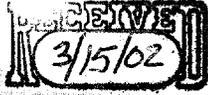


CALIFORNIA



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**HEALTH CLAIM PETITION:  
DIETS INCLUDING WALNUTS CAN REDUCE  
THE RISK OF HEART DISEASE**

March 15, 2002

**California Walnut Commission**

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CP 1

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March 15, 2002

PETITIONERS: California Walnut Commission

ADDRESS: 1540 River Park Drive, Suite 203  
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SUBJECT: Health Claim Petition: Diets Including Walnuts Can Reduce The Risk Of  
Heart Disease

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## I. Introduction

The undersigned, Dennis A. Balint, Chief Executive Officer, submits this petition on behalf of the California Walnut Commission pursuant to Section 403(r)(4) of the Federal Food, Drug & Cosmetic Act (FD&C Act), 21 U.S.C. § 343(r)(4), requesting that FDA approve, for use in the labeling of foods comprising whole and chopped walnuts, health claims communicating that diets including walnuts can reduce the risk of coronary heart disease (CHD).

All of the items specified in 21 C.F.R. § 101.70(f) are included in or attached to this petition.

The California Walnut Commission is a non-profit statutory corporation with all of the powers of a California corporation. Cal. Food & Agric. Code § 77064. The Commission is expressly empowered to engage in research, including the dissemination and publication of the results of that research, so that the public may be made aware of accurate and scientific information relative to human nutrition and of the beneficial qualities of walnuts. *Id.* §§ 77003 & 77095.

As discussed below and in the accompanying literature review conducted by the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences (Attachment 1), the scientific evidence establishes that diets including walnuts can reduce the risk of CHD by lowering serum total and low-density lipoprotein (LDL) cholesterol levels and other cardioprotective mechanisms. The cardioprotective benefits of diets including walnuts have been attributed to the favorable fatty acid and overall nutrient profile of walnuts. Walnuts, like other tree nuts, are low in saturated fatty acids and rich in monosaturated and polyunsaturated fatty acids. In addition, walnuts are important sources of protein, dietary fiber, micronutrients, and bioactive phytochemicals that may contribute to the cardioprotective benefits established for diets including walnuts. While the body of scientific evidence suggests that the benefits of walnuts are attributable to multiple favorable metabolic mechanisms, the evidence linking the unique fatty acid profile of walnuts to the cholesterol-lowering effects established has been characterized most fully.

Walnuts are well recognized as being among the most concentrated dietary sources of  $\alpha$ -linolenic acid available. Alpha-linolenic acid is an omega-3 fatty acid essential for human health, and functions as the parent compound used by the body to synthesize the omega-3 fatty acids commonly found in fish and fish oils, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Chronic, widespread undernutrition of  $\alpha$ -linolenic acid and other omega-3 fatty acids has been documented in the United States and is attributable to both the underconsumption of omega-3 fatty acids and the overconsumption of omega-6 fatty acids from vegetable oils and other commonly consumed foods. It is well established that the imbalance of fatty acids currently consumed in the U.S. and other Western industrialized nations is grossly distorted in relation to actual human nutritional needs and is an important contributor to the high

risk of CHD morbidity and mortality. Public health experts in the United States and other industrialized countries have issued dietary recommendations for  $\alpha$ -linolenic acid and other omega-3 fatty acids and called for aggressive measures to remedy dietary deficiencies of these nutrients to reduce the risk of CHD.

This petition requests that FDA authorize, for use in the labeling of whole and chopped walnuts, health claims that are consistent with the following model claim: "Diets including walnuts can reduce the risk of heart disease." This claim satisfies all applicable legal requirements, and would promote public health by encouraging improvements in omega-3 fatty acid intake, through increased walnut consumption, and by promoting the reductions in serum cholesterol that occur when walnuts are included in the diet.

The proposed health claim is fully consistent with current nutritional guidelines recommending moderate fat intake and modest intake of saturated fat and cholesterol. Approving the claim would afford FDA an opportunity to facilitate health communications with consumers concerning the cardioprotective and nutritional benefits of walnuts that, because of their total fat content, have been excluded from the diets of many consumers including those relying on the total fat declaration required in the Nutrition Facts box to guide food choices. FDA approval of the proposed health claim would help remedy the widespread consumer confusion concerning fat intake, and would encourage fatty acid intake patterns that reduce CHD risk and support nutritional health generally.

## **II. Preliminary Requirements**

Under FD&C Act § 403(r)(1)(B), 21 U.S.C. § 343(r)(1)(B), FDA is required to allow food manufacturers to promote the health benefits of their products by means of labeling claims "characteriz[ing] the relationship of any nutrient . . . to a disease or health-related

condition,” where such claims are substantiated by appropriate scientific evidence. FDA implementing regulations expand upon the statutory requirements for approving health claims, specifying that health claim petitions must provide information addressing several prescribed “Preliminary Requirements.” 21 C.F.R. § 101.70(f). The proposed walnut/CHD health claim satisfies all applicable preliminary requirements under FDA rules.

First, a health claim petition must establish that the article that is the subject of the claim qualifies as a “substance,” which is defined as “a specific food or component of food, regardless of whether the food is in conventional food form” or another form. 21 C.F.R. § 101.14(a)(2). Claims characterizing the relationship between diets containing walnuts and the reduced risk of CHD concern the benefit of walnuts, a food constituting a “substance” within the meaning of FDA regulations.

Second, a health claim petition must establish that “the substance . . . [is] . . . associated with a disease or health-related condition for which the general U.S. population . . . is at risk . . . .” 21 C.F.R. § 101.14(b)(1). As already recognized by FDA in the existing regulations authorizing health claims, CHD constitutes a “disease or health-related condition” within the meaning of FDA rules. *See, e.g.*, 21 C.F.R. §§ 101.75, 101.77, 101.81, 101.82, 101.83. The relationship between walnuts and the reduced risk of CHD satisfies the second preliminary requirement.

Third, a health claim petition must establish that the substance that is the subject of the claim meets the definition of “food,” being consumed principally for taste, aroma or nutritive value. 21 C.F.R. § 101.14(b)(3)(1). Walnuts have a long history of use as human food, and walnut consumption for food purposes has been documented from as early as 7000 BC in Persia. *See* LSRO Review 20. While the safety and sensory attributes of walnuts help explain

the long history of walnut consumption as human food, the scientific evidence characterizing the distinctive nutritional and health benefits of walnuts has further justified the value of walnuts as human food. The growing recognition among nutritional scientists concerning imbalance in the consumption of omega-6 relative to omega-3 fatty acids, and the increasing appreciation of the link between omega-3 fatty acid imbalance and deficiency and CHD risk, have helped to establish the distinctive nutritional importance of walnuts. Data demonstrating the presence in walnuts of other significant bioactive substances, such as phytosterols, also illustrate the nutritive value of this food.

Fourth, a health claim petition must establish that foods qualifying for the proposed health claim are safe and otherwise lawful. 21 C.F.R. § 101.14(b)(3)(ii). The long history of consumption of walnuts as human food at a wide range of intake levels firmly establishes the safety of walnut consumption. Since the proposed walnut/CHD health claim would apply to walnuts only, and not to oils, or other extracts or isolates derived from walnuts, the existing limits on walnut consumption enforced by the ordinary mechanisms of human satiety would continue to safeguard public health. For those persons who are allergic to walnuts, the existing FDA food labeling requirements for walnuts would continue to ensure the continued safe use of the food. *Cf.* 64 Fed. Reg. at 57,707 (“FDA does not believe that, because some persons may have allergic reactions to a food, it is unsafe.”).

