative statements, FDAMA also sets forth criteria that proposed claims based on authoritative statements must meet. The form and content of the proposed whole grain health claim satisfy these criteria. In particular, the form and content of the proposed claim (1) provide an accurate representation of the authoritative statement; (2) are truthful and not misleading, consistent with sections 403(a) and 201(n) of the Act; (3) enable the public to comprehend the information and to understand its significance in the context of the total daily diet; and (4) are supported by significant scientific agreement concerning diets rich in whole grains and low in saturated fat and cholesterol.

Additionally, the proposed claim is distinct from, and not equivalent to, any health claim the agency has authorized by regulation, including FDA-approved health claims addressing the relationship between CHD risk and soy protein, plant sterol and stanol esters, or certain types of fiber-containing foods. Significantly, the proposed health claim is distinct from approved claims concerning fiber-containing foods because whole grain foods as such have been shown to confer beneficial health effects. The anticipated benefits of whole grains are not attributed to fiber, *per se*, or any other isolated component of whole grains.

VI. NATURE OF THE FOOD ELIGIBLE TO BEAR THE CLAIM

Foods bearing the claim would meet the following criteria: first, as specified in the 1999 whole grain notification, “whole grain foods” would contain 51% or more whole grain ingredient(s) by weight per RACC using dietary fiber as a compliance marker; second, foods would meet the FDA definitions for low saturated fat (21 CFR § 101.62 (c)(2)) and low cholesterol (21 CFR § 101.62 (d)(2)); third, the Nutrition Facts on the label would include trans fat labeling consistent with the final rule published in the July 11, 2003 *Federal Register* (68 Fed. Reg. 41434); fourth, foods would contain less than 6.5 grams of total fat and 0.5 grams or less trans fat per RACC (following standard rounding rules); and fifth, foods would meet all general requirements for health claims in 21 CFR § 101.14. The claim would be used on appropriate whole grain products, including whole grain cereals, crackers, breads and whole grain based snack mixes and bars. Label examples that illustrate the application of these criteria for a whole grain cereal and a whole grain cracker product are provided in Appendix D. The basis for selecting these criteria is discussed in detail below.

A. Whole grain content

Kraft intends to use the eligibility criterion for whole grain content as specified in the 1999 whole grain notification. This criterion was described in detail in the 1999 submission (see p. 11-12 of Appendix B) and is summarized in Part III of this document. Specifically, weight of fiber per RACC is used as a marker for foods that contain at least 51% whole grain ingredients according to the following formula: grams of minimum fiber per RACC = (11 grams fiber x 51% x RACC)/100.

B. Fat and Cholesterol Content

To qualify for the proposed claim, whole grain foods would be required to meet the FDA definitions for low saturated fat and low cholesterol, as set forth in 21

C.F.R. §§ 101.62 (c)(2) and 101.62 (d)(2), respectively. Use of the claim for such foods is justified based on the *Diet and Health* report and the studies underlying this report. The concern expressed by FNB regarding total fat was based on indirect effects that may result from high fat diets, primarily, high intakes of saturated fat. The FNB characterized saturated fat intake as “the major dietary determinant of the serum total cholesterol and LDL cholesterol levels in populations and thereby of coronary heart disease risk in populations.” (*Diet and Health*, at 7-8).

With respect to total fat, the eligibility criteria discussed in this notification will limit the amount of total fat that can be present in foods bearing the health claim, thereby facilitating a total fat intake that is consistent with dietary guidelines. Specifically, the less than 6.5 grams per RACC criterion will ensure that increased consumption of whole grain foods prompted by the health claim will not result in excessive intakes of total fat.⁵ Moreover, Kraft anticipates that the physical nature of whole grain products, together with the proposed saturated fat limitation, will act as significant practical restraints on the fat levels of foods bearing the claim.

With regard to trans fat, Kraft is limiting those foods that will bear the claim to those that contain 0.5 grams or less of trans fat per RACC. This criterion reflects FDA’s recent recognition of a link between trans fat consumption and increased serum low density lipoprotein cholesterol levels, a risk factor for CHD. See, e.g., Final Rules; Trans Fatty Acids in Nutrition Labeling, Nutrient Content Claims, and Health Claims, 68 Fed. Reg. 41434 (July 11, 2003).

⁵ In this regard, Kraft notes that the restriction on total fat content to less than 6.5 grams 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. The 6.5 gram criterion is not, and should not be interpreted as, a judgment by Kraft that fat levels of 6.5 grams or higher in an individual food are inconsistent with healthy dietary practices.

1. Physical nature of whole grain foods

The physical characteristics of whole grain foods tend to limit fat content. In Table 2, we have compiled the average fat content of a broad sample of existing grain based products.

Table 2
Average Fat Content of Grain Based Foods: Breads, Cereals, Crackers and Certain Snacks

Product Category ^a	RACC	Fat Content of Other Grain Based Foods (g per RACC)		Fat Content of Whole Grain Foods ^b (g per RACC)	
		Average	Range	Average	Range
Breads	50 g	2.0	1.4 – 2.9	1.8	1.1 – 2.7
Cereals	30 g	1.0	0 – 3.5	1.1	0.5 – 2.0
Cereals	55 g	2.2	0.6 – 4.0	2.2	0.6 – 6.2
Crackers	30 g	3.4	0 – 6.2	2.6	0 – 4.8
Snack Mixes	30 g	5.3	2.0 – 6.0	None found	

^aProducts included are listed in Appendix C.

