

Health Claim Petition for Nuts and Coronary Heart Disease

Volume 1 of 3

The International Tree Nut Council
Nutrition Research and Education
Foundation

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SUBJECT OF THE PETITION: Authorization of a health claim for nuts and
coronary heart disease

SUBMITTED TO: Office of Nutritional Products, Labeling and
Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
	A. Public Health Implications.....	2
	B. Walnut Health Claim Petition.....	6
II.	PRELIMINARY REQUIREMENTS.....	6
	A. Nuts are a substance under 21 CFR § 101.14 (a)(2).....	7
	B. The U.S. population is at risk for heart disease.....	8
	C. Nuts contribute taste, aroma and nutritive value to the diet.....	8
	D. Nuts are safe and lawful.....	9
III.	SUMMARY OF SCIENTIFIC DATA SUPPORTING THE CLAIM....	10
	A. Introduction/Overview.....	10
	B. Mechanism of action.....	12
	C. Review papers.....	16
	D. Epidemiologic studies.....	21
	E. Dietary intervention studies.....	35
	F. Statements from Public Health and Professional Organizations.....	72
	G. Significant Scientific Agreement (SSA).....	76
IV.	DIETARY CONSIDERATIONS.....	81
	A. Micronutrients.....	81
	B. Energy/body weight.....	83
	C. Fat/saturated fat.....	88
V.	EFFECTIVE DOSE.....	90
VI.	NATURE OF THE FOOD ELIGIBLE TO BEAR THE CLAIM.....	95
	A. Minimum content of nuts per RACC.....	95
	B. Total fat content.....	99
	C. Cholesterol content.....	101
	C. Saturated fat content.....	101
VII.	EXEMPTIONS TO GENERAL HEALTH CLAIM PROVISIONS.....	105
	A. Total fat disqualifier level.....	105
	B. Saturated fat disqualifier level.....	108
	C. 10% DV nutrient contribution requirement.....	110
VIII.	PROPOSED MODEL HEALTH CLAIM.....	113
IX.	DETERMINATION OF COMPLIANCE.....	114
X.	REQUEST FOR INTERIM FINAL RULE.....	115
XI.	ENVIRONMENTAL IMPACT ASSESSMENT.....	117
XII.	CONCLUSION.....	117
XIII.	PROPOSED REGULATORY TEXT.....	118
XIV.	CERTIFICATION.....	123
	APPENDICES	
	A. Bibliography	
	B. Adult Treatment Panel III sample menus	
	C. Meta analysis	
	D. CSFII and NHANES statistical methodology	
	E. Literature search	
	F. References	

I. INTRODUCTION

The undersigned, the International Tree Nut Council Nutrition Research and Education Foundation (INCNREF), submits this petition pursuant to section 403(r)(4) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 343(r)(4), and 21 CFR § 101.70 (f), requesting that the Food and Drug Administration (FDA) authorize a health claim for use in the labeling of nuts and eligible nut-containing products regarding the ability of such foods to reduce the risk of coronary heart disease (CHD). The claim would apply to eligible products that consist of or contain at least 7.1 grams of nuts per reference amount customarily consumed (RACC), composed of almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, peanuts, pecans, pine nuts, pistachio nuts and/or walnuts. A model wording of the proposed claim is, “Diets containing one ounce of nuts per day can reduce your risk of heart disease.”

INCNREF represents the research and education arm of the International Tree Nut Council (INC). INCNREF is an international, non-profit, non-governmental organization dedicated to supporting nutrition research and education for consumers and health professionals throughout the world and promoting new product development for tree nut products. Members include those associations and organizations that represent the nine tree nuts (almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, pecans, pine nuts, pistachio nuts and walnuts) in more than 40 producing countries.

INCNREF respectfully requests that FDA authorize the proposed health claim because the totality of available evidence demonstrates that the significant scientific agreement

(SSA) standard has been met, and because there is a significant opportunity to benefit public health by disseminating this information to American consumers in food labeling.

A. Public Health Implications

The mission of the FDA, as defined by the FDA Modernization Act of 1997 (Pub. L. No. 105-115), relates primarily to public health. The following priorities are set forth by this Act (21 U.S.C. §393 (b)):

- 1) Promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;
- (2) with respect to such products, protect the public health by ensuring that...foods are safe, wholesome, sanitary, and properly labeled...

FDA has a unique opportunity to address this public health mission by authorizing the proposed health claim. Such a claim is important because the available scientific information suggests eating at least one ounce of nuts per day has the potential to reduce the incidence of CHD in the U.S. by 30-50% (Fraser, 1999). A 30% reduction in CHD incidence could save 138,000 lives, prevent 600,000 hospitalizations, and reduce direct health care costs by \$16 billion per year based on statistics compiled by the American Heart Association (2000). Furthermore, consumer research suggests that a health claim for nuts is important because it would deliver a simple message that would be appealing to U.S. consumers and easy for them to implement.

A health claim for nuts is particularly appealing from a public health perspective because consumers like the taste of nuts – a trend that is increasing. Taste is the most important factor cited by U.S. consumers in determining the foods they purchase. Glanz *et al.* (1998) reported that a sample of 2,967 consumers rated the importance of taste 4.68 on a 5-point scale. African American and Hispanic respondents reported slightly higher ratings (4.74 and 4.73, respectively) than did white subjects (4.67). In addition, consumer research conducted by the Food Marketing Institute (1999, 2000) reveals that in every year since 1990, “taste” has been the factor most frequently rated “very important” by U.S. grocery store shoppers in determining the foods they buy. Eighty-nine percent of respondents rated this factor as “very important” in 2000. (By comparison, “nutrition” was cited by 71% of consumers in this survey as “very important” in 2000 and has been the second most important factor each year since 1990.)

Data presented in Table 1 show that a majority of 750 U.S. consumers who participated in a recent study rated their liking for nuts as 9 or 10 on a ten-point scale, and that the trend has been increasing since 1998.

Table 1
Overall Liking For Nuts among U.S. Consumers*

Year	Percent Score Distribution				
	1-2	3-4	5-6	7-8	9-10
2001	1	1	11	30	57
1999	2	2	12	31	54
1998	1	2	13	35	48

* Consumer Attitude, Awareness and Usage Study conducted by The Sterling-Rice Group, Boulder, CO 80302

These data suggest that taste would be an incentive for most consumers to include nuts in their daily diet. Consumption of nuts would provide an additional option to reduce the risk of CHD that may be particularly attractive to individuals who have been unsuccessful in implementing other strategies (e.g. a low fat, high carbohydrate diet; consuming 25 grams of soy protein per day) due to concerns about taste and/or lifestyle.

In addition to taste, a health claim for nuts would be particularly effective from a public health perspective because consumers would find the message compelling. Interviews with 416 consumers (201 of them female) aged 18-70 who rated themselves as current or potential purchasers of nuts were conducted for the Planters[®] division of Kraft Foods, Inc. “Heart Healthy” was ranked first or second from a list of 33 potential health and nutrition-related claims by consumers aged 35-54 and 55-70 based on importance, believability and ability to motivate. The complete list of claims that were evaluated is presented in Table 2.

In summary, INCNREF strongly believes that an FDA-authorized health claim about the ability of nuts to reduce the risk of CHD is highly desirable because it is based on sound science, has significant potential to improve public health, and would be relevant and compelling for consumers.

Table 2
Potential Claims for Planters® Nuts*

Claim
Can be part of a balanced diet
Can be part of a healthy diet
Can be part of a healthy lifestyle
Contributes to healthy metabolism
Has natural goodness
Has no cholesterol
Is a good source of antioxidants
Is a good source of fiber
Is a good source of protein
Is good for you
Is naturally nutritious
Is packed with good nutrition
Is packed with vitamins and minerals
Has no trans fat
Has the good fat, just like in olive oil
Has the good fats – the unsaturated ones
Is low in saturated fats
Is a good source of energy
Is a satisfying snack
Is a substantial snack
Is satisfying, to help you manage your weight
Provides you with long lasting energy
Provides you with long lasting hunger satisfaction
Satisfies your hunger
Tides you over
Helps lower blood pressure
Helps lower cholesterol
Helps lower Triglycerides
Helps maintain your good (HDL) cholesterol
<i>Is heart healthy</i>
May reduce the risk of cardiovascular disease
Is naturally low in carbohydrates
Is naturally low in sugar

*Consumer Research conducted for Kraft Foods, Inc (2002).