### **III. Standard for Review of Petition**

Section 403(r)(3)(B)(i) of the FD&C Act directs FDA to authorize a health claim when it finds, “based on the totality of publicly available scientific evidence . . . there is significant scientific agreement, among [qualified] experts . . . , that the claim is supported by such evidence.” 21 U.S.C. § 343(r)(3)(B)(i). This “significant scientific agreement” standard is flexible, and enables FDA to approve well supported health claims without regard to the specific

nature of the scientific evidence the claim relies on. At the same time, FDA's discretion to deny approval of a health claim is confined to those claims that the agency establishes are false or inherently misleading. *In re R.M.J.*, 455 U.S. 191, 203 (1982); *Ibanez v. Florida Dep't*, 512 U.S. 136, 144-46 (1994); *Peel v. Attorney Registration and Disciplinary Comm'n*, 496 U.S. 91, 99-111 (1990). In addition, FDA does not have authority to deny potentially misleading claims that can be expressed in a manner that accurately characterizes the nature and weight of the substantiating scientific evidence.

While the specific language of the "significant scientific agreement" standard is distinctive, the anti-deception principles the standard embodies are not. The legal standards which govern determinations concerning the potential for consumer-directed claims to mislead are well characterized in the large and consistent body of case law enforcing the antideception requirements of federal and state consumer protection statutes, including cases interpreting provisions of the Federal Trade Commission Act in the context of health messages. It is well established that claims substantiated by competent and reliable scientific evidence are not deceptive and, therefore, cannot be prohibited on antideception grounds. *See, e.g.*, Federal Trade Commission Act §§ 12 & 15, 15 U.S.C. §§ 52 & 55; FTC, Dietary Supplements: **An Advertising Guide for Industry** (1998) (available at <http://www.ftc.gov/bcp/online/pubs/buspubs/dietsupp.htm>); FTC, Policy Statement Regarding Advertising Substantiation ("reasonable basis") (available at <http://www.ftc.gov/bcp/guides/ad3subst.htm>); FTC, Policy Statement on Deception (October 14, 1983) (available at <http://www.ftc.gov/bcp/policystmt/ad-decept.htm>); FTC, Enforcement Policy Statement on Food Advertising § II (May 1994) (a claim must have a "reasonable basis," meaning that it must be supported by "competent and reliable scientific evidence") (available at

<<http://www.ftc.gov/bcp/policystmt/ad-food.htm>>). The corresponding relationship between the established antideception legal standards and the scope of First Amendment protection of commercial speech means that any exercise of government power to block the dissemination of health claims which are substantiated by competent and reliable scientific evidence is vulnerable to constitutional challenge. *See National Commission on Egg Nutrition v. FTC*, 570 F.2d 157 (7th Cir. 1977), *cert. denied*, 439 U.S. 821 (1978). *See also* Daniel E. Troy, Advertising: Not “Low Value” Speech, 16 Yale J. on Reg. 85, 92 (1999).

In *Pearson*, the United States Court of Appeals for the District of Columbia Circuit evaluated the FDA policy interpreting the “significant scientific agreement” standard, as FDA has applied that standard to restrict health claims—not only for dietary supplements, but also for conventional foods. *See* 59 Fed. Reg. 395,403 (January 4, 1994) (“Applying the same standard and procedure to health claims on dietary supplements as that [sic] that applies to foods in conventional food form . . . will subject all segments of the food industry to regulation in a fair and consistent manner.”); Brief for Appellees in *Pearson v. Shalala* (No. 98-5043) (D.C. Cir.) at 6, 8 (confirming that FDA adopted a policy “subject[ing] dietary supplements to the same standard that applies to foods in conventional form”). FDA presented the panoply of arguments it has made repeatedly since the NLEA was adopted to excuse its health claims policy from First Amendment scrutiny on the ground that health claims are inherently misleading and require uniquely tight regulatory controls. The *Pearson* court rejected the longstanding FDA rationale in full:

“As best we understand the government, its first argument runs along the following lines: that health claims lacking ‘significant scientific agreement’ are inherently misleading because they have such an awesome impact on consumers as to make it virtually impossible for them to exercise any judgment *at the point of sale*. It would be as if the consumers were asked to buy something while

hypnotized, and therefore they are bound to be misled. We think this contention is almost frivolous.” 164 F.3d at 655.

It is well established in Supreme Court case law that claims that are not inherently misleading cannot be prohibited, and even claims that have some potential to mislead cannot be restricted by means of qualifying language unless the specific restriction is established to be necessary and effective in remedying genuine deception. On remand in *Pearson*, the District Court noted that the Court of Appeals “implied, though it did not declare explicitly, that when ‘credible evidence’ supports a claim . . . that claim may not be absolutely prohibited.” *Pearson v. Shalala*, 130 F. Supp. 2d 105, 114 (D.D.C. 2001) (citation omitted). *See also Ibanez v. Florida Dep’t*, 512 U.S. 136, 143 (1994) (the government’s “burden is not slight”); *Edenfield v. Fane*, 507 U.S. 761, 770-71 (1993) (the government’s “burden is not satisfied by mere speculation or conjecture; rather, a governmental body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree.”) (citations omitted). *See also* Edward Dunkelberger & Sarah E. Taylor, *The NLEA, Health Claims, and the First Amendment*, 48 *Food & Drug L. J.* 631 (1993); *International Dairy Foods Ass’n v. Amestoy*, 92 F.3d 67 (2d Cir. 1996).

The approval of a health claim by FDA reflects the agency’s recognition that the scientific evidence substantiates the characterization of the diet/disease relationship expressed in the claim, and that the substantiation accounts for the “totality of publicly available scientific evidence,” as that term would be understood by “experts qualified by scientific training and experience” to evaluate the scope of information relevant in evaluating the proposed claim. 21 C.F.R. § 101.14(c). In this respect, the standard is consistent with the guidance the Federal Trade Commission (FTC) has provided concerning the importance of evaluating scientific evidence in the context of the entire body of relevant scientific evidence. *See* FTC, *Dietary*

Supplements: An Advertising Guide for Industry § II. B (1988) (available at <http://www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.htm>) (“The surrounding context of the scientific evidence is just as important as the internal validity of individual studies.”). In the context of nutritional claims for foods, FTC, like FDA, has recognized the necessity of considering specific studies together with the overall weight of the relevant scientific evidence in the public domain. FTC, Enforcement Policy Statement on Food Advertising § IV.A (May 1994) (available at <http://www.ftc.gov/bcp/policystmt/ad-food.htm>) (In evaluating health claims for foods, both FTC and FDA “look to well-designed studies, including clinical research and other forms of reliable and probative scientific evidence,” and “evaluate[,] substantiation. . . in the context of the surrounding body of evidence . . .”).

As discussed in detail in Part IV of this petition, a sound, valid and consistent body of scientific evidence supports the claim that diets containing walnuts lower total and LDL cholesterol and can help reduce the risk of CHD. The studies demonstrating this substance/disease relationship were controlled clinical trials, and the data from these trials are corroborated by data from large-scale, long-term prospective cohort studies. The studies appropriately specified and measured the substance and disease that are the subject of the proposed claim, and were conducted with scientific accuracy and integrity. The results were consistent across a variety of settings and subject populations. The LSRO Expert Panel concluded that the clinical trials were well designed, executed and controlled, and found the observational studies to be “supportive” of the clinical data. LSRO Review 28. Based upon the entire body of relevant scientific evidence, the LSRO Expert Panel concluded that walnuts, as part of a heart-healthy diet, lower blood cholesterol concentrations. LSRO Review 29.