^bIncludes whole-grain products that meet the proposed health claim eligibility criteria but are *not* necessarily low in fat.

The data in Table 2 show that the fat content of whole grain products is similar to (or slightly lower than) that of other grain based foods and typically well below the disqualifier level. The fat content of new products developed to take advantage of the proposed claim would be comparable to those of whole grain products already in the marketplace.

2. Low saturated fat criterion—effect on total fat

The low saturated fat criterion also will influence the amount of fat that can be added to products that qualify for the whole grain health claim. This criterion would disqualify any product that contains more than one gram of saturated fat per RACC or more than 15% of calories from saturated fat. The practical significance of this constraint is to encourage the use of fats with a desirable fatty acid profile in whole grain products that are formulated to bear the claim.

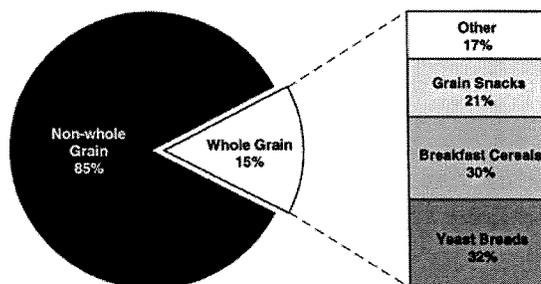
C. Trans fat criterion and labeling

As noted earlier, foods that bear the claim will be restricted to 0.5 grams or less trans fat per RACC and will bear labeling in the manner required by the final rule published in the July 11, 2003 *Federal Register* (68 Fed. Reg. 41434 (amending 21 C.F.R. § 101.9)). The required information concerning trans fat content would be provided in the Nutrition Facts box regardless of the January 1, 2006 effective date imposed by FDA in the final rule. These criteria will limit the trans fat content of foods bearing the claim and will effectively mandate early compliance with the final trans fat labeling rule for those foods, thereby ensuring that consumers have adequate information regarding trans fat content at the point of purchase.

D. Product categories

Use of the proposed claim is permitted on appropriate whole grain foods, including, but not limited to, products in the following categories: cereals, crackers, breads, whole grain based snack mixes and bars. The product categories identified in this notification are the major contributors of whole grains in the U.S. diet (Cleveland, 2000). The data in Figure 1 show that breads, cereals and snacks comprise 83% of all whole grain servings. These categories present an excellent opportunity to increase whole grain consumption.

Figure I
 Proportion of Total Grain Servings from Whole Grains and Non-Whole Grains
 and Major Food Source of Whole-Grain Servings



Source: Cleveland, L.E. *et.al.* J. Am. Col. Nutr. 19:331S (2000).

VII. REVIEW OF SCIENTIFIC LITERATURE REGARDING THE RELATIONSHIP BETWEEN WHOLE GRAINS AND CHD

The appropriateness of a health claim concerning CHD and diets rich in whole grains and low in saturated fat and cholesterol is corroborated by the studies published before the *Diet and Health* report as well as more recent literature concerning the health benefits of whole grains.

A. Literature Review

1. Literature published before *Diet and Health*

Nineteen studies that examined the effect of whole grain foods or dietary fiber on the risk of CHD were cited in the *Diet and Health* report or the 1999 whole grains notification. The relevance of these studies to the current notification is discussed below.

a. Literature cited in *Diet and Health*

As expected, the studies cited in *Diet and Health* provide strong support for the conclusion that whole grain foods reduce the risk of CHD. Seven observational

studies (Morris *et.al.*, 1977; Burr and Sweetnam, 1982; Kromhout *et.al.*, 1982; Liu *et.al.*, 1982; Kromhout and de Lezenne Coulander, 1984; Kushi *et.al.*, 1985; Khaw and Barrett-Connor, 1987) and seven dietary intervention studies (Keys *et.al.*, 1960; Grande *et.al.*, 1965; Schweizer *et.al.*, 1983; Challen *et.al.*, 1983, Karlstrom *et.al.* 1984; Anderson *et.al.*, 1984; Kay *et.al.*, 1985) were discussed in this report. The *Diet and Health* report did not specifically address whether whole grain foods that are low in saturated fat and cholesterol, but not necessarily low in total fat, have a protective effect on CHD. As discussed below, although the studies cited in this report were not designed to assess the effects of total fat intake on the cardioprotective effects of whole grains or fiber, they do provide some evidence that cardioprotective effects are independent of total dietary fat content.

Observational Studies

Of the 7 observational studies, two failed to provide evidence for a protective effect of dietary fiber or whole grain foods on a risk factor or incidence of CHD. Kromhout *et.al.* (1982) initially found a 4-fold increase in mortality from CHD in men in the lowest quartile of dietary fiber intake, but this inverse relationship was lost during multivariate analyses. Similarly, Kushi et al (1985) had a fairly strong ($p=0.05$) inverse relationship between dietary fiber intake and risk of death from CVD, but the significance was lost when other factors were controlled.