B. Walnut Health Claim Petition

INCNREF is incorporating by reference into this document the contents of the health claim petition recently submitted to FDA by the California Walnut Commission¹. In so doing, INCNREF generally invokes and affirms the legal and scientific arguments described in that petition². However, we believe the totality of observational and clinical data on the cardioprotective properties of *all* nuts (as described below) provide stronger evidence of the ability of nuts generally to reduce the risk of CHD than the walnut data in isolation provide for walnuts alone. Specifically, the epidemiologic data demonstrate a strong association between nut consumption and reduced risk of CHD. INCNREF believes that these data alone are sufficient to establish SSA. However, because these observational data pertain to all nuts rather than walnuts alone, they cannot be used to substantiate a claim for walnuts or any other single nut. In addition, while there are six well-controlled clinical trials that support the ability of walnuts to improve serum CHD biomarkers, an additional 13 clinical trials provide similar evidence for other nuts. Taken together, the epidemiologic studies and the feeding trials for nuts in general, provide a critical mass of information that complements the walnut data, and convincingly demonstrates that the SSA standard has been met for a claim for nuts as a group.

II. PRELIMINARY REQUIREMENTS

Pursuant to 21 CFR § 101.70 (f), health claim petitions are required to, "...demonstrate that the substance of the proposed claim conforms to the definition of the term

¹ California Walnut Commission. "*Diets Including Walnuts Can Reduce the Risk of Heart Disease*" March 15, 2002. Docket 02P-0292

² INCNREF is in general agreement with the content of the Walnut Commission petition, but does not necessarily agree with all of the individual statements in that document.

‘substance’ in § 101.14 (a)(2),” and to explain, “...how the substance conforms to the requirements of § 101.14 (b).” The requirements of 21 CFR § 101.14 (b) that are applicable to petitions for whole foods (e.g. nuts) that are to be consumed at other than reduced levels in the diet are: 1) to demonstrate that the substance is, “... associated with a disease or health-related condition for which the general U.S. population...is at risk...”; 2) to show that the substance, “...contribute[s] taste, aroma, or nutritive value...”; and 3) to demonstrate that the substance is, “... a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA’s satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act.”

A. Nuts are a “substance” under 21 CFR § 101.14 (a)(2)

The definition of a “substance” under 21 CFR § 101.14 (a)(2) is, “...a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances.” All nuts that are the objects of the proposed health claim (almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, peanuts, pecans, pine nuts, pistachio nuts and walnuts) are conventional foods, regulated by FDA, and clearly meet the regulatory definition of a “substance”.

B. The U.S. population is at risk for heart disease

Data from the Centers for Disease Control and Prevention (2001) indicate that 709,894 U.S. citizens died of diseases of the heart during 2000. CHD was the leading cause of mortality during that year and accounted for 29.5% of all U.S. deaths. In addition, FDA has accepted CHD as “a health-related condition for which the general U.S. population...is at risk” in authorizing other CHD-related claims including: dietary saturated fat and cholesterol and risk of coronary heart disease (21 CFR § 101.75); fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease (21 CFR § 101.77); soluble fiber from certain foods and risk of coronary heart disease (21 CFR § 101.81); soy protein and risk of coronary heart disease (21 CFR § 101.82); and plant sterol/stanol esters and risk of coronary heart disease (21 CFR § 101.83).

C. Nuts contribute taste, aroma and nutritive value to the diet

All nuts that are the objects of the proposed health claim (almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, peanuts, pecans, pine nuts, pistachio nuts or walnuts) contribute taste, aroma and nutritive value to the diet. As noted previously (see Table 1), consumer research shows that a majority of U.S. consumers polled rated the taste of nuts as either 9 or 10 on a ten-point scale.³

Recent review papers (Dreher and Maher, 1996; de Lorgeril, *et al.*, 2001; Kris-Etherton *et al.*, 2001) have summarized the range of essential nutrients nuts contribute to the diet. Nuts are a nutrient dense package that can make substantial contributions to the diet.

³ Consumer Attitude, Awareness and Usage Study conducted by The Sterling-Rice Group, Boulder, CO 80302

Many of the nutrients in nuts are thought to contribute cardioprotective properties (e.g. protein, fiber, vitamin E, folic acid, vitamin B6, niacin, magnesium, copper, zinc and potassium). Furthermore, the nuts that are the objects of the proposed claim are meaningful sources of unsaturated (i.e. monounsaturated and/or polyunsaturated) fatty acids, which have been shown to reduce the concentration of total cholesterol (T-C) and low-density lipoprotein-cholesterol (LDL-C) in the blood – both accepted biomarkers for CHD. Nuts do not contain *trans* fatty acids. This fact may become increasingly important as public awareness of the nutritional properties of *trans* fats increases and consumers look for more *trans* fatty acid-free sources of “healthy” fats. Finally, a recent report from USDA (Lino *et al.*, 2000) found that the nutritional quality of the diet (as measured by a modified Healthy Eating Index) was significantly higher for nut eaters than for non-nut eaters.

D. Nuts are safe and lawful

The nuts that are the objects of the proposed claim are well recognized by U.S. consumers and have been a part of the diet for many years. Annual U.S. consumption of tree nuts and peanuts was 8.5 pounds per person in 1997 (Lino *et al.*, 2000).

Tree nuts and peanuts are among eight foods that are most frequently implicated in serious allergic responses. However, the nut industry has worked diligently to address this issue by cooperating with and supporting the Food Allergy and Anaphylaxis Network in an effort to educate consumers and alert them to labeling and issues of potential concern. In addition, organizations representing the manufacturers of tree nut and

peanut-containing products have developed guidelines for food allergen labeling through the Food Allergy Issues Alliance (Hildwine *et al.* 2001). Although the nut industry will continue to act responsibly in the area of food allergy, this issue is not relevant to the proposed claim because FDA has stated that allergenic potential is not a safety issue with respect to authorization of health claims (64 FR 57700, 57707, October 26, 1999):

FDA does not believe that, because some persons may have allergic reactions to a food, it is unsafe. FDA has previously stated that the declaration of an allergenic substance in the ingredient statement on the food label provides adequate information for consumers regarding the presence of the allergenic ingredient in the product (63 FR 8103 at 8113), and sees no reason to change this view with respect to soy. FDA notes, in agreement with one of the comments received, that authorization of a health claim for soy protein and CHD will highlight the presence of soy protein in those food products that bear the claim. The agency, therefore, anticipates that persons with known soy allergies will be able more easily to avoid soy protein based products.

The same comments are equally applicable to tree nuts and peanuts.

III. SUMMARY OF SCIENTIFIC DATA SUPPORTING THE CLAIM

A. Introduction/Overview

Spiller *et al.* (1992) published the first dietary intervention study that showed nuts could reduce the risk of CHD a decade ago. This study showed that feeding 100 g of almonds per day for nine weeks to 26 moderately hypercholesterolemic subjects, as part of a low saturated fat, low cholesterol diet, reduced serum T-C by 8.9% compared to the baseline diet.

During the past 10 years, sufficient additional evidence has accumulated to convincingly demonstrate that there is SSA in this area. This conclusion is supported by seven separate reports from observational studies that consistently find a protective association between consumption of tree nuts and/or peanuts and CHD morbidity and mortality, and by 19 controlled intervention trials with normo- and/or moderately hypercholesterolemic subjects. Suggestive evidence is provided by six additional intervention studies, which reported favorable effects on serum lipids among subjects who consumed nuts as part of dietary interventions that included other foods.

These observational studies and intervention trials prompted the publication of six major review articles that strongly support the conclusion that nuts, when consumed regularly as part of a balanced diet, reduce the risk of CHD.

Statements consistent with the position that nuts have cardioprotective properties have also been published by the American Heart Association (2000), the U.S. Department of Agriculture (Lino *et al.*, 2000), the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (FASEB) (Feldman, 2002) and the National Heart Lung Blood Institute (2001) in its revised National Cholesterol Education Program, Adult Treatment Panel III (ATP III) report.

INCNREF is confident that FDA will agree that the following review of the literature provides compelling evidence that the SSA standard has been achieved relative to the

ability of nuts to reduce risk of CHD, and that a health claim relative to this important diet-disease area should be authorized.

B. Mechanism of action

The primary mechanism by which tree nuts and peanuts reduce the risk of CHD is likely their ability to lower T-C and LDL-C concentrations in response to dietary unsaturated fat. The most popular tree nuts and peanuts contain substantial amounts of monounsaturated (MUFA) and/or polyunsaturated (PUFA) fat in relation to total fat content on a per serving basis as shown in Table 3.

Table 3
The Fatty Acid Class Distribution of Common Nuts per Serving

Nut	Monounsaturated Fat (g/1 oz. serving)	Polyunsaturated Fat (g/1 oz. serving)	Saturated Fat (g/1 oz. serving)	Unsaturated Fat (% of total fat)	Total Fat (g/1 oz. serving)
Almonds	9.1	3.5	1.1	87.5	14.4
Brazil nuts	6.5	6.8	4.6	70.7	18.8
Cashew nuts	7.2	2.4	2.3	72.1	13.3
Hazelnuts	12.9	2.3	1.3	88.3	17.2
Macadamia nuts	16.7	0.43	3.4	79.7	21.5
Peanuts	6.9	4.4	1.9	80.7	14.0
Pecans	11.6	6.1	1.8	86.8	20.4
Pine nuts	5.4	6.1	2.2	79.9	14.4
Pistachio nuts	6.6	3.8	1.5	82.5	12.6
Walnuts	2.5	13.4	1.7	85.9	18.5

Source: USDA Nutrient Database for Standard Reference, Release 15

These data show that MUFA and/or PUFA forms of fat dominate the fatty acid profile of all common nuts. The lipid distribution of nuts provides consumers with an excellent

opportunity to use them as substitutes for more concentrated sources of saturated fat in the diet, thereby reducing the risk of CHD.