As the LSRO review recognizes, and as the discussion below shows, based on the totality of the publicly available scientific evidence, there is significant scientific agreement that diets including walnuts can reduce the risk of CHD, including by lowering total and LDL cholesterol levels. Because the proposed health claim satisfies all legal requirements of the NLEA, the claim is entitled to approval by FDA.

#### **IV. Statement of Grounds**

##### **A. Scientific Overview**

###### **1. Public Health Importance of CHD Health Claims**

CHD is the most common and serious form of cardiovascular disease and the leading cause of death and disability in the United States, accounting for more deaths than any other disease or group of diseases. Reducing CHD risk is a national public health priority, and substantial research, public health and medical resources have been devoted to programs aimed at reducing CHD risk in the United States. It is well established that dietary modifications which can reduce elevated serum cholesterol levels have substantial power to reduce CHD risk. *See, e.g.,* 64 Fed. Reg. 57,700, 57,700 (October 26, 1999) (“ . . . [T]here is general agreement that elevated blood cholesterol levels are one of the major ‘modifiable’ risk factors in the development of CHD.”).

FDA’s consideration of health claims under the Nutrition Labeling and Education Act of 1990 (NLEA) has recognized the valuable contribution such claims can make in encouraging dietary modifications which can lower serum cholesterol levels and thus CHD risk. FDA’s approval of CHD-related health claims has acknowledged the importance of early and life-long management of the risk factors related to CHD, and the substantial public health benefits that can be contributed by even modest improvements in dietary intake patterns directed toward CHD risk reduction. While FDA’s health claims policy generally has been restrictive,

FDA has authorized several health claims promoting dietary intake patterns that can reduce CHD risk. Of the approved health claims codified in FDA regulations, more are concerned with CHD risk than with any other disease or health-related condition. *See* 21 C.F.R. §§ 101.74, 101.75, 101.77, 101.81, 101.82, 101.83. FDA has approved CHD claims encouraging the consumption of higher fat foods which otherwise would have been disqualified under the FDA health claim policy where the public health benefit of the food consumption pattern was substantiated by appropriate scientific evidence. *See* 21 C.F.R. § 101.83.

In addition, FDA has approved CHD claims encouraging food consumption patterns that would be new to many sectors of the population, where the evidence substantiated the claimed benefits to public health. For example, FDA has approved CHD claims encouraging the consumption of psyllium husk, soy protein and plant stanol esters under conditions having no established relationship to historical or reasonably projected food intake patterns.

## **2. CHD Health Claims and Dietary Intake Patterns**

In approving CHD health claims, FDA has sometimes evaluated the scientific support for the CHD benefits claimed with reference to hypothetical dietary intake patterns. While this method has provided a useful framework within which to assess the strength and weight of the body of scientific evidence, in no case has the scientific merit of the health claim depended on the probability that the hypothetical diet would, in fact, be adopted by any population group. Moreover, since health claim approval depends on the accuracy of the message conveyed, and not the anticipated consumer response to the message, there would be no legal basis for imposing limits on health claims through qualifying language or disclaimers which convey conditions of a hypothetical diet which have no relationship to the consumption patterns that reasonably can be projected.

Because the benefits of walnuts have been shown under a broad range of dietary conditions, any representation that would suggest that the CHD benefits of walnuts are available only to those consumers who consume a specified “dosage” of walnuts per day would not accurately characterize the body of relevant scientific evidence. Moreover, consumers could not reasonably be expected to implement any specific dosage recommendation concerning walnut intake conveyed in a health claim, regardless of the scientific evidence concerning any dose-response relationship. For example, while the scientific evidence supports the benefits of daily walnut consumption at levels of two ounces daily, it would be unreasonable to expect consumers to eat two ounces of walnuts daily, 365 days per year. Outside the confines of a controlled metabolic diet study, no one could be expected to confine food choices in such a restrictive manner. Accordingly, any requirement that would limit the expression of the walnut health claim with reference to walnut dosage would be artificial, misleading and unjustified.

The deceptive potential of implied dose-response messages in health claims for conventional foods relates to the distinctive nutritional role of foods, which are intended to be consumed as part of an ordinary *ad libitum* diet. This intended use contrasts with that of drugs, for which dosage limitations and the claims themselves operate to define the intended conditions of use. The distinctions in the intended use standards for foods and drugs have justified corresponding distinctions in the statutory standards governing health claims and drug claims. FDA approval of a drug product is conditioned upon a determination that the drug, when consumed at the approved dosage level, is effective in preventing, mitigating or treating a specific disease or condition in the patient. Accordingly, the drug formulation and claims are regulated to enable the physician (for prescription products) or patient (for OTC products) to

consume the drug under the specific conditions defined in the drug approval process which have been shown to optimize the health benefits and mitigate the risks to actual product consumers.

By contrast, implicit in the statutory standards governing health claims is the recognition that the consumption of conventional foods involves established patterns of dietary intake which define the intended use and justify the value of the product to consumers. This justification originates with the organoleptic, psychological and nutritional value the food provides in supporting the structure and function of the body. The intended use of the food, thus, is not defined by a health claim. Rather, a health claim simply adds to the existing rationale justifying the value of the food to consumers.

Health claims, unlike drug claims, never were intended to characterize the intended use of the article itself. Health claims serve an important but more limited educational purpose than defining the intended use of a drug. Health claims for conventional foods are intended to inform consumers about the health benefits of foods they are already enjoying or could readily incorporate into an ordinary diet.

### **3. Health Claims and Consumer Motivation**

The proposed model health claim is consistent with the public health objectives of the NLEA health claims provisions. Health claims were conceived as an educational and motivational tool to promote healthy dietary intake patterns and promote public health. The expectation and promise of the NLEA health claims policy was that, by encouraging food marketing experts to direct their creative energies and resources toward developing attractive and highly motivating health messages for nutritious foods, over time, the individual food choices made by consumers increasingly would be shaped in directions offering long term gains for public health. The proposed walnut health claim would encourage increased consumption of walnuts, which offer CHD benefits, and is consistent with a healthy balance of fatty acid intake.

The NLEA requires FDA to give careful consideration to the language of the proposed claim, and the “take away” message conveyed by it. Under the NLEA, health claims are not intended to serve the functions of a scientific monograph, but rather to convey motivating health information to consumers. As evidenced by the creative health communication programs FDA itself has employed, *see* Attachment 2, the health messages that motivate best are crisp and uncluttered by distracting details or caveats. Creative, concise health claims that capture the “bottom-line” consumer benefit have far greater value in influencing consumer food choices, and thus, promoting public health, than statements filled with scientific precision but drained of meaning for consumers. Health claims that are not meaningful to consumers will fail to motivate them and ultimately provide no value to public health.

The proposed claim, “Diets including walnuts can help reduce the risk of heart disease,” conveys the CHD benefit of walnuts to consumers in plain terms, and encourages the simple dietary modification of incorporating walnuts into the diet. The scientific support for this health message is undeniable. While the body of scientific evidence concerning walnuts and CHD risk is rich and would fully support claims embellished with more detailed characterizations of the mechanisms by which the health benefits of walnuts are achieved, such details are not required to ensure the accuracy of the core health message.

#### **B. Evaluation of Scientific Evidence**

Data regarding the mechanism by which walnut consumption promotes reductions in serum total and LDL cholesterol, and is thus cardioprotective, are not required for FDA to authorize health claims regarding walnuts and CHD risk reduction. A description of the unique nutritional characteristics of walnuts, and of the data regarding the ratio of essential fatty acids and the significance of that ratio for cardiovascular health, is nevertheless set forth in this part of

the petition to provide context for the clinical trial data and corroborative epidemiological and observational data described in Part IV.C.