Two prospective cohort studies found that intake of dietary fiber or whole grain foods was associated with reduced risk of CHD, but found no apparent association with total fat. The populations studied included 859 men and women aged 50-79 living in California (Khaw and Barret-Connor, 1987), and 327 middle-aged men from the United Kingdom (Morris *et.al.*, 1977). In Khaw and Barrett-Connor (1987), a 6 gm increment in daily fiber was associated with a 25% reduction in Ischemic Heart Disease (IHD) mortality ($p<0.01$) independent of other dietary variables including total fat. In this study, the fat intakes averaged between 36% to 38% of total kcal. In Morris et al (1977), men with a high energy

intake had a lower rate of CHD than the rest and independently of this, so did men with a high intake of dietary fiber from cereals. Though not included in the statistical analyses, the high energy group had the highest intake of total dietary fat ranging from 41% to 56% of total energy.

Three additional observational studies did not provide information on dietary fat (Burr and Sweetnam, 1982; Liu *et.al.*, 1982; Kromhout and de Lezenne Coulander, 1984).

In summary, of the two out of 7 studies reporting dietary fat intakes and cardioprotective effects of whole grains or dietary fiber, fat intakes ranged from 36% to 56% of total energy intake. Importantly, one of these studies showed total fat intake not to be associated with CHD risk (Khaw and Barrett-Connor 1987)

Intervention Studies

Of the 7 intervention studies discussed, 3 had study designs that did not allow for isolation of fat and fiber interactions since multiple dietary variables relevant to CVD biomarkers were changing at the same time (Keys et al 1965, Kay et al 1985, Schweizer et al 1985).

It is important to note that Kay *et. al.* (1985) fed diets of varying fat and fiber contents for five weeks to 12 moderately hypercholesterolemic subjects in a randomized, crossover study. Increasing dietary fat from 27% to 40% of energy did not diminish the ability of a diet containing 53-55 g fiber per 2,500 kcal to lower TC (175 mg/dl and 186 mg/dl, respectively) or LDLC (117 mg/dl and 122 mg/dl, respectively) compared to a control diet with 40% fat and 19 g fiber per 2,500 kcal. However, the control diet had 617 mg of cholesterol per 2500 kcal while the experimental diets had 252 and 245 mg of cholesterol per 2500 kcal as well as higher linoleic acid and PUFA contents of the diets – making interpretation of these findings difficult.

In 3 studies where total fat levels were controlled, higher dietary whole grain or legume intakes still significantly decreased CVD biomarkers of total and LDL cholesterol (Grande et al 1965, Anderson et al 1984, Karlstrom et al 1984). Grande et al (1965) compared the isocaloric substitution of carbohydrates from leguminous seeds for sucrose in diets containing 40% of total energy from fat and was still able to demonstrate a significant decrease in serum cholesterol concentration with the leguminous seeds. In this study both the level and type of fats [saturated, polyunsaturated, monounsaturated] were controlled. In Anderson et al (1984) the control and test diets provided equivalent energy, fat (37% of total kcal) and cholesterol but the test diets had twice more total and 3-fold more soluble fiber than the control resulting in significantly reduced total and LDL cholesterol in subjects consuming the oat-bran or bean containing diets. Karlstrom et al (1984) compared a diabetic diet, containing 18.9 g dietary fiber per 1600 kcal to a similar higher fiber diet containing 42.4 g dietary fiber per 1600 kcal in a 3 week cross-over study in 14 Type 2 diabetic subjects. The fat content in both diets was 34% of total energy. In addition to the high fiber diet significantly lowering the blood glucose level and urinary glucose excretion, there were significant reductions in LDL triglyceride and cholesterol concentrations. These lipoprotein differences, however, were small.

Finally, one study (Challen *et.al.*, 1983), did not provide information on the fat content of the experimental diets.

In summary, in the 3 out of 7 studies where dietary fat intakes were controlled, there were no indications of attenuating effects on the cardioprotective effects of whole grains or dietary fiber from moderate levels of total dietary fat. In these studies fat intakes ranged between 34 % and 40% of total energy.

b. Literature not cited in *Diet and Health*

Five intervention studies published before 1989 were cited in the 1999 whole grains notification but not in the *Diet and Health* report (de Groot *et.al.*, 1963; Judd and Truswell, 1981; Fraser *et.al.*, 1981; Van Horn *et.al.*, 1986; Van Horn *et. al.* 1988). Four of these studies provide direct evidence that whole grains or vegetables have favorable effects on cardiovascular risk factors. One study (Judd and Truswell, 1981) showed that a diet containing 125 g rolled oats per day reduced T-C in seven of 10 subjects, but the results were only of borderline statistical significance.

Two studies demonstrating beneficial effects of whole grains or vegetables controlled for fat intake with intakes ranging from 30% to 42% of total energy (Van Horn et al 1986, Fraser et al 1981). Van Horn et al (1986) provided 60 gm per day of oatbran or oatmeal to study subjects receiving an AHA fat modified diet containing no more than 30% total energy as fat resulting in significant reductions in total cholesterol by 12 weeks of study. Fraser et al (1981) provided 42% of total kcal as fat while providing 400 kcal/day of whole grains noting significant reductions in total and LDL cholesterol as compared to the control.

The studies conducted by de Groot *et.al.* (1963) and Van Horn *et.al.* (1988) did not provide information on the fat content of the experimental diets.

Of these 5 studies not reported in the original *Diet & Health*, 2 provided sufficient information to evaluate the effects of dietary total fat intake on the cardioprotective effects of dietary whole grains or fiber intakes. The fat intakes ranged from 30 – 42% of total energy.