This petition will present evidence that regular consumption of reasonable quantities of nuts has favorable effects on serum lipids. FDA has been clear in its position that LDL-C, and to a lesser extent high-density lipoprotein cholesterol (HDL-C), are appropriate biomarkers for risk of CHD, and has used these criteria to justify the authorization of all CHD-related health claims. The preamble to the Interim Final Rule for the health claim on plant sterol/stanol esters and CHD (65 FR 54686, 54690, September 8, 2000) states:

... the agency based its evaluation of the relationship between consumption of plant sterol/stanol esters and the risk of CHD primarily on changes in blood total and LDL cholesterol resulting from dietary intervention with plant sterol/stanol ester-containing products. A secondary consideration was that beneficial changes in total and LDL cholesterol should not be accompanied by potentially adverse changes in HDL cholesterol. This focus is consistent with that used by the agency in deciding on the dietary saturated fat and cholesterol and CHD health claim, §101.75 (56 FR 60727 and 58 FR 2739); the fiber-containing fruits, vegetables, and grain products and CHD claim, §101.77 (56 FR 60582 and 58 FR 2552); the soluble fiber from certain foods and CHD claim, §101.81 (61 FR 296, 62 FR 3584, 62 FR 28234, and 63 FR 8119) and the soy protein and CHD claim §101.82 (63FR 62977 and 64 FR 57700).

In addition to their unsaturated fat content, nuts contain a variety of other substances that may contribute to their cardioprotective properties. These constituents include macronutrients (protein – including arginine, dietary fiber), B-vitamins (folic acid, vitamin B-6, niacin), minerals (magnesium, copper, zinc, calcium, potassium) and a wide range of other bioactive compounds (e.g. phytosterols, β -sitosterol, ellagic acid, flavonoids, phenolic compounds and isoflavones). The potentially cardioprotective

Table 4
Concentration of Potentially Cardioprotective Substances in Nuts

Nut (per 1 oz serving)	Protein (g)	Dietary Fiber (g)	Vitamin E (mg, ATE)	Folate (μ g DFE)	Vitamin B ₆ (mg)	Niacin (mg)	Magnesium (mg)	Copper (mg)	Zinc (mg)	Potassium (mg)	Phytosterols (mg)
Almonds	6.0	3.3	7.4	8.2	0.04	1.1	78	0.3	1.0	206	34
Brazil nuts	4.1	1.5	2.1	1.1	0.07	0.5	64	0.5	1.3	170	N/A
Cashew nuts	5.1	0.94	0.41	7.1	0.12	0.3	83	0.6	1.6	187	N/A
Hazelnuts	4.2	2.8	4.3	32	0.16	0.5	46	0.5	0.7	193	27
Macadamia nuts	2.2	2.4	0.15	3.1	0.08	0.7	37	0.2	0.4	105	33
Peanuts	7.3	2.4	2.6	68	0.10	3.4	48	0.3	0.9	200	62
Pecans	2.6	2.7	1.2	6.2	0.06	0.3	34	0.3	1.3	116	29
Pine nuts	6.8	1.3	0.99	16	0.03	1.0	66	0.3	1.2	170	40
Pistachios	5.8	2.9	1.3	15	0.48	0.4	34	0.4	0.6	291	61
Walnuts	4.3	1.9	0.83	28	0.15	0.6	45	0.5	0.9	125	20

Source: USDA Nutrient Database for Standard Reference, Release 15

factors in nuts have been reviewed (Dreher and Maher, 1996; de Lorgeril *et al.*, 2001; Kris-Etherton *et al.*, 2001) and the concentrations of some of the major components according to the most recent USDA data (2001) are presented in the Table 4.

The exact mechanism by which nuts reduce the risk of CHD cannot be definitively attributed to a single component. Their unsaturated fatty acid content alone is sufficient to demonstrate that these foods reduce the risk of CHD. It is likely that unsaturated fat works in combination with a range of other cardioprotective substances in nuts to produce the beneficial effect. FDA has been clear that it is not necessary to identify either an exact mechanism or a specific substance in a food(s) in order to justify authorization of a health claim. Specifically, the Final Rule authorizing a health claim for soy protein and coronary heart disease (64 FR 57700 at 57709) states,

Other comments reviewed various possible mechanisms for the cholesterol-lowering effects of soy protein and some argued that until the mechanism of action of soy protein is clearly established, no health claim should be authorized. **FDA notes, however, that such knowledge is not necessarily required for authorization of a health claim.** (Emphasis added)

In addition, the agency's document, "Guidance for Industry – Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (December 22, 1999) states,

Measurement issues generally focus on substances in food, but the same principles apply when the substance of interest is itself a food. While a single food can be the subject of a health claim, existing experience is that the subject is more likely to be a group of foods,

such as fruits, vegetables, and grains, which have been associated with a reduced risk of heart disease and of cancer. This identification, and consequently measurement, of a food group is, in turn, most likely to occur because it is not possible to identify and, therefore, measure a particular component of these foods that is responsible for the benefit.

These FDA positions provide ample precedent for the authorization of a health claim for nuts. The data presented below will demonstrate that nuts have a significant potential to improve public health by reducing the risk of CHD, and will provide the agency with ample evidence to grant this petition so that the information can be more widely disseminated to American consumers.

C. Review Papers

Six comprehensive review articles published since 1996 (Dreher and Maher, 1996; Fraser *et al.*, 1999; Hu and Stampfer, 1999; Kris-Etherton *et al.*, 1999; Sabaté *et al.*, 1999; Kris-Etherton, *et al.* 2001) conclude that tree nuts and peanuts reduce the risk of CHD in the U.S. population. These articles, written by experts qualified by scientific training and experience to evaluate such information, are strong evidence that the SSA standard has been met. The major findings of these papers are summarized below.

Fraser (1999) reviewed epidemiologic data from four major studies: the Adventists' Study, the Iowa Women's Study, the Nurses' Health Study and the Physicians' Health Study. These studies consistently found that increased frequency of nut consumption is associated with decreased risk of coronary heart disease morbidity

and/or mortality in the range of 30-50%. Results were consistent across virtually all population segments including men, women, vegetarians, omnivores, hypertensives, nonhypertensives, obese, nonobese, young and old. This association was seen in all studies despite differing ranges of nut intakes from greater than once per week in the Iowa Women's Study (Kushi *et al.*, 1996) to more than once a day in the Adventists' Health Study (Fraser *et al.* 1992). Adjustment for potential confounding variables such as dietary fats, fiber, vegetables and fruits did not alter the conclusions. Fraser *et al.* (1999) concluded, "Four of the best and largest cohort studies in nutritional epidemiology have now reported that eating nuts frequently is associated with a decreased risk of coronary heart disease of the order of 30-50%. The findings are very consistent in subgroup analyses and unlikely to be due to confounding."

Fraser (1999) also noted that data from feeding trials consistently suggested that reasonable quantities of nuts in the diet were as effective or superior to the recommended Step I Heart Association diet in reducing LDL-cholesterol and that weight gain was not associated with increased nut consumption. Feeding studies have consistently demonstrated reductions of LDL-C in the range of 8-12%, which would be expected to result in a reduction in CHD events by as much as 25%. The fact that nuts contain a broad array of other constituents (e.g. vitamin E, dietary fiber, magnesium, arginine, phytosterols) that could contribute to their cardioprotective properties was cited as a possible explanation of why the observational studies showed a significantly larger than expected reduction in CHD incidence of 30-50%.

Hu and Stampfer (1999) also reviewed the observational studies that examined the association between nut consumption and risk of CHD. Analysis of seven population samples from five prospective cohort studies found that consumption of nuts was associated with a reduced risk of CHD of 43 to 75%. Data from the Nurses' Health Study showed that substituting one ounce of nuts for an equivalent amount of energy from carbohydrate was associated with a 30% reduction in CHD while an isocaloric substitution of one ounce of nuts for saturated fat was associated with a 45% decrease in CHD incidence. The authors conclude, "Given the strong scientific evidence for the beneficial effects of nuts, it seems justifiable to move nuts to a more prominent place in the United States Department of Agriculture Food Guide Pyramid."