**1. The Proper Balance of Essential Linoleic and  $\alpha$ -Linolenic Fatty Acids Supports Heart Health**

There are two fatty acids that have been established as essential for human health:

$\alpha$ -linolenic acid (omega-3 or n-3) and linoleic acid (omega-6 or n-6). In the body,  $\alpha$ -linolenic acid functions as the parent of eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA), which are the omega-3 fatty acids found in fish oils. EPA and DHA can be synthesized from  $\alpha$ -linolenic acid in the body through a process of desaturation and elongation. The health benefits of  $\alpha$ -linolenic acid are believed to be attributable, in part, to this synthesis. (Cunnane 1995; Gibson & Makrides 2000.)

Alpha-linolenic acid, EPA and DHA each play a distinctive role in the structure and function of membranes in the retina and central nervous system and are especially important in the development of the brain and retina during the prenatal and infancy periods. Alpha-linolenic acid is also one of the precursors for eicosanoids, prostaglandins, leukotrienes and thromboxanes, which are important for cell membrane function. (Gould 1997.) Alpha-linolenic acid has been shown to inhibit platelet reactivity and prevent arrhythmias, and also has anti-inflammatory benefits. (Kang & Leaf 2000; Connor 1999; James, *et al.* 2000.)

Clinical trials and epidemiological and observational studies have demonstrated that  $\alpha$ -linolenic acid can reduce the risk of CHD. In the Lyon Diet Heart Study, a secondary prevention trial among patients with MI, a 70 percent reduction in CHD was observed in the experimental group on an  $\alpha$ -linolenic acid-rich Mediterranean diet, even though cholesterol levels did not change. (de Lorgeril, 1994, 1999.) Significantly, among fatty acids, only  $\alpha$ -

linolenic acid was significantly associated with an improved prognosis. The researchers did not find any correlation between EPA and DHA and recurrence.

In the Nurses' Health Study (Hu, *et al.* 1999), a higher intake of  $\alpha$ -linolenic acid was significantly associated with a lower relative risk of fatal ischemic heart disease (IHD) in women. This association was believed to result from the antiarrhythmic effect of  $\alpha$ -linolenic acid, and possibly from its antithrombotic effect.

In a study involving a large cohort of healthy men in the United States, intake of  $\alpha$ -linolenic acid was inversely associated with MI, independently of other dietary and non-dietary risk factors. (Ascherio, *et al.* 1996.) As in the Lyon trial, intake of marine omega-3 fatty acids (EPA and DHA) was not inversely associated with the **risk**, suggesting that the cardiovascular effects of  $\alpha$ -linolenic acid may be different from those of the longer chain omega-3 fatty acids. This study also cites others in which  $\alpha$ -linolenic acid intake was associated with reduced risk of coronary death or may have contributed to reduced coronary disease, including the Multiple Risk Factor Intervention Trial.

The American Heart Association (AHA) recognizes that recent randomized controlled trials have demonstrated beneficial effects of  $\alpha$ -linolenic acid on both coronary morbidity and mortality in patients with coronary disease. American Heart Association, Fish Oil (AHA Recommendation) (available at <http://216.185.112.5/presenter.jhtml?identifier=4632>) (“[S]tudies have demonstrated beneficial effects of . . . alpha-linolenic acid (8 percent of energy) in subjects with CHD.”). Epidemiological data show inverse associations between dietary  $\alpha$ -linolenic acid and risk of MI or cardiovascular mortality. An inverse association between serum EPA, DHA and  $\alpha$ -linolenic acid and hemostatic factors has also been reported. (Freese and Mutanen 1997.)

The same enzymes are involved in the synthesis of EPA and DHA from  $\alpha$ -linolenic acid and the synthesis of arachidonic acid from linoleic acid. Because of this competition, the ratio of intake of linoleic acid to  $\alpha$ -linolenic acid is important, for lower ratios increase endogenous conversion of  $\alpha$ -linolenic acid to EPA and DHA. An optimal intake of linoleic acid relative to  $\alpha$ -linolenic acid is considered crucial for normal metabolism.

The clinical data highlight the importance of the proper ratio of linoleic acid to  $\alpha$ -linolenic acid. Studies show that as the ratio of omega-6 to omega-3 fatty acids in platelet phospholipids increases, so does the death rate from cardiovascular disease and the prevalence of type 2 diabetes. (Simopoulos 1999.) In the Lyon Diet Heart Study, only the trials that lowered intake of omega-6 fatty acids while increasing omega-3 fatty acids lowered cardiovascular and all-cause mortality. (Leaf 1999.) The two populations with the greatest life expectancy, the Japanese and the Cretans, have a high intake of  $\alpha$ -linolenic acid and a low intake of linoleic acid and saturated fatty acids.

## **2. The Gross Dietary Imbalance of Essential Fatty Acids and $\alpha$ -Linolenic Acid Deficiency Are Significant Risk Factors For Heart Disease in the United States**

An expert panel of nutrition scientists has recommended an intake of 2.22 g/day of  $\alpha$ -linolenic acid and an upper limit for linoleic acid intake of 6.67 g/day. (Simopoulos, *et al.* 1999.)<sup>1</sup> Some researchers have observed that a dietary intake of 0.5 to 1.0 percent of energy from  $\alpha$ -linolenic acid gives maximum tissue levels of DHA and also avoids any apparent deficiency symptoms. Others have estimated that the daily intake of  $\alpha$ -linolenic acid required to

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<sup>1</sup> The NAS Food and Nutrition Board's Panel on Dietary Reference Intakes for Macronutrients currently is evaluating the human nutritional requirements for macronutrients including linolenic acid and other omega-3 fatty acids.

avoid deficiency symptoms is approximately 0.3 to 0.5 percent of energy. (Gibson & Makrides 2000.) Several scientists have recommended a linolenic:  $\alpha$ -linolenic acid ratio of 4:1 (Simopoulos, *et al.* 1999; Holman 1998; Yehuda & Carasso 1993).

Current average intake of omega-3 fatty acids in the United States is estimated at about 1.6 grams/day (about 0.7 percent of energy), of which 1.4 g is  $\alpha$ -linolenic acid. Based on this estimate, as much as half the U.S. population may be consuming diets deficient in  $\alpha$ -linolenic acid. In addition, current estimates of average intake indicate that the ratio of omega-6 to omega-3 fatty acids in the diet is approximately 9.8:1, a gross distortion in relation to the 2.3:1 and 4:1 ratios recommended for meeting human nutritional needs. (Kris-Etherton, *et al.* 2000.) As Harper and Jacobson observed in their 2001 review of the epidemiological and clinical trial evidence of the cardioprotective benefits of omega-3 fatty acids, "One challenge facing physicians and other primary care providers is recommending palatable sources of ALA, EPA, and DHA." Walnuts are a readily available source of omega-3 fatty acids.

**3. Walnuts Are A Concentrated Source of  $\alpha$ -Linolenic Acids and Possess Other Unique Nutritional Attributes Important for Cardiovascular Health**

English walnuts (*Juglans regia* L.) are a high-energy food relatively high in protein, potassium, phosphorus and folate. They also contain significant quantities of fiber and vitamin E, and are low in sugar. Selected nutrient values for whole and chopped walnuts, which are the foods in the labeling of which the proposed claims would be used, are shown below in Table 1, as required by 21 C.F.R. § 101.70(f). Additional values are set forth in the accompanying LSRO Review.