In summary, the studies discussed in this section provide consistent evidence that whole grain foods can reduce the risk of CHD. In addition, these studies provide no evidence that whole grain containing diets with moderate amounts of

total fat would be less effective in reducing CHD risk than their low-fat counterparts.

2. New scientific evidence corroborating conclusions set forth in *Diet and Health*

The findings published in *Diet and Health* are also corroborated by newer scientific evidence that confirms the cardioprotective properties of whole grain products that are low in saturated fat and cholesterol but not necessarily low in total fat. This body of literature includes 11 review papers as well as 15 observational and six intervention studies published since 1989. A brief discussion of these papers is provided below.

a. Observational studies

A case-control study with 287 females who had experienced acute myocardial infarction (MI) and 659 hospital-based controls with acute disorders unrelated to ischaemic heart disease (IHD) was reported by Gramenzi *et.al.* (1990). CHD incidence was associated with frequency of consumption of meat (1.5 odds ratio (OR) for the upper vs. lower thirds of consumption), ham and salami (1.4), butter (2.3), total fat added to food (1.6) and coffee (2.8). Inverse associations were seen for fish (0.6), carrots (0.4) and moderate alcohol intake (0.7). The only source of whole grain examined in this study (wholemeal bread) was not related to incidence of MI (OR = 1.1), but there was a very narrow range of consumption (1 to 3 servings per week). This study does not provide evidence for a cardioprotective role of whole grains, but the dietary data are very limited and the range of whole grain consumption may have been too narrow to see an effect. In addition, case-control studies are less persuasive than cohort studies due to a variety of methodological limitations.

Unlike the previous study, Fraser *et.al.* (1992) found that the Relative Risk (RR) of nonfatal MI was significantly lower among subjects who usually consumed

whole wheat bread compared to those who usually ate white bread (RR = 0.56; 95% Confidence Interval (CI) 0.35, 0.89). The study was conducted among 26,473 Seventh-Day Adventists living in California who were followed for up to six years. These results were adjusted for age, gender, smoking, physical activity, body weight, hypertension and intake of nuts and beef which were the only other foods found to be related to CHD risk. This study did not provide data on total fat intake or use it to adjust the results. The authors conclude, "A reduction in the incidence of nonfatal myocardial infarction was demonstrated for those who consumed only whole wheat bread."

A cross-sectional cohort study among 850 members of an ethnic minority in China (He *et.al.*, 1995) found that consumption of oats and buckwheat was associated with lower serum lipids. Values for the lowest vs. highest quartile of oat consumption for T-C were 4.03 and 3.59 mmol/L, respectively. Corresponding values for other lipids were LDL-C (1.85 vs. 1.76mmol/L), HDL-C (1.49 vs. 1.23mmol/L) and TGs (1.59 vs. 1.32mmol/L). The effect of oat consumption on T-C and LDL-C was no longer statistically significant after the data were corrected for age, BMI and dietary intakes of energy, cholesterol, alcohol, fat and the ratio of polyunsaturated (PUFA) to saturated (SFA) fatty acids whereas the effect of buckwheat on T-C and LDL-C remained significant with fat intakes ranging from 14% to 25% of total energy. However, the applicability of these data to the U.S. population is limited because the subjects were consuming diets low in fat (14 to 25% of energy), had low T-C levels (average = 150 mg/dL) and were very lean (average BMI = 20.8).

Rimm *et.al.* (1996) reported a significant inverse association of dietary fiber intake and CHD (age adjusted RR = 0.59; 95% CI 0.46, 0.76) among 43,757 male health professionals age 40 – 75 years. These prospective cohort data were based on 734 cases of MI during a six-year follow-up period. The inverse association remained statistically significant after the data were corrected for saturated fat, vitamin E, age, BMI, physical activity, smoking, alcohol,

hypertension, hypercholesterolemia, family history of MI and profession.

Multivariate analysis of these data by source of fiber showed that the inverse association of cereal fiber and MI (RR = 0.71; 95% CI = 0.54, 0.92) was stronger than fiber from fruit (RR = 0.81; 95% CI = 0.62, 1.06) or from vegetables (RR = 0.83; 95% CI = 0.64, 1.08) after adjusting for the variables listed above. Total fat was not used to adjust the data in this study; presumably because it was not shown to be a risk factor for CHD in this population. The authors observed:

Most of the available epidemiological evidence strongly supports an inverse association between fiber and coronary heart disease. Some have argued that the inverse association between fiber and coronary heart disease can partially be explained by a displacement of fat in the diet. Our results suggest the contrary; among participants in the Health Professionals Follow-up Study, the positive association between saturated fat intake and coronary heart disease is almost entirely explained by lower fiber intake among the men who consumed more fat.

Pietinen *et.al.* (1996) also reported an inverse association between dietary fiber and CHD mortality in a prospective cohort study of 21,930 Finnish subjects followed for 6.1 years. The RR of fatal CHD among the upper quintile of dietary fiber intake compared to the lowest was 0.73 (95% CI = 0.56, 0.95) after adjustment for age, smoking, BMI, blood pressure, education, physical activity and dietary intakes of energy, alcohol, saturated fatty acids, beta-carotene, vitamin C and vitamin E. Intake of rye products (a source of whole grain) was also inversely associated with CHD fatality after adjustment for these variables (RR = 0.75; 95% CI = 0.58, 0.98) as was cereal fiber (RR = 0.74; 95% CI = 0.57, 0.96), but not fiber from vegetables (RR = 0.88; 95% CI = 0.66, 1.10) or fruits (RR = 1.16; 95% CI = 0.08, 1.68). Total fat intakes were available but not reported nor used to adjust the data in this study. The authors conclude, "These findings suggest that independent of other risk factors, greater intake of foods rich in fiber can substantially reduce the risk of coronary heart disease, and particularly coronary death, in middle-aged, smoking men."