Another review of the epidemiologic data (Sabaté, 1999) concluded that consuming nuts five times or more per week is associated with lower mortality rates ranging from 18 to 44%. This benefit extends to whites, blacks and the elderly and was not offset by increased mortality from other competing causes. The paper concludes, "...the effect of nuts on all-cause mortality seems to be independent of other risk factors and the potential confounding effect of vegetarian status or meat consumption. Thus, nut consumption may not only offer protection against ischemic heart disease but may also increase longevity."

Kris-Etherton *et al.* (2001) reached similar conclusions after reviewing the epidemiologic and clinical data with respect to nut consumption and incidence of CHD. These authors stated, "Epidemiologic studies have consistently demonstrated

beneficial effects of nut consumption on coronary heart disease (CHD) morbidity and mortality in different population groups. Clinical studies have reported total and low-density lipoprotein cholesterol-lowering effects of heart-healthy diets that contain various nuts or legume peanuts.”

Kris-Etherton *et al.* (2001) conclude, “...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.”

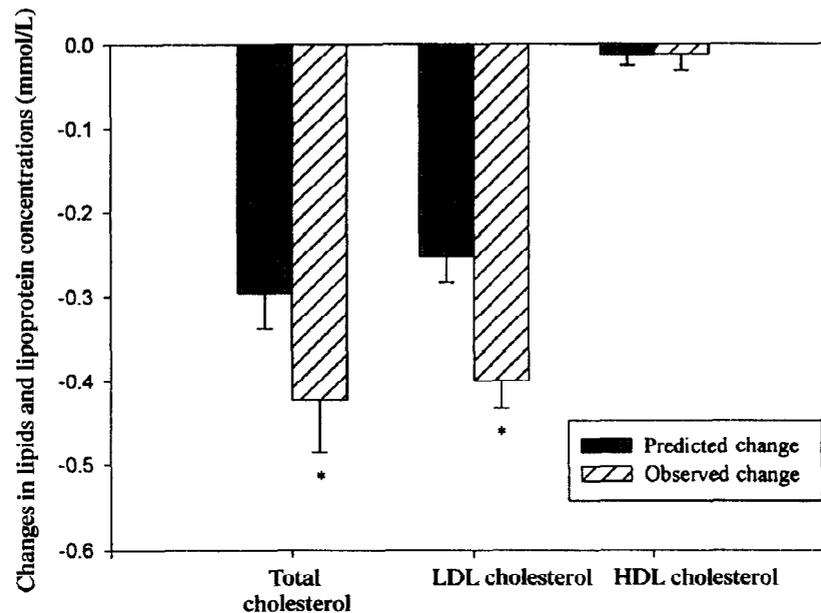
An earlier review by this group (Kris-Etherton *et al.*, 1999) compared the reductions in serum lipids seen in four controlled nut feeding trials with those predicted from changes in fatty acid intake using the equation derived by Hegsted and that of Mensink and Katan. As shown in Figure 1, nut-containing diets resulted in a more potent lipid lowering effect than would be expected based on their fatty acid composition. The authors conclude that it is not yet clear what specific protective compounds in nuts contribute to their cardioprotective effect as reported in epidemiologic studies. It is plausible that bioactive compounds involving mechanisms other than blood lipid changes contribute to their ability to reduce the risk of CHD.

Two review papers noted earlier (Dreher and Maher, 1996; de Lorgeril *et al.*, 2001) summarized the potentially cardioprotective substances in nuts. These foods are rich

sources of oleic acid, linoleic acid and α -linolenic acid, and are low in saturated fats.

Nuts are also sources of plant protein, dietary fiber, vitamins such as vitamin E, folic

Figure 1



Source: Kris-Etherton *et al* Am. J. Clin. Nutr. 1999 (suppl); 70:504S

Comparison of observed changes (mean \pm SE) in total-, LDL-, and HDL-cholesterol concentrations (12–15, 18) with those calculated by using the predictive equations for plasma cholesterol of Hegsted *et al.* and Mensink and Katan. Observed change was significantly different from the predicted change, $P < 0.05$ (t test).

acid, vitamin B-6 and niacin, and minerals such as copper, magnesium, zinc, and potassium, in addition to plant sterols and other phytochemicals. Additionally, the high arginine content of nuts may help raise levels of endogenous nitric oxide, which promotes normal endothelia function and inhibits platelet aggregation.

Dreher and Maher (1996) also reported that a review of intervention studies supported the view that frequent nut consumers have *lower* body weights than non-nut eaters despite the fact that nuts are an energy-dense food.

In summary, all of the review papers that have examined the health effects of tree nuts and peanuts have concluded that increased intake of these foods is associated with decreased morbidity and mortality from CHD. The effect occurs among many population segments and is independent of other dietary or life-style factors. The observational data suggest that frequent consumption of nuts would reduce the risk of CHD by approximately 30 – 50%. A comparison of the lipid-lowering effect of feeding nuts with theoretical calculations based on dietary fatty acid effects suggests that part of the benefit of nuts is due to non-lipid components. Furthermore, evidence from intervention studies suggests that subjects provided with controlled amounts of nuts tended not to gain weight over the course of the experiments. Taken together, these review papers provide strong evidence that experts qualified by scientific training and experience to evaluate such information agree that nuts have the ability to reduce the incidence of CHD. This consensus is strong evidence that the SSA standard has been met, and that a health claim should be authorized. The individual studies considered in these review papers will be discussed in detail below.

D. Epidemiologic studies

FDA's Guidance for Industry on Significant Scientific Agreement (December, 1999) explicitly states that compelling observational data are sufficient to infer causality and

to support the conclusion that SSA has been achieved. Causality can be demonstrated using observational data by assessing the strength of the association, the consistency of the association, the independence of the association, evidence of a dose-response relationship, temporal correctness of the association, evidence of a dechallenge effect, specificity of the association and whether or not there is a biologically plausible mechanism.

FDA used this approach when it relied solely on epidemiologic data to authorize the health claim on fruits, vegetables and reduced risk of cancer. This claim was authorized, despite the lack of dietary intervention studies, because observational data on the association between whole fruits and vegetables and cancer was compelling, and there was a lack of data linking individual components in such foods (e.g. antioxidant vitamins) with an effect. In authorizing the final regulation (58 FR 2262, 2634, January 6, 1993), the agency observed that the protective association between fruits and vegetables and cancer could be due to several different mechanisms. These foods could displace fat (a substance associated with increased cancer risk) in the diet, they contain antioxidant nutrients (e.g. vitamin C and beta-carotene) which were shown to be associated with reduced cancer incidence, they contain dietary fiber which may reduce the risk of cancer, and fruits and vegetables contain nonnutritional substances including indoles, phenols, flavones and terpenes which were hypothesized to have anti-cancer properties.

The rationale used to authorize the health claim for fruits, vegetables and cancer is directly applicable to the authorization of a claim for nuts and CHD. Specifically, the epidemiologic data associating the consumption of nuts with reduced CHD morbidity and mortality is very strong based on the criteria important to FDA. In addition, there is ample evidence of a biologically plausible mechanism because nuts contain unsaturated fats, which have been shown to lower the risk of CHD. Furthermore, nuts contain a variety of nutrient and nonnutrient components that have been hypothesized to have protective effects on the cardiovascular system. However, unlike the health claim for fruits, vegetables and cancer, which is based exclusively on observational studies, we will present compelling data from well-controlled dietary intervention trials that demonstrate that feeding nuts produces favorable changes in biomarkers for CHD, especially the lowering of T-C, LDL-C and the ratio of T-C/HDL-C.

The epidemiologic data discussed below are sufficient in their own right to justify authorization of the proposed health claim. However, the appropriateness of this decision will become even more apparent when the observational data are considered in conjunction with data from dietary intervention trials that will be summarized later in this document.

The published observational studies that address the association between nut consumption and morbidity and/or mortality from CHD are summarized (in chronological order) in Table 5 and are discussed in additional detail below.