LSRO Review 20-21.

**Table 1. Selected values for *Juglans regia* L. (per 100 g edible portion)**

Energy	654 kcal
Fat	65.21 g
Protein	15.23 g
Fiber	6.7 g
Phosphorus	346 mg
Potassium	441 mg
Folate	98 µg
Vitamin E	2.9 mg ATE
Phytosterols	72 mg

Walnuts are relatively high in polyunsaturated fats. A 100 g portion contains 47.17 g, comprising linoleic acid (38.09 g) and  $\alpha$ -linolenic acid (9.08 g). Saturated fats (principally palmitic and stearic acids), by contrast, are present at approximately one eighth that level, and the concentration of monounsaturated fatty acids (virtually all oleate) is only slightly greater. See Agricultural Research Service, USDA Nutrient Database for Standard Reference, Release 14 (2001) (available at <http://www.nal.usda.gov/fnic/foodcomp>). A detailed analysis of the nutritional profile of walnuts is provided in the LSRO review.

The relatively high concentration of  $\alpha$ -linolenic and fatty acids distinguishes walnuts from other nuts. LSRO Review 29. Walnuts, like other nuts, are rich sources of essential fatty acids, and contribute little saturated fatty acid to the diet. *Id.* These properties confer unique cardioprotective benefits on walnuts.

**C. There is Significant Scientific Agreement That The Totality of Publicly Available Scientific Evidence Fully Supports the Claim: "Diets Including Walnuts Can Reduce The Risk of Heart Disease"**

**1. Evidence From Clinical Trials Establishes The Benefits of Diets Including Walnuts in Reducing Serum Total and LDL Cholesterol**

The results of controlled clinical trials demonstrate that diets containing walnuts lower serum total and LDL cholesterol, thereby reducing the risk of CHD. These results were observed whether the walnuts were included in a usual diet higher in fat, a diet based on

recommendations from the American Health Association (AHA) or the Expert Panel on the Step 1 diet of the National Cholesterol Education Program (NCEP), a low-fat diet, a cholesterol-lowering high-monounsaturated fatty acid diet or a diet already increased in polyunsaturated fatty acids. A summary of the clinical trials, demonstrating the effect of walnut consumption on plasma lipids and lipoproteins, appears in Table 2.

Table 2. Effects of Walnuts on Plasma Lipids and Lipoproteins: Summary of Clinical Trials (adapted from Kris-Etherton *et al.* 2001)

Study and Subjects	Study Design	Treatment	Duration	TF	Diet Composition			Chol (mg/day)	Baseline Lipids/Lipoproteins				Endpoint Lipids/Lipoproteins			
					SFA (% total energy)	MUFA	PUFA		TC	LDL (mmol/L)	HDL	TG	TC	LDL (mmol/L)	HDL	TG
Sabaté <i>et al.</i> , 1993 n = 18 M	Randomized, controlled, single-blind, crossover	Walnuts (84 g/day)	4 weeks	31.3	6	7.4	16.5	125	5.1	NR	NR	1.32	4.14 <sup>§</sup>	2.43 <sup>§</sup>	1.16 <sup>†</sup>	1.16 <sup>†</sup>
		Step 1 diet	4 weeks	29.3	9	8.8	9.5	237	5.1	NR	NR	1.32	4.71	2.90	1.22	1.29
Abbey <i>et al.</i> , 1994 n = 16 M	Consecutive supplemental field study	Almonds (84 g/day)	3 weeks	35.9	8.2	17.3	8	199	5.15	NR	NR	NR	4.81 <sup>b</sup>	3.21 <sup>c</sup>	0.96	1.43
		Walnuts (68 g/day)	3 weeks	36.5	8.9	9.9	15.8	235	5.15	NR	NR	NR	4.92 <sup>b</sup>	3.26 <sup>c</sup>	0.99	1.47
		Control	3 weeks	35.7	15.9	11.5	6.6	205	5.15	NR	NR	NR	5.17	3.58	0.96	1.41
Chisholm <i>et al.</i> , 1998 n = 21 M with hyper- cholesterolemia	Dietary advice, randomized, crossover	Walnuts (78 g/day)	4 weeks	38	10	10	16	230	6.24	4.30	1.06	1.95	5.99 <sup>a</sup>	3.94 <sup>b</sup>	1.21 <sup>b</sup>	2.00
		Low fat diet	4 weeks	30	12	10	5	320	6.24	4.30	1.06	1.95	6.11	4.10	1.18 <sup>b</sup>	1.86
Zambón <i>et al.</i> , 2000 n = 26 M, 23 F with hyper- cholesterolemia	Randomized, crossover	Walnuts (41- 56 g/day)	6 weeks	33.2	6.0	13.5	11.7	166	7.16	5.05	1.44	1.54	6.52 <sup>c</sup>	4.48 <sup>c</sup>	1.42	1.42 <sup>d</sup>
		Mediterranean diet	6 weeks	31.2	6.9	17.5	4.8	221	7.16	5.05	1.44	1.54	6.81	4.77	1.37	1.51
Muñoz <i>et al.</i> , 2001 n = 10 M with polygenic hyper- cholesterolemia	Randomized, controlled, crossover	Walnuts (41- 56 g/day)	6 weeks	31.8	5.5	12.9	11.2	167	NR	NR	NR	NR	6.45	4.48	1.29	1.40
		Mediterranean diet	6 weeks	30.9	6.0	17.5	3.9	222	NR	NR	NR	NR	6.73	4.77	1.29	1.48
Iwamoto <i>et al.</i> , 2002 n = 10 M, 10 F	Randomized, controlled, crossover	Walnuts (43- 57 g/day)	4 weeks	26	48	6.7	14.5	252	M 4.75	NR	NR	NR	M 4.0	1.85	1.32	1.83
		Japanese diet	4 weeks	24	6.9	10.3	6.8	279	F 4.53	NR	NR	NR	F 4.05	1.86	1.65	1.16
			4 weeks	24	6.9	10.3	6.8	279	M 4.75	NR	NR	NR	M 4.17	2.02	1.32	1.86
									F 4.53	NR	NR	NR	F 4.26	2.08	1.68	1.13

Note: M=male; F=female; TF=total fat; SFA=saturated fatty acids; MUFA=monounsaturated fatty acids; PUFA=polyunsaturated fatty acids; Chol=cholesterol; TC=total cholesterol; LDL=low-density lipoprotein cholesterol; HDL=high-density lipoprotein cholesterol; TG=triglycerides; NR=no reported values.

<sup>a</sup>P<0.05, <sup>b</sup>P<0.01, <sup>c</sup>P<0.001, <sup>d</sup>P<0.1, compared with values from control group or baseline.

<sup>§</sup>P<0.001, <sup>†</sup>P<0.01, <sup>‡</sup>P<0.1, compared with values from cholesterol-lowering diet groups with nuts.

Two of the trials suggested possible mechanisms of CHD risk reduction for walnuts. Zambón *et al.* pointed to the antiarrhythmic and other antiatherogenic effects of  $\alpha$ -linolenic acid. Almario *et al.* and Almario & Kasim-Karakas found that adding walnuts to the diet caused a redistribution of LDL cholesterol from the more atherogenic small, dense LDL to larger LDL particles, and caused a redistribution of HDL cholesterol from larger into smaller particles. They observed that lipid particle changes occurred in the absence of lipid lowering, suggesting a favorable antiatherogenic effect of walnuts that is independent of any changes in circulating lipid levels.