Intake of whole grain products was found to be inversely associated with CHD mortality independent of dietary fiber in a cohort of 34,492 postmenopausal women aged 55 – 69 followed for up to 9 years (Jacobs *et.al.*, 1998). The RR of death due to IHD was 0.6 (95% CI = 0.45, 0.81) for the highest quintile of total whole grain servings per week compared to the lowest after adjustment for age and energy intake. This inverse association remained significant (RR = 0.7; 95% CI = 0.5, 0.98) after additional adjustment for education, marital status, hypertension, diabetes, BMI, waist-to-hip ratio, physical activity smoking, alcohol intake, vitamin supplement use, oral contraceptive use, estrogen replacement therapy, Keys score, and dietary intake of fruit and vegetables (except juice), red meat, fish and seafood as well as sucrose. Total fat intake was not provided, nor was it used to adjust the data. The authors concluded that there is a clear inverse association between whole-grain intake and risk of IHD death.

Liu *et.al.* (1999) reported that consumption of whole grain foods was inversely associated with the incidence of fatal and non-fatal CHD in a cohort of 75,521 women aged 38-63 years. Participants were members of the Nurses' Health Study cohort and were followed prospectively for a period of 10 years. After adjustment for age and smoking, whole grain intake was inversely associated with risk of CHD. RRs from lowest to highest quintile of intake were 1.0, 0.92, 0.93, 0.83, 0.75 (95% CI for the upper quintile compared to the lowest was 0.54, 0.84). Further adjustment for BMI, post-menopausal hormone use, alcohol intake, multivitamin use, vitamin E supplement use, aspirin use, physical activity and types of fat intake did not appreciably change the results: RRs for quintiles of whole grain consumption were 1.0, 0.92, 0.93, 0.83, 0.75 (95% CI 0.59, 0.95). The RRs remained virtually unchanged when types of fat (i.e. SFA, PUFA, MUFA and TFA) were added to the multivariate model as a group. Fat intakes as % of total energy were not available. This result strongly suggests that the type of fat intake does not attenuate the beneficial effect of whole grains on CHD mortality. These researchers concluded, "Increased consumption of whole grains may protect against CHD."

Following two years of additional data collection, the Nurses' Health Study cohort was examined again for a relationship between whole grain consumption and CVD (Liu *et.al.*, 2000). A sample of 75,521 women 38-63 years of age was followed for of 12 years. Whole grain consumption was significantly associated with reduced incidence of stroke after adjustment for age: RRs for quintiles of consumption were 1.0, 0.68, 0.69, 0.49, 0.57 (the 95% CI did not include unity for quintiles 2 through 5). This association remained significant after adjustment for smoking: RR for the upper quintile = 0.64; (95% CI = 0.47, 0.89) and numerous CVD risk factors (RR = 0.69; 95% CI = 0.50, 0.98) including SFA, TFA and total energy intake, but total fat was not adjusted for. The authors concluded, "In this cohort, higher intake of whole grain foods was associated with a lower risk of ischemic stroke among women, independent of known CVD risk factors. These prospective data support the notion that higher intake of whole grains may reduce the risk of ischemic stroke."

Whole grain consumption was inversely associated with all-cause mortality in a cohort of 38,740 Iowa women aged 55-69 years during a 9-year follow up period (Jacobs *et.al.*, 1999). Median whole grain consumption ranged from 1.5 servings per week in the lowest quintile to 22.5 servings per week in the highest. RRs for total mortality after adjustment for age and energy intake were 1.0, 0.76, 0.65, 0.66, 0.64 (the 95% CI did not include unity for any of the second through fifth quintiles). Analogous results after adjustment for age, energy intake, educational attainment, marital status, hypertension, diabetes, CHD, cancer, BMI, waist-to-hip ratio, age at first childbirth, physical activity, cigarette smoking, alcohol intake, vitamin supplement use, estrogen replacement therapy, total fat and saturated fat intake [values not reported], and intake of fruits, vegetables, red meat, fish and seafood were: RR= 1.0, 0.95, 0.87, 0.81, 0.86 (the 95% CI did not include unity for quintiles 3 through 5). Whole grain consumption was significantly associated with reduced incidence of cancer and total cardiovascular disease (CVD), but not to CHD itself. The associations were not explained by dietary fiber the authors

concluded, "Substitution of whole for refined grain may reduce chronic disease risk in the United States."

An analysis of the Iowa Women's Health Study cohort (Jacobs *et.al.*, 2000) reported that fiber from whole grains, but not from refined grains, was associated with reduced all-cause mortality. A population of 11,040 postmenopausal women was followed for 11 years. Women who consumed predominantly whole grain fiber (an average of 1.9 g and 4.7 g refined and whole grain fiber per 2,000 calories, respectively) had a 17% lower all-cause mortality rate than women who consumed diets predominant in refined grain fiber (RR = 0.83; 95% CI = 0.73, 0.94) after adjustment for age and a wide range of dietary, anthropometric, life-style and medical risk factors including total fat. The mean intakes of total fat as % of energy intake for the predominately whole grain group were 33.4%. As noted in a previous study with this cohort (Jacobs *et.al.*, 1999), whole grain consumption was not specifically associated with mortality due to CHD itself. The authors conclude that public health policy should recommend increased consumption of whole grain foods.