Table 5
Summary of Observational Studies Regarding Nuts and CHD

Author	Title	Literature Citation	Purpose of Study	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Conclusions
Albert, C M , Gaziano, J M , Willett, W.C and Manson, J E	Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study	Archives of Internal Medicine, 2002, 162 1382	To examine the association between nut intake and coronary heart disease mortality in male health professionals	Prospective cohort study	22,071 male physicians in the United States who were between 40 and 84 years of age when enrolled in the study in 1982	Nut consumption during the previous year was categorized into one of seven categories that ranged from "two or more times per day" to "rarely or never" using a 20-item food frequency questionnaire 21,454 participants returned the survey Incidence of cardiovascular events were collected every six months and cause of death was determined by interviews and examination of medical records	The average follow-up period for the study was 17 years During this period there were 176 definite and 25 probable cardiac-related sudden deaths Compared with men who rarely or never consumed nuts, those who consumed nuts two or more times per week had reduced risks of sudden cardiac death (RR= 0.53, 95% CI 0.30 – 0.92) and total coronary heart disease death (RR= 0.70, 95% CI 0.50 – 0.98) after correcting for age, aspirin and beta-carotene treatment, evidence of CVD before the 12 month questionnaire, BMI, smoking, history of diabetes, hypertension or hypercholesterolemia, alcohol consumption, vigorous exercise, vitamin E, vitamin C and multivitamin use at baseline, consumption of fish, red meat, fruits and vegetable and dairy intake Nut consumption was not related to incidence of non-fatal MI	The data suggest that nut consumption is associated with reduced risk of total coronary disease death primarily due to reduction in sudden death
Lavedrine, F , Zmirou, D., Ravel, A , Balducci, F , and Alary, J	Blood cholesterol and walnut consumption A cross-sectional survey in France	Preventive Medicine, 1999, 28 333-339	To assess the association between walnut consumption as a source of polyunsaturated fatty acids and blood lipid levels among individuals living in a walnut-producing region of France	Cross-sectional survey	793 males and females ages 18-65 living in Dauphine, France	Habitual diet was assessed for the past year using a food frequency questionnaire that included questions about dairy and animal fat consumption as well as intake of alcohol Specific questions about consumption of walnuts and walnut oil were included Blood samples were collected for analysis of serum lipids	Subjects were classified as "frequent", "intermediate", or "nonconsumers" of walnut oil and walnut oil and kernels Multiple linear regression adjusted for gender, age, BMI, alcohol intake and animal fat consumption showed increased concentrations of HDL-C and Apo A1 among walnut consumers There were no correlations between frequency of walnut consumption and T-C or LDL-C among this population	Walnut consumption is associated with beneficial changes in HDL-C and Apo A1

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Summary of Observational Studies Regarding Nuts and CHD

Author	Title	Literature Citation	Purpose of Study	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Conclusions
Hu, F B , Stampfer, M J, Manson, J E , Rimm, E B , Colditz, G A , Rosner, B A , Speizer, F E , Hennekens, C H and Willett, W C	Frequent nut consumption and risk of coronary heart disease in women prospective cohort study	British Medical Journal, 1998, 317 1341-1345	To examine the relation between nut consumption and risk of coronary heart disease in a cohort of women from the Nurses' Health Study	Prospective cohort study	86,016 women, age 34 – 59 years with no previously diagnosed coronary heart disease, stroke, or cancer	Food frequency questionnaires with 61 items used to assess nut consumption at baseline (1980) The FFQ was expanded to include 116 items in 1984, and also administered in 1986 and 1990. Study endpoints were either non-fatal myocardial infarction or fatal coronary heart disease that occurred prior to June 1994	1,255 coronary events occurred during 14 years follow up. After adjusting for age, smoking, and other known risk factors for CHD, women who ate more than five units of nuts (defined as 1 oz) a week had significantly lower risk of total CHD (RR= 0.65, 95% CI 0.47-0.89 P for trend =0.0009) than women who never ate nuts or who ate less than one unit per month The magnitude of risk reduction was similar for both fatal CHD (RR=0.61, 95% CI 0.35-1.05, P for trend = 0.007) and non-fatal MI (RR=0.68, 95% CI 0.47 – 1.00, P for trend =0.04)	Frequent nut consumption, 5 times or more per week, were associated with a reduced risk of CHD
Fraser, G E and Shavlik, D.J	Risk factors for all-cause and coronary heart disease mortality in the oldest-old	Archives of Internal Medicine, 1997, 157 2249-2258.	To examine a subgroup of the Adventist Health study, 84 years and older, for dietary habits and their correlation to CHD	Prospective cohort study	White, Seventh-day Adventists, who were 84 years at baseline or reached 84 during the 12 years of follow-up Subjects with heart disease or cancer were excluded.	Food frequency questionnaires listing 65 items were used, with responses on a scale of 1 to 8, being never consumed to consumed more than once a day Endpoint was all cause mortality or mortality from CHD	Subjects who consumed nuts 5 times per week had RRs of death of 0.82 (95% CI 0.70-0.96), P<0.01) and 0.61 (0.45-0.83; P<0.001) for death from CHD compared with those consuming nuts less than weekly	In this group of oldest-old, dietary habits such as eating nuts and traditional risk factors for CHD are still associated with total and CHD mortality
Kushi, L.H , Folsom, A R , Prineas, R , J , Mink, P J , Wu, Y and Bostick, R M	Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women	The New England Journal of Medicine, 1996, 334 1156-1162	Evaluation of whether dietary intake of antioxidants is related to mortality from coronary heart disease	Prospective cohort study with 7 years follow-up	34,486 Iowa postmenopausal women aged 55 to 69 who completed a baseline questionnaire.	Dietary assessment at baseline using a 127-item food frequency questionnaire. Endpoints were defined as death from coronary heart disease.	Vitamin E was inversely associated with CHD mortality Consuming nuts more than 4 times per month lowered CHD risk (RR=0.60 versus 0.98 for 1 or 2 times per week) after adjusting for hypertension, diabetes mellitus, smoking, level of physical activity and estrogen replacement therapy	Nut consumption was inversely associated with coronary mortality, possibly due to their fatty acid composition and Vitamin E content

Table 5
Summary of Observational Studies Regarding Nuts and CHD

Author	Title	Literature Citation	Purpose of Study	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Conclusions
Fraser, G E , Lindsted, K D and Beeson, W L	Effect of risk factor values on lifetime risk of and age at first coronary event	American Journal of Epidemiology 1995, 142 746-758	To assess the effect of CHD risk factors on lifetime risk, age at onset, and survival free of CHD	Prospective cohort study	27,321 white Seventh-day Adventist living in California. Subjects with a previous history of coronary disease were excluded	Dietary assessment was obtained with a 65-item semi-quantitative food frequency questionnaire. Three outcomes were measured, lifetime risk, mean age at onset of fatal or nonfatal coronary disease combined and life expectancy free of coronary disease	Years free of coronary disease and lifetime risk were greater in low nut consumers. On average consuming nuts decreases the risk of CHD by 12.4%. This analysis found that confounding was minor in assessing relative risk.	Frequent nut consumption is associated with lower risk of CHD and greater years free of the disease.
Fraser, G R , Sabaté, J , Beeson, W L and Strahan, M	A possible protective effect of nut consumption on risk of coronary heart disease, the Adventist Health study	Archives of Internal Medicine, 1992, 152 1416-1424	Evaluation of consumption of specific foods and risk of incident fatal and nonfatal CHD events	Prospective cohort study with 6 years follow-up	White, Seventh-day Adventist men (n=10,003) and women (n=16,740). Average age 51 and 53, respectively. Those with previous or unknown history of heart disease and all diabetics were excluded	A semi quantitative 65-item food frequency questionnaire was obtained at baseline. CHD event was defined as nonfatal myocardial infarction, definite fatal myocardial infarction, or other definite fatal CHD. Foods or food groups were tested for the association with CHD.	Stratifying for age and sex, consumption of nuts at 5 servings or more per week showed strong and consistent protective effects. The relative risk was 0.42 and 0.47 for nonfatal and definite fatal CHD respectively. When stratified for age, sex, smoking, exercise, weight and hypertension the strong negative associations remained.	There is a negative association between frequent consumption of nuts (5 or more servings per week) and fatal and nonfatal CHD events.

Fraser, *et al.* (1992) reported data on nuts and CHD risk from the Adventists' Health Study. This prospective cohort study followed 26,473 non-Hispanic white men and women. Subjects who were free of any history of heart disease or diabetes at baseline were followed for an average of six years or to an endpoint of either fatal or nonfatal CHD. Cases were identified by medial records, autopsy reports and death certificates.

Dietary data were collected using a validated food frequency questionnaire containing 65 items developed specifically for this population. Frequency of consumption was rated on an 8-point scale from, "never consume" to "more than once per day." Frequent consumption of nuts (5 or more 1-ounce servings per week) showed consistent protective effects when stratified for age and gender. Relative Risk (RR) of nonfatal myocardial infarction and fatal CHD among this group were 0.49 and 0.52, respectively, compared to those who ate nuts one time a week or less. Similar results from subjects who ate nuts one to 4 times per week were RR= 0.78 and 0.76, respectively. There was a wide range of nut consumption among this cohort with nearly 25% consuming nuts at least 5 times per week, 42% doing so 1-4 times per week and approximately 33% less than once a week. The protective associations remained significant after controlling for traditional risk factors including age, sex, smoking, exercise, weight, and hypertension. Additionally, while vegetarians in this group tended to eat nuts more frequently, the favorable relative risk against CHD was seen across both vegetarian and non-vegetarian groups. Consumption of whole wheat bread was

the only other food significantly associated with reduced risk of nonfatal CHD, but this association was not seen for fatal CHD. The protective association of nuts with CHD remained after adjusting for intake of bread, beef, cheese, fish, coffee, legumes (beans and peas) and fruit. Consumption of nuts was not significantly correlated with any of these foods. The different types of nuts were not distinguished in this study but a sub-group of the population reported that 32% of nuts eaten were peanuts, 29% almonds, 16% walnuts and 23% other varieties.