**a) Substituting Walnuts for Other Foods In an NCEP Diet Among Free-Living Healthy Men With Normal Lipid Levels Reduced Serum Total and LDL Cholesterol By 12.4 and 16.3 Percent, Respectively**

A single-blind, randomized crossover trial reported by Sabaté and colleagues in 1993 investigated the effects of consuming walnuts on serum lipid levels and blood pressure among free-living healthy men. The subject population (n=18) comprised healthy adult males aged 21-43 (mean 30 y) of normal weight (mean 73 kg), lipid levels (20th to 80th percentile) and blood pressure (average 109/72 mm Hg).

Following a five-day run-in period during which subjects consumed a reference diet based on the NCEP diet, the subjects followed each of two consecutive four-week diets. Half were randomized to the walnut diet group and received 20 percent of their calories from walnuts by having three servings of 28g each of walnuts substituted for other foods. The other half continued the reference diet. Meals were prepared in the research kitchen. Personnel conducting measuring and analysis functions in the study were blinded to the sequence of the subjects' diets.

Blood samples were taken during the run-in phase and again at the end of each dietary period, and were analyzed for cholesterol and triglyceride concentrations. The subjects' serum fatty acid compositions were also determined. Blood pressure was measured throughout the study.

The walnut diet reduced mean serum total cholesterol by 12.4 percent and LDL cholesterol by 16.3 percent, relative to the reference diet. The responses were consistent in both groups, among subjects of all baseline serum cholesterol values and body mass indexes. No effect on blood pressure was observed, and the researchers reported no side effects from the walnut diet. The favorable effects of consuming walnuts on the subjects' lipid profiles were seen despite the subjects' "relatively low base-line cholesterol levels . . . ."

**b) Substituting Walnuts for Other Foods In a 36 Percent Fat Diet Among Normolipidemic Men Reduced Serum Total and LDL Cholesterol By 5 and 9 Percent**

In 1994, Abbey and colleagues reported the results of a study comparing the effects of two types of nuts having different fatty acid profiles on plasma lipids. They compared a reference diet reflecting the ratio of polyunsaturated to monounsaturated to saturated fats typical of the Australian diet to two nut-rich diets: a diet containing almonds, with their high concentration of monounsaturated fatty acids, and a walnut diet, rich in polyunsaturated fatty acids. The study subjects were 16 normolipidemic (mean 5.15 mmol/L) adult males, of mean age 41 and mean weight 86 kg.

After a two-week "familiarization period," the subjects were given each of the three diets sequentially for three week periods. The walnut diet was continued for a further three weeks. Blood samples were drawn on three consecutive days at the end of each three-week period following twelve hours of fasting. Sixteen subjects completed the study.

The walnut diet reduced serum total and LDL cholesterol levels by 5 and 9 percent, respectively. Although the almond diet yielded similar reductions (7 and 10 percent), significant increases in plasma levels of  $\alpha$ -linolenic acid were observed only with the walnut diet.

**c) Among Hypercholesterolemic Men, Statistically Significant Cholesterol Reductions Were Observed When Walnuts Were Included In A Relatively High-Fat Diet**

In this randomized, crossover study reported in 1998, Chisholm and colleagues compared the effects on lipid metabolism of adding walnuts to the diets of 16 moderately hypercholesterolemic males (mean age 45 y) without CHD, familial hypercholesterolemia, familial combined hyperlipidemia or secondary hyperlipidemia. Following a one-week run-in period during which a standard lipid-lowering diet was advised, the subjects were randomized to two groups: one continuing the reference diet and one consuming a walnut diet. The walnut diet was a 2500 kcal diet containing 46 g fat from walnuts and 37 g fat from other foods.

Blood samples were taken at the end of the run-in period and at the end of each experimental period, and cholesterol concentrations in plasma and lipoprotein fractions were measured. Lipid fractions were separated and the fatty acid composition of each fraction measured.

Both experimental diets showed mean total and LDL cholesterol levels that were lower than at baseline (TC: 6.24 mmol/L vs. 5.99 walnut diet and 6.11 reference diet; LDL-C: 4.30 mmol/L vs. 3.94 walnut diet and 4.10 reference diet), but only the walnut diet yielded reductions that were statistically significant. Total and LDL cholesterol were lower at the end of the walnut diet than at the end of the reference diet, but this difference was not statistically significant.

**d) Diets Including Walnuts Reduced Serum Total and LDL Cholesterol By 10 Percent Among Hyperlipidemic Men and Women in the Barcelona Walnut Trial**

In 1998, Zambón and colleagues reported results from the Barcelona Walnut Trial, a randomized, crossover trial evaluating the effect of walnuts on serum lipids in 49 male and female hyperlipidemic subjects of mean age 56 y (mean TC 278 mg/d; mean LDL-C 193 mg/d). The subjects were randomly assigned to one of two isocaloric diets: a walnut diet (–50 g/day, 33 percent fat) or a “Mediterranean” diet relatively high in monounsaturated fat (30 percent fat). After six weeks on each experimental diet, blood samples were taken for serum lipoprotein analysis.

Total and LDL cholesterol levels decreased 10 percent each ( $p < 0.001$ ) after the walnut diet compared with the “Mediterranean” diet. Both male and female subjects exhibited similar reductions. The investigators concluded, “walnut consumption favorably modifies the plasma lipid profile in hypercholesterolemic subjects.”

**e) Including Walnuts As Part of a Low-Fat Diet Reduced Serum Total and LDL Cholesterol By 7.7 and 12.3 Percent Among Men and Postmenopausal Women**

In 2000 and 2001, Almario and Kasim-Karakas and Almario and others reported the results of their assessment of the effects of a walnut diet on plasma lipids and lipoproteins in patients with combined hyperlipidemia. The study population comprised 13 postmenopausal females and five males, of mean age 60 y. Each subject completed four diets in free-living conditions: (1) a habitual diet for four weeks; (2) a habitual diet plus walnuts for six weeks; (3) a low-fat (20 percent fat) diet for six weeks; and (4) a low-fat diet plus walnuts for six weeks. Blood samples were drawn at the mid- and endpoints of each diet, but only the latter samples were used for analysis.

With the addition of walnuts to the low-fat diet, serum total cholesterol levels decreased from 5.84 to 5.39 mmol/L and LDL cholesterol fell from 3.67 to 3.22 mmol/L. The low-fat diet with walnuts also yielded significant decreases in total serum cholesterol compared with the habitual diet (5.97 versus 5.39 mmol/L). In addition, although plasma lipids remained constant, the small-density fraction of LDL cholesterol, which is among the most atherogenic lipoproteins, decreased when walnuts were added to the habitual diet.

**f) The Reductions in Serum Total and LDL Cholesterol in a Small Group of Men With Polygenic Hypercholesterolemia Corroborate The Results of the Larger Trials**

In 2001, Muñoz and colleagues reported on the results of a randomized, crossover feeding trial--a substudy of the Barcelona Walnut Trial--evaluating the effect of adding walnuts to a Mediterranean-type cholesterol-lowering control diet in a population of ten men (aged 48-71 y) with polygenic hypercholesterolemia. Following a 4-week preinclusion period, subjects were randomly assigned to one of two diets: a "Mediterranean" control diet relatively high in monounsaturated fatty acids and a walnut diet in which walnuts replaced approximately 35 percent of the total energy supplied by sources of monounsaturated fat. Each experimental period lasted six weeks.