A study of 51,529 U.S. health professionals (Hu *et.al.*, 2000) reported that individuals who consistently followed a "prudent" dietary pattern characterized by whole grains, vegetables, fruits, fish and poultry experienced significantly lower incidence of CHD than subjects who followed a "Western" pattern characterized by higher intakes of refined grains, meats, sweets, french fries, and high-fat dairy products. After adjustment for age and CHD risk factors (excluding saturated fatty acids), the RRs for CHD from the lowest to highest scores of the "prudent" pattern were 1.0, 0.87, 0.79, 0.75, 0.90 (95% CI = 0.56, 0.86). Total fat intakes as a % of energy were not provided. There was an analogous increase in CHD risk for increasing scores for the "Western" dietary pattern. Although the effect of whole grains on CHD could not be isolated from other dietary components in this analysis, it is consistent with the hypothesis that whole grains reduce the risk of CHD.

Liu *et.al.* (2002) examined the relationship between dietary fiber and incidence of CVD and CHD using the Nurses' Health Study cohort of 39,876 female health professionals. During a six-year follow-up period, age-adjusted incidence of CVD was inversely associated with dietary fiber intake (RR for lowest to highest quintile = 1.0, 0.71, 0.72, 0.64, 0.65; 95% CIs did not contain unity for quartiles 2 through 5). Analogous results for MI were RR = 1.0, 0.54, 0.54, 0.43, 0.46; 95% CIs did not contain unity for quartiles 2 through 5. However, adjustment for age, randomized treatment assignment, smoking, exercise, alcohol intake, hormone replacement therapy, BMI, use of multivitamin supplements, hypertension, hypercholesterolemia, diabetes, parental history of MI before age 60 and dietary folate, total fat, protein and energy attenuated both of these associations so that they were no longer statistically significant. The authors speculate that other characteristics of fiber-containing foods, rather than the fiber itself, may be responsible for the unadjusted inverse association of dietary fiber. It was concluded, " these prospective data generally support current dietary recommendations to increase the consumption of fiber-rich whole grains, and fruits and vegetables as a primary preventive measure against CVD. This conclusion is particularly relevant in light of a previous analysis of this cohort (Liu *et.al.*, 1999) that found a significant inverse association between whole grain consumption and CHD incidence.

Another study of the effect of a "prudent" dietary pattern including whole grain foods was reported by Michels and Wolk (2002) using a Swedish cohort of 59,038 women born between 1914 and 1948. The frequency of consumption of "recommend foods" (RF) including whole grain breads, cereals, fruits, vegetables, fish and low-fat dairy products was inversely associated with age-adjusted all-cause mortality. RRs for the lowest to highest quintile were 1.0, 0.78, 0.72, 0.68, 0.71; 95% CIs did not include unity for quintiles 2 through 5. Adjustment for age, height, BMI, number of children, age at first birth, education, marital status, alcohol consumption, energy intake and consumption of "not recommended

foods” (e.g. red meats, refined carbohydrates including sugars and foods high in saturated or *trans* fats) but not total fat intakes did not significantly alter this association. The intake of “not recommended foods” was not associated with all-cause mortality in this cohort. It is not possible to isolate the effect of whole grain foods from this study because multiple dietary factors were considered simultaneously. Nevertheless, the study provides suggestive evidence that whole grain foods promote health. The authors concluded, “A healthy diet can affect longevity. It appears more important to increase the number of healthy foods regularly consumed than to reduce the number of less healthy foods regularly consumed.”

Whole grain consumption was found to be favorably associated with risk factors for CVD and type 2 diabetes in the Framingham Offspring Study cohort (McKeown *et.al.*, 2002). This cross-sectional study of 2,941 subjects found that whole grain intake was inversely associated with BMI, waist-to-hip ratio, diastolic blood pressure, T-C, LDL-C, TG, fasting glucose and fasting insulin after adjustment for age, sex, energy intake, treatment of hypertension, smoking, alcohol use, multivitamin use, estrogen use, physical activity, BMI, percent energy from SFA and PUFA as well as intake of meat, fish, fruit and vegetables. Dietary intakes of total fat as % of total energy were not provided nor were used to adjust the data. The authors concluded that increased intake of whole grains may reduce disease risk by exerting favorable affects on metabolic risk factors.

Liu *et.al.* (2003) reported an inverse association between consumption of whole grain breakfast cereals and deaths due to CVD and CHD among 86,190 members of the Physicians’ Health Study cohort during a 5.5-year follow-up period. Whole-grain breakfast cereal intake was inversely associated with total and CVD-specific mortality, independent of age; body mass index; smoking; alcohol intake; physical activity; history of diabetes, hypertension, or high cholesterol; and use of multivitamins. The multivariate RR for CVD mortality for subjects who consumed ≥ 1 serving per day of these foods was 0.8 (95% CI =

0.66, 0.97) compared to participants who rarely consumed these foods. Analogous results for MI were RR = 0.71 (95% CI = 0.51, 0.98). The data were not adjusted for total fat or other dietary factors and total fat intakes were not reported. Cereals from refined grains were not associated with mortality from CVD or MI. The authors concluded, "These prospective data highlight the importance of distinguishing whole-grain from refined grain cereals in the prevention of chronic diseases."