Despite the high fat content of nuts, the authors noted an inverse relation to obesity with the more frequent nut consumers being less obese. In summary, this study provides important support for the association between intake of nuts and reduced risk of CHD. Dietary data were collected using a validated 65-item food frequency questionnaire. There was a wide range of nut consumption within the population, which strengthens the likelihood of detecting a true effect. The prospective study design assures temporal appropriateness, and the RR's with CHD are highly significant and exhibit a dose-response relationship. In addition, the results remained statistically significant after being adjusted for both potential dietary and nondietary confounding variables.

Fraser *et al.* (1995) also examined the Adventists' Health Study database to determine the effect of risk factor values on lifetime risk and age at first coronary event. Population characteristics and methodology were as described above (Fraser *et al.*, 1992). This univariate analysis included 27,321 subjects with no

previous history of coronary disease who were followed for 6 years. Coronary heart disease outcomes were stratified by nut consumption (5 or more times per week vs. less than once per week). Outcomes included lifetime risk of CHD, mean age at onset and life expectancy free of coronary disease. The predicted lifetime risk of CHD among male low nut consumers (31.1%) was significantly greater than high nut consumers (18.7%). Analogous results for women were 29.0% and 17.0% for high and low nut consumers, respectively. This study also reported significant benefits of high nut consumption for both men and women in predicted age of CHD onset as well as life expectancy free of this disease. These data provide additional support for the hypothesis that nuts reduce the risk of CHD.

Fraser *et al.* (1997) reported CHD and all-cause mortality in the “oldest-old” subgroup within the Adventists’ Health Study population. A baseline sample of 603 subjects older than 84 years was followed for 12 years. During nearly 12,000 person-years of observation, there were almost 1,400 deaths. The same food frequency questionnaire described earlier (Fraser, 1992) was used to assess nut consumption and other dietary parameters. The end point was either all-cause mortality or fatal coronary disease. All subjects with evident heart disease or cancer were excluded from the study. Nut consumption ranged from five or more times per week among 33% of the cohort to less than once per week among 32%. No attempt was made to differentiate between individual types of nuts. Nut consumption was significantly, inversely associated with CHD and all-cause mortality according to a univariate analysis stratified by age and gender. RR of

CHD mortality was 1.0, 0.71 and 0.55 among participants who consumed nuts 5 or more times per week, 1-4 times per week or less than once per week, respectively. Analogous results for all-cause mortality by nut consumption were 1.0, 0.82 and 0.75. Multivariate analysis which controlled for other dietary and non-dietary factors revealed that only nuts showed a significant independent positive effect for both all-cause mortality and mortality from CHD.

Hu *et al.* (1998) reported data on nut consumption and CHD incidence in a cohort of 86,106 participants in the Nurses' Health Study who were followed for 14 years. The subjects were identified from the overall Nurses' Health population of 98,462 by excluding incomplete and implausible questionnaires as well as questionnaires from women with previously diagnosed cancer and/or cardiovascular diseases (CVDs). Dietary data were obtained at baseline using a validated 61-item food frequency questionnaire, which was expanded to 116 items for subsequent data collections. Nut consumption was defined as one-ounce equivalents of tree nuts, peanuts or peanut butter and divided into four consumption categories: almost never, 1-3 per month to once per week, 2-4 times per week, and 5 or more times per week. The relative risk for CHD among women at baseline, who were frequent consumers of nuts (5 times or more per week of 1 ounce servings) was 0.48 compared with those who almost never ate nuts. A significant beneficial effect of high nut consumption (RR = 0.66) persisted after adjusting for potentially confounding dietary variables including intake of saturated fat, PUFA, *trans* fat, fiber, vegetables and fruits. Similarly, the inverse

association between nuts and CHD remained significant in the analysis of subgroups of this population including participants with self-reported hypertension, diabetes, hypercholesterolemia, multivitamin use, vitamin E supplement use, parental history of myocardial infarction before age 60, current smoking, current alcohol use, body mass index (BMI) and vigorous exercise. BMI was negatively associated with nut consumption among participants with a BMI of less than 25 for the four intake categories (RR=1.0, 0.90, 0.69 and 0.58; 95% CI 0.38 to 0.89). There was no statistically significant association between BMI and nut consumption among participants with a BMI of 25 or above.

The authors conclude, "...frequent nut consumption was associated with a reduced risk of both fatal coronary heart disease and non-fatal myocardial infarction in our large prospective study. These data, and those of other epidemiological and clinical studies, support a role for nuts in reducing coronary heart disease risk."

Data from the Nurses' Health Study provide strong support for the hypothesis that increased nut consumption reduces the risk of CHD based on FDA's own evaluation criteria. The RR's for this relationship are highly significant and exhibit a statistically significant dose-response relationship. The prospective nature of the study ensures temporal appropriateness, and dietary data were collected using a well-established instrument that has been validated for accuracy. In addition, great care was taken to control for possible dietary and nondietary confounding variables.

Kushi, *et al.* (1996) examined the effect of antioxidant vitamin intake on CHD mortality during a 7-year follow-up period in a cohort of 34,486 postmenopausal Iowa women. Participants completed a 127-item food frequency questionnaire that was derived from the survey used in the 1984 Nurses' Health Study (Willett *et al.*, 1988). Vitamin E consumed in whole foods versus supplements had an inverse relationship to CHD mortality. Nut intake among 19,411 non-supplement users was divided into four categories based on the number of servings per month: 0, 1-3, 3-4 and more than 4. The multivariate adjusted RR for women in the upper level of nut consumption was of 0.60 compared to women who did not eat nuts. This inverse relationship remained statistically significant after adjustment for total energy, BMI, waist-to-hip ratio, cigarette smoking, hypertension, diabetes, oral-contraceptive use, estrogen-replacement therapy, physical activity, alcohol intake, marital status and level of education. The findings from this large prospective study once again support the hypothesis that consumption of nuts reduces the risk of CHD. The multivariate adjusted RR of 0.60 for the upper consumption level of nuts and CHD mortality is borderline significant (95% CI 0.036-1.01) and the overall association is significant for trend (P=0.016) indicating a dose-response relationship. The range of nut consumption among this cohort was narrower than in the Nurses' Health Study or the Adventists' Health Study, which may explain why the benefit was limited to participants with the highest intake of nuts. This study was designed primarily to examine the potential relationship between antioxidant vitamins and CHD. Nuts were included in this analysis because they are sources of vitamin E, which the authors suggest may be at least partially

responsible for their cardioprotective effect. This paper is very consistent with the other observational studies, and provides further support for the proposed health claim.

Lavedrine *et al.* (1999) provided suggestive evidence that consumption of walnuts and/or walnut oil are associated with reduced risk of CHD in a population of 793 male and female subjects living in a walnut producing area of France. A food frequency questionnaire was used to assess consumption of animal fat, walnuts and/or walnut oil as well as alcohol intake during the past one year. Consumers were classified by consumption of walnut oil and walnut oil plus kernels as “non-consumers”, “intermediate consumers” or “frequent consumers”. Walnut consumption was relatively low with 13.8% of the population reporting frequent consumption of walnut oil and 20.7% of walnut oil and kernels. Walnut oil was not consumed by 57.8% of the population and 34.3% were non-consumers of walnut oil and kernels. Analysis of blood samples obtained from the population showed that frequent consumption of walnut oil and of walnut oil and kernels was associated with a significant increase in HDL-C as well as Apo A1 after adjustment for gender, age, BMI, alcohol intake and animal fat consumption. There were no significant changes in T-C or LDL-C. The conclusions that can be drawn from this study are limited due to a narrow assessment of dietary intake, a relatively small population and the inability to adjust for many potentially confounding dietary and non-dietary variables. In addition, this study was designed to examine the effect of walnut intake on CHD risk factors, but not CHD

incidence. Nevertheless, this study provides suggestive evidence that frequent consumption of walnuts reduces the risk of CHD.

Albert *et al.* (2002) reported data from the Physicians' Health Study that examined the relationship between nut intake and incidence of coronary heart disease morbidity and mortality during an average 17-year follow-up period among a cohort of 21,454 male physicians who were aged 40 to 84 at enrollment into the study in 1984. Intake of nuts during the previous year was assessed using a 20-item food frequency questionnaire that classified consumption into one of seven categories: two or more times per day, 5-6 times per week, 2-4 times per week, once per week, 1-3 times per month and rarely or never. There was a significant ($P = 0.04$) trend for reduced incidence of sudden death from cardiovascular disease adjusted for age among this large cohort. The protective association became stronger ($P = 0.01$ for trend) when the data were corrected for multiple potential confounding variables including: age, aspirin and beta-carotene supplementation, evidence of cardiovascular disease at baseline, BMI, smoking, history of diabetes, hypertension or hypercholesterolemia, alcohol consumption, vigorous exercise, vitamin E, vitamin C or multivitamin use, and dietary consumption of fish, red meat, fruits and vegetables, and dairy. Relative risk of sudden cardiac death among participants who consumed nuts twice per week or more was 0.53 (95% CI 0.30 – 0.92) compared to subjects who rarely or never ate nuts. Multivariate regression analysis (using the potential confounders noted above) also showed a protective association for nut consumption in the highest category (RR = 0.70;

95% CI 0.50 – 0.98) and total CHD death, but most of the effect was due to sudden death. There was no association between nut consumption and nonfatal incidence of myocardial infarction.