Blood samples were taken during the last two weeks of each experimental period, and analyzed for serum lipid and lipoprotein concentration. At the end of the control diet, the mean serum total cholesterol level was 6.73 mM. In subjects consuming the walnut diet the mean was 6.45 mM. For LDL cholesterol, the mean value for the control diet was 4.77 mM. For subjects on the walnut diet, the mean concentration was 4.48 mM. The walnut diet thus reduced serum total and LDL cholesterol concentration in then subjects by 4.2 (p=0.176) and 6.0 percent (p=0.087), respectively.

The investigators attributed the lack of statistical significance to the small size of the sample and noted that the effect observed was similar in magnitude to that seen in the larger study (n=49).

**g) Including Walnuts in The Diet Reduced Serum Total and LDL Cholesterol In Japanese Women**

In a controlled, single blind, cross-over study to be published in 2002, Iwamoto and colleagues examined the effect of walnut consumption on the serum lipids of a population of young male and female subjects (n=40) consuming a diet based on the National Nutrition Survey of Japan and the Recommended Dietary Allowance for the Japanese.

Following a five-day lead-in period in which all subjects consumed the reference diet, each subject was assigned (with stratification based on age, baseline serum cholesterol concentration and BMI) to either the walnut diet group or the group continuing the reference diet, and then crossed over to the other diet. Each group included ten men and ten women. Meals were prepared in a university research kitchen and a registered dietitian weighed and apportioned foods for the subjects. Each experimental period lasted for four weeks.

Serum cholesterol was measured at the end of the lead-in period and at the end of each experimental period. In women, the mean serum total cholesterol concentration decreased by 4.9 percent with the addition of walnuts to the reference diet. In men, the mean decrease was 3.8 percent. For serum LDL cholesterol, the reductions were 11 percent in women but not statistically significant in men.

**2. Data From the Walnut Clinical Trials Are Corroborated by Epidemiological and Observational Data**

Large-scale, long-term human prospective observational studies demonstrate an inverse association of CHD with the frequent consumption of nuts, including walnuts. The association was observed in both sexes and across racial lines, with a 30-50 percent decreased

relative risk of CHD reported. LSRO Review 29. The effects were achieved with levels of nut consumption much lower than those used in the walnut clinical trials.

**a) The Adventist Health Study Showed An Inverse Relationship Between Nut Consumption And Risk of MI or Fatal IHD**

In the Adventist Health Study (AHS), 26,473 non-Hispanic white males and females without heart disease or diabetes were followed up for six years and were evaluated for first events. Many potential confounders could be ruled out, for the population was predominantly non-smoking, did not use alcohol and generally followed a lacto-ovo-vegetarian diet, and there was not any significant confounding by other foods. LSRO Review 15.

Investigators concluded that frequency of nut consumption was related inversely to the risk of MI or death from IHD. The effect was not dependent on age, gender, relative weight, smoking or other established cardiac risk factors. Relative risk of MI and IHD of persons who ate nuts at least five times per week was about half that of subjects who consumed nuts less than once weekly. People who ate nuts one to four times per week had a 22 percent reduced risk of MI, compared with those eating nuts less than once a week. (Sabaté 1999).

Several publications by investigators involved in the AHS observational studies further analyzed the cardioprotective effects of nut consumption. One demonstrated that the age of onset of CHD in both males and females was delayed by about 4 years when comparing high (5x/wk) to low (rare) nut consumption, and that the predicted life expectancy free of CHD was significantly longer (5.6 y,  $p > 0.05$ ) with high nut consumption. (Fraser *et al.* 1995) The study predicted that lifetime risk of IHD was 12 percent less in high nut consumers compared to low. Frequent nut consumption was associated with lower mortality in whites, black and the elderly.

**b) The Iowa Women's Health Study Showed An Inverse Association Between Nut Consumption and Coronary Mortality**

In the Iowa Women's Health Study (IWHS), a prospective cohort study of 41,837 postmenopausal, predominantly white females, the subjects were asked about the frequency of nut consumption as one-ounce (28 g) portions. The study over five years showed that coronary mortality was inversely associated with nut intake, with an adjusted relative risk of 0.6 for eating nuts 1-3 times a month, 0.75 for eating nuts once a week and 0.43 for eating nuts 2-3 times a week. (Prineas, *et al.* 1993)

**c) In The Nurses' Health Study, Nut Consumption Was Associated with Lower Nonfatal MI and IHD**

In the Nurses' Health Study (NHS), a prospective cohort study of a large population of female registered nurses followed up for 10 years, subjects consuming at least 5 ounces of nuts per week had a 32 percent lowering in nonfatal MI compared with those eating less than 1 ounce of nuts per month. (Fraser 1999c)

Hu *et al.* (1999) reported data relating dietary intake of  $\alpha$ -linolenic acid and the risk of IHD among the subjects in the NHS study. Energy-adjusted intake of  $\alpha$ -linolenic acid, found in exceptionally elevated amounts in walnuts, was inversely associated with risk of fatal IHD. Among women with prevalent MI, the investigators observed a trend toward lower risk of fatal IHD among subjects with higher  $\alpha$ -linolenic acid intake.

**d) The Physicians' Health Study Observed a Link Between Nut Consumption and a Lower Risk of Cardiac Death or Sudden Death**

In 1998, Albert and colleagues reported the results of their examination of the relationship between nut consumption and the incidence of sudden and total cardiac death in the cohort of over 22,000 U.S. male physicians established by the Physicians' Health Study (PHS).

The investigators found a significant age and treatment adjusted inverse association between the quantity of nuts consumed and the risk of cardiac death (P for trend, .003) and sudden death (P for trend, .047). The linear relationship persisted after adjustments were made for other potential cofounders, such as smoking. (Albert, et al. 1998b)

**3. There is Significant Scientific Agreement That The Totality of the Publicly Available Scientific Evidence Supports the Cardioprotective Effects of Diets Including Walnuts**

The clinical trials demonstrated a significant beneficial effect on blood cholesterol levels when walnuts were incorporated into the diet. The results were observed whether the subjects were normolipidemic or hypercholesterolemic and whether the walnuts were added to a diet relatively high in fat, a low-fat diet or a "Mediterranean" diet. Both men and women subjects reported statistically significant reductions in serum total and LDL cholesterol levels. Collectively, the subjects in these trials are representative of the 51 percent of the adult population in the U.S. now at higher risk of CHD. LSRO Review 14 (citation omitted).

The observational studies provide substantial, competent and compelling scientific evidence that diets containing nuts, and particularly walnuts, may reduce the risk of CHD, and round out the picture presented by the clinical studies. The observational studies demonstrated the cardioprotective effects of nuts, including walnuts, in tens of thousands of subjects, showing that the results of the clinical trials can be legitimately extrapolated to a much larger population. The concordance of the clinical and observational data is compelling evidence of the consistency and generalizability of the beneficial cardioprotective effect of diets containing walnuts.

The consistency of the findings among the clinical trials and between the clinical trials and the observational and epidemiological studies supports the validity and reliability of the evidence that diets including walnuts reduce CHD risk across a broad range of dietary

conditions. The observational and epidemiological studies also confirm the suggestion from the clinical trials that CHD risk can be reduced by adding as little as one serving of walnuts per week. The observational studies observed that the greatest benefits were achieved by subjects who ate only four or five servings of nuts a week—significantly less than the two to three servings (about 28 g each) of walnuts per day administered in the clinical trials. Finally, the observational studies corroborate the findings in the clinical trials that the walnut diet did not yield significant adverse effects and that walnut consumption could be sustained over time.

The scientific evidence of the cardioprotective benefits of walnuts is reflected in dietary guidance issued by scientific organizations. The revised AHA guidelines recognize the importance of consuming foods containing long-chain omega-3 polyunsaturated fatty acids, such as walnuts, because of their cardioprotective effects. LSRO Review 4.