In summary, the observational studies published since *Diet and Health* confirm the validity of the authoritative statement that is the basis for this notification. Eight studies provide direct evidence that whole grain foods (or dietary fiber) reduce the risk of CHD or CVD (Fraser *et.al.*, 1992; Rimm *et.al.*, 1996; Pietinen *et.al.*, 1996; Jacobs *et.al.*, 1998; Liu *et.al.*, 1999; Liu *et.al.*, 2000; McKeown *et.al.*, 2002 and Liu *et.al.*, 2003

Five studies provided suggestive evidence that whole grains are cardioprotective. He *et.al.* (1995), Jacobs *et.al.* (1999) and Liu *et.al.* (2002) reported that whole grains or dietary fiber were associated with reduced incidence of CHD, but the results were no longer statistically significant after adjustment for multiple potentially confounding variables. Hu *et.al.* (2000) and Michels and Wolk. (2002) reported that diets with "healthy" foods (including whole grains) were associated with reduced risk of CHD.

Only two studies failed to provide support for the cardioprotective properties of whole grain foods. No association was seen in a case-control study by Gramenzi *et.al.* (1990) and Jacobs *et.al.* (2000) reported a significant association between whole grains and all-cause mortality, but not for CHD after adjustment for potentially confounding variables.

As with the studies cited in *Diet and Health*, none of these observational studies provides evidence that the fat content of whole grain diets influences their

cardioprotective effect. It appears the majority of these investigators did not consider total fat as a significant factor impacting the effectiveness of whole grains or fiber on protection from CHD or CVD (*Diet and Health* at 7; National Cholesterol Education Program, 2001; Food and Nutrition Board, 2002) (see Part VIII below.)

Two studies (Hu *et.al.*, 2000; Michels *et.al.*, 2002) examined the effect of dietary patterns (i.e. whole grains in conjunction with other foods) on CHD risk, which does not allow for assessment of the effect of total fat content on the cardioprotective properties of whole grains *per se*.

Of the more recent 13 observational studies demonstrating the cardioprotective effects of whole grains or fiber, only four included fat intake data. Liu et al (1999) found that the inverse association between whole grain foods and CHD remained after the data were adjusted for type of fat. The remaining three studies found that adjustment of the data for multiple factors including total fat intake eliminated an inverse association between whole grains or dietary fiber and CHD seen in the uncorrected data. One of these studies (Liu *et.al.*, 2002) examined dietary fiber (not whole grains), and the authors hypothesized that the unadjusted protective effect they observed may have been due to non-fiber constituents of whole grain foods. The other two studies (He *et.al.*, 1995; Jacobs *et.al.* 1999) found that the inverse association between whole grain foods and risk of CHD was eliminated by a correction for total fat, but numerous factors including age, total energy intake, educational attainment, marital status, high blood pressure, diabetes, CHD, cancer, BMI, waist-to-hip ratio, age at first childbirth, physical activity, cigarette smoking, alcohol intake, use of vitamin supplements, estrogen replacement therapy, and the intake of saturated fat, fruits and vegetables, red meat as well as fish and seafood were adjusted simultaneously. Therefore, it is not possible to determine the relative importance of total fat intake, compared to other potentially confounding variables, in eliminating the statistical significance seen in the uncorrected data.

In conclusion, as with the studies published prior to *Diet and Health*, the newer observational studies discussed in this section provide consistent evidence that whole grains can reduce the risk of CHD, but fail to reveal evidence that diets with moderate amounts of total fat, but low in saturated fat and cholesterol, are any less effective than their low fat counterparts.

b. Intervention studies

A secondary prevention trial of CHD was conducted by Burr *et.al.* (1989) among 2,033 men (average age 56 years) who had recovered from MI. The subjects were randomized into one of four dietary treatments including a group who were instructed to increase intake of cereal fiber. Subjects in this group were successful in approximately doubling cereal fiber intake at six months (19 vs. 9 g per day in the control group) and at two years (17 vs. 9 g per day). There were no differences in the reoccurrence of IHD events or all-cause mortality between the fiber group and controls during a two-year follow-up period. No information on dietary fat or other constituents was provided for the fiber vs. control groups. This study does not provide evidence that dietary fiber can reduce the risk of CHD, but several factors limit its applicability. All subjects in this study had established heart disease (many were taking medications) and therefore do not reflect the healthy U.S. population. The intake of whole grain foods was not reported, and it is possible that dietary fiber acts to reduce the risk of CHD in healthy individuals, but is ineffective after CHD is already established.