These data provide additional strong evidence for a protective effect of nuts on CHD. The prospective design of this study, its large cohort and lengthy follow-up period all give credence to the overall conclusion. The authors speculate that at least some of the protective effect of nuts may be due to α -linolenic acid (particularly from walnuts), which has been shown to have antiarrhythmic effects or additional factors including other unsaturated fats, magnesium or vitamin E which may improve the serum lipoprotein profile and reduce the incidence of sudden death.

E. Dietary intervention studies

FDA described the criteria it used to identify pertinent studies for consideration of CHD risk reduction in its Interim Final Rule for the Sterol/Stanol ester health claim (65 FR 54686 at 54691). These criteria are:

...(1) Present data and adequate descriptions of the study design and methods; (2) be available in English; (3) include estimates of, or enough information to estimate, intakes of plant sterols or stanols and their esters; (4) include direct measurement of blood total cholesterol and other blood lipids related to CHD; and (5) be conducted in persons who represent the general U.S. population. In the case of criterion (5), these persons can be considered to be adults with blood total cholesterol levels less than 300 mg/ dL, as explained below.

FDA provided further clarification of the design parameters it used to assess the veracity of individual studies in establishing a link between dietary components and serum lipid biomarkers (65 FR 54686 at 54692):

The general study design characteristics for which the agency looked included selection criteria for subjects, appropriateness of controls, randomization of subjects, blinding, statistical power of the studies, presence of recall bias and interviewer bias, attrition rates (including reasons for attrition), potential for misclassification of individuals with regard to dietary intakes, recognition and control of confounding factors (for example monitoring body weight and control for weight loss), and appropriateness of statistical tests and comparisons. The agency considered whether the intervention studies that it evaluated had been of long enough duration, greater than or equal to 3 weeks duration, to ensure reasonable stabilization of blood lipids.)

An additional prerequisite for authorization of a health claim for CHD reduction is that the dietary component must result in a significant reduction in serum biomarkers. FDA has not provided specific criteria on the minimum reduction in total cholesterol and/or LDL-C it considers necessary to warrant authorization of a claim. However a decrease in total cholesterol of 4.4 percent (10.0 milligrams mg/dL) and in LDL-cholesterol of 4.9 percent (7.8 mg/dL) was regarded as significant in authorizing a health claim for oats and coronary heart disease (62 FR 3584, 3586, January 23, 1997), and similar levels were used to justify authorizing the health claim for soy protein and CHD (64 FR 57700 at 57708).

The human intervention studies that meet FDA's minimum standards for consideration as substantiation for health claims are summarized in Table 6 and grouped according to the nut being examined in the narrative description below.

Table 6
Summary of Intervention Studies Regarding Nuts and CHD

Author	Title	Literature Citation	Purpose of Study	Design	Sample Size and Characteristic	Dietary Treatment	Length of Intervention	Summary of Results	Conclusions
Jenkins, DJA, Kendall, CWC, Marche, A, Parker, T L, Connelly, PW, Qian, W, Haight, J S, Faulkner, D, Idgen, E, Lapsley, K and Spiller, G A	Dose response of almonds on coronary heart disease risk factors – blood lipids, oxidized LDL, Lp(a), homocysteine and pulmonary nitric oxide a randomized controlled cross-over trial	2002, in press in Circulation	To determine the therapeutic role of nuts independent of their favorable PUFA/SFA ratio	Randomized crossover design	27 generally healthy moderately hyperlipidemic (mean serum LDL-C 168 mg/dl) adult men and women mean age 64 years.	Participants ate a self-selected low fat diet to which 3 different supplements were provided, muffins (control diet with 26% fat, 7.0% SFA), muffins containing 50 to 100 grams unblanched almonds per day based on energy needs (36% fat, 7.2% SFA) muffins containing a half portion almonds (32.1% fat, 7.5% SFA) The average half dose of almonds was 37g per day	Minimum of a 7 day run-in period prior to 3 one-month interventions separated by a minimum of 2-week washout periods	In the full almond group and the half dose almond group lipids decreased significantly at 5.6 and 3.1% for cholesterol, 9.4 and 4.4% for LDL-C and 7.3 and 3% for apoB HDL increased 3.8 and 4.6%. With the control muffin period, there were no significant changes from baseline. There were no changes in body weight between the different diet periods	Even in diets already low in fat, almonds produced a dose response that showed a 1% decrease in LDL-C with each 7 g almonds consumed, which in turn translates into a 2% reduction for CHD

Table 6
Summary of Intervention Studies Regarding Nuts and CHD

Author	Title	Literature Citation	Purpose of Study	Design	Sample Size and Characteristic	Dietary Treatment	Length of Intervention	Summary of Results	Conclusions
Sabaté, J. Haddad, E and Rajaram, S	Dose response of almonds on serum lipids and lipoproteins in healthy adults a randomized feeding trial	2002. Pre-publication manuscript	To determine the effect of two different doses of almonds and a Step I diet on serum lipids compared to a baseline diet in normo- and moderately hypercholesterolemic subjects	Randomized, controlled, crossover feeding trial	27 healthy adults (14 males) with normal or moderately elevated T-C (exclusion criteria < 15 th and > 90 th percentile), BMI ≤30, TG ≤200 mg/dL	Participants consumed a baseline diet (34% of energy as fat) and were randomized to either a Step I diet (30% fat, 8 25% SFA), a low almond diet (35% fat, 8 0% SFA with 10% of calories as almonds) or a high almond diet (39% fat, 7 7% SFA with 20% calories from almonds. Diets were controlled to maintain body weight	Baseline diet consumed for two weeks. Intervention periods were 4 weeks with no washout between treatments	Both almond diets decreased T-C and LDL-C compared to the baseline diet. Low almond: T-C -4.4%, LDL-C -4.1%. High almond: T-C -7.8%, LDL-C -9.8%. HDL-C decreased 4.0% and 1.6% on the low and high almond diet, respectively. Compared to the Step I diet there were NS changes in T-C and LDL-C, by the low almond diet, but the high almond diet lowered these parameters by 4.4% and 7.0%, respectively (P≤0.01). HDL-C was unaffected by almond dose compared to the Step I diet. There were significant differences in T-C and LDL-C between the low and high almond diet indicating a dose-response	Isoenergetic incorporation of ~68 g of almonds into a 2000 kcal Step I diet markedly improves serum lipid profiles of normo and moderately hypercholesterolemic adults. T-C and LDL-C declines with progressively higher intakes of almonds, suggesting a dose response relation

Table 6
Summary of Intervention Studies Regarding Nuts and CHD

Author	Title	Literature Citation	Purpose of Study	Design	Sample Size and Characteristic	Dietary Treatment	Length of Intervention	Summary of Results	Conclusions
Yi, L., Ying, X., Yi, T., Shao-fang, Y., Junn-bo, W and Xue-jun, L	Health effects of almond on hyperlipemic patients and rats	2002. Pre-publication manuscript	To determine whether serum lipids could be lowered by a diet high in almonds in hyperlipidemia patients and rats	Self-controlled, randomized design	85 Chinese moderately hyperlipemic (mean serum T-C 263 mg/dl or lower) subjects, 40 men and 45 women, mean age 56.3 years	Maintained their usual and customary diet (33.8% fat, 9.9% SFA) with the addition of 75 g of almonds per day for the intervention period (41.7% fat, 9.4% SFA)	Intervention diet was 4 weeks	Total cholesterol decreased by 7.6% ($P < 0.05$), LDL-C by 8.9% (NS). HDL-C did not change significantly. Among moderately hypercholesterolemics T-C decreased 9.6% ($P, 0.01$), LDL-C – 14%. Total fat increased yet there was no increase in body weight.	Almonds added to the Chinese diet for hyperlipemic patients could decrease T-C and LDL-C while not increasing body weight
Hyson, D A., Richter, B D., Schneeman, B O and Davis, P A	Effect of whole almond versus almond oil on serum lipids and cardiovascular risk factors in healthy men and women	J. Nutr 2002, 132 703-707	To compare the effects of almonds versus almond oil on CVD risk factors	Randomized crossover design	24 generally healthy normocholesterolemic adults, mean age 43.5 years, mean BMI 23.7	The almond diet consisted of an average of 66 grams whole almonds, providing 35 grams of fat and 50% of average daily fat intake. The almond oil group had 35 grams of oil per day. There were no differences in the amount of total or saturated fat between the diets	Seven day run-in followed by two 6-week intervention diet periods	Total cholesterol and LDL decreased significantly in the almond group 4.3 and 6.0% and in the oil group 4.5 and 4.6%. HDL increased in the almond group 4.3% and oil group 6.8%. TG decreased in both groups 14% and 15%. Body weights remained stable	This study suggests that nuts can lower total and LDL-C, while preventing HDL from decreasing and can help improve lipid profiles and lead to the reduced risk for CVD