The National Academy of Sciences, through a unit of its Food and Nutrition Board, has established a Panel on Macronutrients “to review and evaluate the scientific literature and interpret the depth of current knowledge on,” among other macronutrients, fatty acids, including specifically omega-3 and omega-6 fatty acids. The Panel will “analyze the scientific literature regarding human requirements for macronutrients throughout the lifespan, including the relationship to chronic diseases and data on dietary intake.” The Petitioner expects that the Panel’s report, which is scheduled to be released in 2002, will address the cardioprotective attributes of specific foods because of their favorable fatty acid profile, and that the report will corroborate the data described in the LSRO review and in this petition demonstrating that diets including walnuts can reduce the risk of CHD.

One of the NAS panel members in May 2001 published the most comprehensive review to date of the epidemiological and clinical evidence supporting the ability of nuts to

reduce the risk of CHD. (Kris-Etherton 2001) As she observed, it “is appropriate to recommend inclusion of nuts in a healthy diet that meets energy needs to reduce risk of CHD, which emphasizes the need to provide dietary guidance to help people understand how to plan heart healthy diets that include nuts.”

#### **V. Proposed Model Claim**

Petitioner requests that FDA promulgate a regulation authorizing use of a health claim associating diets including walnuts with reduced risk of heart disease on the label or in the labeling of walnuts. Petitioner further requests that the regulation provide that the foods for which such claims may be made are whole or chopped walnuts. FDA should authorize the model health claim, “Diets including walnuts can reduce the risk of heart disease,” but Petitioner requests that the regulation expressly authorize the use of all such health claims that accurately characterize the nature and weight of the substantiating scientific evidence concerning the benefits of diets including walnuts in reducing the risk of heart disease when made for whole or chopped walnuts.

Authorizing CHD claims for walnuts would be consistent with NLEA provisions relating to federal nutritional guidelines. Under Section 403(r)(3)(A) and (B) of the FD&C Act, 21 U.S.C. § 343(r)(3)(A) & (B), which were added by the NLEA, in issuing health claim regulations, FDA must take into account the role of nutrients to encourage consumers to adopt healthy dietary practices. Pursuant to this provision, FDA relies on dietary guidelines in health claim rulemaking proceedings and has authorized CHD claims for foods containing soy protein from whole soybeans, even though the foods might not conform with the “disqualifying” levels

provision of the health claim regulation or meet the regulatory requirements for “low fat” nutrient content claims in 21 C.F.R. § 101.62. *See* 21 C.F.R. § 101.82(c)(2)(iii).

FDA’s treatment of soy protein supports the granting of an exception from 21 C.F.R. § 101.14(e)(4) in the instant case. Current dietary guidelines reflecting the state of scientific evidence assign first priority to reducing cholesterol and saturated fat and no longer simply recommend a “low fat” diet. Walnut consumption meets these recommendations because walnuts are low in saturated fat and cholesterol and confer significant nutritional and health benefits. The cardioprotective polyunsaturated fatty acids in walnuts are not present in many other foods, and therefore consumers would not easily be able to obtain this beneficial substance from other lower-fat sources. Far from increasing the risk of CHD—the concern underlying the disqualifying levels rule for fat—the proposed claim would encourage consumption of cardioprotective foods and advance the public health goal of promoting dietary practices that reduce the risk of CHD.

Authorizing the proposed claim also would be fully consistent with the First Amendment principles applied to FDA’s health claim policy in *Pearson*. The disqualifying levels rule sets an arbitrary nutritional contribution that a food must make to the diet to qualify for any claim, even though the claim might be truthful and nonmisleading when made with respect to that food. This policy subjects health claims to greater regulation than is necessary to realize the public health goal of encouraging consumers to make dietary choices that promote good health. To the extent that the disqualifying levels rule is based on a concern that consumers will be unable to make appropriate dietary choices at the point of sale because of the influence of

labeling claims, the rule presents serious constitutional concerns. *See Pearson*, 164 F.3d at 656-57. *See also 44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996) (“The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good.”) (plurality). Information regarding fat and other nutrient levels is readily available to consumers in nutrition labeling, enabling consumers to evaluate for themselves whether a food is an appropriate addition to their dietary practices. This approach—disclosure rather than suppression—is mandatory under the First Amendment.

Use of a disclaimer in conjunction with CHD claims for walnuts would be inappropriate because the proposed model claim is tailored to the substantiating scientific evidence. The ability of walnuts to precipitate significant reductions in serum total and LDL cholesterol is accurately and comprehensively captured by the word “can.” The scientific evidence consistently demonstrates the cardioprotective properties of walnuts, rather than a particular constituent of walnuts. Under these circumstances, additional qualifying language is not required.

## VI. Description of Attachments

Included among the attachments accompanying this petition is a review, commissioned by the Petitioner and conducted by the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences, of the publicly available scientific evidence regarding the relationship between ingestion of walnuts and the risk of CHD. *See Attachment 1*. The review was prepared by well-qualified scientific experts. Together with the supplementary evidence discussed in this petition, the review demonstrates that the proposed health claim is fully supported in accordance with the legal requirements of the NLEA “significant scientific agreement” standard. While the convening of an expert panel of the kind represented in the

LSRO review is not required by the NLEA, the statute recognizes explicitly that scientific conclusions formalized through consensus reports of this kind are important and deserve to be given special weight by FDA. *See* FD&C Act § 403(r)(3)(C), 21 U.S.C. § 343(r)(3)(c).

Attachment 2 contains examples of public health messages developed and disseminated by FDA and other federal public health authorities. *See supra* pages 13-14.

The LSRO report was completed in December 2000. The Petitioner has conducted a literature search to identify any pertinent published data and information not included in the LSRO report (*i.e.*, because it was published after the cut-off date for the report), and attaches the results of that search hereto (Attachment 3).

To the best of the Petitioner's knowledge, all non-clinical studies relied upon in the LSRO review were conducted in compliance with FDA's good laboratory practices regulations (21 C.F.R. part 58) and all clinical investigations relied upon were either conducted in compliance with the requirements for institutional review set forth at 21 C.F.R. part 56 or were not subject to such requirements by operation of 21 C.F.R. §§ 56.104 or 56.105. To the best of the Petitioner's knowledge, the clinical trials relied upon in the petition were conducted in compliance with the requirements for informed consent set forth in 21 C.F.R. part 50.

All of the scientific references cited herein or in the accompanying LSRO Review are included in an accompanying binder set, organized alphabetically according to the last name of the first cited author. A list of the scientific references is included as Attachment 4.

#### **VII. Environmental Impact**

The issuance of a regulation by FDA in response to a health claim petition as described in 21 C.F.R. § 101.70 is one of the classes of actions listed in FDA regulations as categorically excluded and, therefore, does not require the preparation of an Environmental Assessment or an Environmental Impact Statement. 21 C.F.R. § 25.32(p).

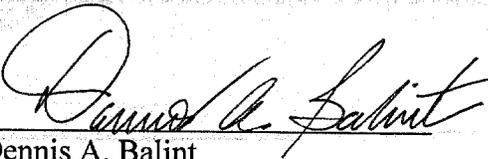
#### **VIII. Conclusion and Certification**

For the foregoing reasons, the Petitioner requests that FDA approve the proposed health claims. On behalf of the Petitioner, I hereby certify that, to the best of my knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information known to me to be pertinent to the evaluation of the proposed health claim.

Respectfully submitted,

**CALIFORNIA WALNUT COMMISSION**

By

  
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