Van Horn *et.al.* (1991) studied the effect of instant oats on serum lipids when added to the diet of 80 male and female, moderately hypercholesterolemic volunteers (average age 42 years). This study used a randomized parallel design and the intervention period was eight weeks. The participants were stratified on the basis of gender and baseline serum cholesterol (above or below 6.34 mmol/L). The experimental group was asked to isocalorically substitute

56.7 g of instant oats per day for other sources of dietary carbohydrate. Subjects in the oat group experienced significant decreases in T-C (0.32 mmol/L; 95% CI = 0.09, 0.54) and LDL-C (0.25 mmol/L; 95% CI = 0.02, 0.48) compared to controls at the end of the intervention period. Subjects with baseline cholesterol concentrations greater than 6.34 mmol/L experienced a greater decline in serum lipids (data not provided). There were no changes in HDL-C or body weight during the study. Interpretation of this study is complicated by the fact that the self-selected diets between the experimental and control groups differed not only in the components of oats (e.g. total fiber, soluble fiber), but also in total fat, SFA, MUFA and several other nutrients. These differences (which were small, but statistically significant) may have partially explained the observed changes in serum lipids. The mean total fat intakes reported as % of total energy were 36.2% for the experimental group and 39.8% for the control group. Nevertheless, results of the study are impressive because oats were shown to be hypocholesterolemic when fed as part of a typical American diet (approximately 37% of energy from fat). The authors conclude, "Daily inclusion of two ounces of oats appeared to facilitate reduction of serum total cholesterol and LDL-C in these hyperlipidemic individuals."

Davidson *et.al.* (1991) conducted a dose-response feeding study using oatmeal, oat bran or farina among 156 adults with LDL-C levels above 160 mg/dL or between 130 and 160 mg/dL. The study used a randomized, placebo-controlled, parallel design with farina serving as the placebo. After six weeks of treatment, subjects who consumed 84 g/d of oatmeal, 56 g/d of oat bran or 84 g/d of oat bran experienced significant reductions in both T-C and LDL-C compared to the farina control. LDL-C decreased in these groups by 10.1, 15.9 and 11.5%, respectively. There were no significant changes in HDL-C or serum TGs. The fat content of the diets (approximately 26% of total energy) did not change during the experiment, and there was no significant difference in BMI. The authors conclude, "A dose-dependent reduction in LDL-C levels with oat cereals supports the independent hypocholesterolemic effects of β -glucan."

Johnston *et.al.* (1998) studied the effect of feeding a whole grain cereal (Cheerios[®]) compared to a non-whole grain control (corn flakes) on the serum lipids of 135 mildly hypercholesterolemic volunteers. The study used a randomized, parallel design and provided the test cereals for six weeks as part of a Step 1 diet. Subjects who consumed the whole grain cereal achieved a 3.8% reduction in T-C ($p = 0.0008$) and a 4.5% decrease in LDL-C ($p = 0.0065$). HDL-C and body weight were not different between the two groups. There were no significant differences in total fat between the control and experimental groups at the end of the treatment period with post-treatment mean intakes of 22.5% of total energy for the control group and 26.5% for the experimental group. The authors conclude, “ individuals can adhere to a cholesterol-lowering diet that includes a whole grain oat cereal that is readily available, convenient to consume, and easy to incorporate into a daily eating plan.”

The effect of replacing refined rice with a mixture of whole-grains and legumes on various CVD risk factors among coronary artery disease patients was reported by Jang *et.al.* (2001). Seventy-six male patients were randomly assigned to consume the whole grain/legume mixture or continue their usual diet for 16 weeks. The use of anti-hypertensive and lipid-lowering drugs was continued throughout the experiment. Subjects in the whole grain/legume group had higher serum HDL-C concentrations, and experienced significant beneficial effects on fasting glucose, insulin, homocysteine concentrations and lipid peroxidation values compared to the controls. There were no differences in T-C or LDL-C between the two groups. The dietary fat content of all diets did not differ between groups with estimates of daily mean intakes of 16.1 % for the control group and 19.5% for the experimental group This study provides suggestive evidence that whole grains exert a beneficial affect on serum lipids, but interpretation is limited due to the fact that whole grains were provided in combination with legumes, seeds and vegetables. In addition, the study does not reflect the healthy U.S. population because the subjects were CHD patients continuing to receive medications for hypertension or hyperlipidemia.

Jacobs *et.al.* (2002) used a randomized, crossover protocol to study the effect of whole grain consumption on enterolactone concentrations in 12 overweight, hyperinsulinemic, non-diabetic men and women aged 26-54 years. Subjects were randomized to diets containing whole grain foods (wheat, oats and rice) or refined grain foods for six weeks and then switched to the opposite diet after a 6-9 week washout period. Enterolactone is a lignan that may protect against CHD and breast cancer. Results of the study showed that whole grain feeding resulted in a significant increase in the serum concentrations of this compound. The total fat content of the diets was not provided. It was concluded that diets rich in whole grains could increase the concentration of serum enterolactone.

In summary, five of the six intervention studies conducted since *Diet and Health* provide direct or suggestive evidence that whole grain foods can reduce the risk of CHD (Van Horn *et.al.*, 1991; Davidson *et.al.*, 1991; Johnston *et.al.*, 1998; Jang *et.al.*, 2001; Jacobs *et.al.*, 2002).

Only one study (Burr *et.al.*, 1989) failed to support the notion that whole grain foods are cardioprotective, but this study utilized dietary fiber rather than whole grain foods and is not applicable to the healthy U.S. population because it was conducted with MI patients.

As with the studies cited in *Diet and Health*, none of these intervention trials provide evidence that the fat content of whole grain diets influences their cardioprotective effect. Mean total dietary fat intakes were reported in 4 of the 6 studies and ranged from 26.5% to 36.2% of energy in the experimental groups.

In conclusion, as with the studies published prior to *Diet and Health*, the newer intervention studies discussed in this section provide consistent evidence that whole grains can reduce the risk of CHD, and fail to provide evidence that diets