Table 6
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Iwamoto, M , Imazumi, K , Sato, M , Hirooka, Y , Sakai, K , Takeshita, A and Kono, M	Serum lipid profiles in Japanese women and men during consumption of walnuts	Europ J Clin Nutr 2002, 56 629	To determine the serum cholesterol, apolipoproteins and LDL oxidizability in young Japanese women and men during walnut consumption	Randomized, single-blind, crossover design	40, (20 female) healthy, normo-cholesterolemic subjects average age 24 yrs	Participants followed the average Japanese diet during the run-in period. Subjects were randomized to the control (24% fat, 6.9% SFA) or walnut (26% fat, 4.8% SFA) diet. Energy intake was controlled throughout the study. The experimental diet provided two servings of walnuts per day (25 or 27g/serving, or 52g walnuts/10 MJ) fed at the expense of fatty foods and visible fats	Two 4-week interventions following a 5-day run-in period	T-C decreased 4.9% in women (P=0.007) and 3.8% in men (P=0.054) in the walnut group. LDL-C fell 10.6% in women (P=0.001) but did not change significantly in men (-8.9%, P=0.78). The LDL-C/HDL-C ratio fell significantly by 8.6% (P=0.009) in women and by 9.7% (P=0.025) in men. TG were unchanged	Moderate quantities of walnuts, without an overall increase in total dietary fat and energy, lowers serum cholesterol concentration and improves lipoprotein profiles in healthy Japanese men and women
Almano, R U , Vonghavaravat, V., Wong, R and Kasim-Karakas, S E	Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia	American Journal of Clinical Nutrition 2001, 74 72-79	To evaluate the results of walnut supplementation on blood lipids with both a low-fat diet and a usual habitual diet	Sequential crossover design	5 men and 13 women, average age 50 with cholesterol > 5.17 mmol/L, triacylglycerol > 2.26 mmol/L, LDL > 3.36 mmol/L and not taking any antihyperlipidemic medicine	4 trial diets: 1) habitual diet (HD) (11% SFA), 2) habitual diet plus 48 g walnuts (HD+W) (9.8% SFA), 3) low-fat diet (LF) (20% fat, 7.5% SFA), and 4) low-fat diet and 48 g walnuts (LF+W) (8.2% SFA)	Habitual diet was 4 weeks, with the other 3 diets 6 weeks each	Total-C in LFD+W decreased 9.8% (P<0.0125) vs. HD and -7.7% (P<0.0125) vs. the LFD group. LDL-C decreased 9.8% vs HD and by 12.2% compared to the LFD group. There was no increase in body weight during the intervention	There are favorable plasma lipoprotein changes among some subclasses of lipoproteins; the mechanisms of these effects are unknown

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Rajaram, S , Burke, K , Connell, B , Myint, T and Sabaté, J	A monounsaturated fatty acid-rich pecan-enriched diet favorably alters the serum lipid profile of healthy men and women	Journal of Nutrition, 2001, 131:2275-2279	To determine the effect of pecans on blood lipids and lipoproteins in healthy men and women compared with the NCEP Step I diet	Single-blinded, randomized, controlled, crossover feeding study	14 men and 9 women with serum T-C between the 15 th and 80 th percentile, mean age 38 years, BMI <30 and no lipid altering medication	2 diet trials, NCEP Step I diet (28% fat, 8.25% SFA) was followed then the "pecan diet" (39.6% fat, 8.1% SFA), which was the same as NCEP Step I, except 20% of calories were replaced with pecans, 72 g per 2400 kcal	2 week run-in followed by 2 diet periods followed for 4 weeks each	Both Step I and the pecan diet showed a better lipid profile, however, the pecan diet lowered total and LDL cholesterol 6.7% and 10.4%, respectively and increased HDL 5.6% beyond the Step I diet	Feeding pecans beneficially altered lipid profiles beyond that of a Step I diet.
Zambon, D , Sabaté, J , Munoz, S , Campero, B , Casals, E , Merriós, M , Laguna, J C and Ros, E	Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women	Annals of Internal Medicine, 2000 132(7) 538-546	To compare the effects of a walnut-rich diet with those of a cholesterol-lowering Mediterranean diet on serum lipid levels, lipoprotein levels, and LDL resistance to oxidation	Randomized crossover trial	27 men and 28 women, average age 56 years with hypercholesterolemia, serum LDL concentrations greater than 130 mg/dL and TG <250mg/dL Mean baseline T-C was 287 mg/dl for women and 270 mg/dL for men	Mediterranean diet served as the control with no nuts allowed (31.2% fat, 6.9% SFA) The "walnut diet" (33.2% fat, 8.1% SFA) was similar to the control, with walnuts replacing olive oil, 41-56g of walnuts were provided daily	One week run and 2-six week interventions	The walnut diet compared to the Mediterranean diet showed a mean change of -4.1% in total cholesterol, -5.9% in LDL cholesterol, and -6.2% in lipoprotein(a) HDL levels were not affected Body weight remained stable during both intervention periods	The walnut diet improved the lipid profile and may provide for additional cardiovascular protection due to the reduction in lipoprotein level

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Morgan, W A and Clayshulte, B J	Pecans lower low-density lipoprotein cholesterol in people with normal lipid levels	Journal of the American Dietetic Association, 2000, 100(3) 312-318.	To examine the effect of consuming pecan nut meats on serum lipid profiles and dietary intakes of people with normal lipid levels who consume self-selected diets	Randomized, controlled study	5 men and 18 women with normal lipid levels, exclusion criteria was lipid-lowering medications	Diets were self-selected for both groups except nuts were not allowed. In the pecan group, they were provided with 68 g of pecan per day. Subjects provided 5 3-day food records. There were no significant differences in SFA intake between diets.	8 weeks	Total-C -10.7% (P<0.05) and LDL-C -6% (P<0.05) in pecan group vs baseline. HDL-C +6.2% (NS) in pecan group vs. baseline. LDL-C -18.8% (P<0.05) for pecan group vs. control group at 8 weeks, T-C -15.9% (P<0.05) and HDL-C -6.8% (P<0.05). Body weights did not change during the course of the study.	Suggests potential benefits from consuming tree nuts which may possibly be a reflection of their high MUFA content.
Curb, J D, Wergowski, G, Dobbs, J C, Abbott, R D and Huang, B	Serum lipid effects of a high-monounsaturated fat diet based on macadamia nuts	Annals of Internal Medicine, 2000, 160 1154-1158	To examine the variations in serum lipid levels in response to a high-monounsaturated fat diet based on macadamia nuts	Randomized, crossover trial	15 men and 15 women, with cholesterol above 150 mg/dL, TG below 400 mg/dL and not on any treatment for hyperlipidemia. Mean T-C for all subjects at baseline was 205 mg/dl	3 diet groups, "typical American" diet, (37% fat, 14.5% SFA), "Macadamia nut diet" (37% fat, 6% SFA) containing 34 gm nuts per 1000 kcal, and AHA Step I "prudent" diet (30% fat, 7% SFA).	6 day run-in and 3 thirty day intervention periods	Total-C -4.9%, and LDL-C -6.9% in the macadamia group vs typical American diet. T-C and LDL-C for Step I diet also decreased 4.0% and 4.6%, respectively. TG -9.6% on macadamia diet vs. 5.9% on Step I vs typical Am. Diet. Mean HDL was lower in both the AHA (5.9%) and macadamia group (4.5%).	Macadamia nuts, which are high in monounsaturated fats appear to lower serum cholesterol levels.

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Edwards, K , Kwaw, I , Matud, J and Kurtz, I	Effect of pistachio nuts on serum lipid levels in patients with moderate hypercholesterolemia	Journal of the American College of Nutrition, 1999, 18(3) 229-232	To determine whether substituting pistachio nuts for high fat snacks would improve lipid level in subjects with moderate hypercholesterolemia	Controlled, randomized crossover	4 men and 6 women, age 28 to 64 years with moderate hypercholesterolemia (mean serum T-C was 243 mg/dL	Pistachio nuts (~68g/d) were substituted for 20% of daily calories. These replaced either fatty snacks or fat calories. The pistachio diet contained 39% fat and 16% SFA while the reference diet had 37% fat and 23% SFA (P<0.01)	2 -- three week diet periods	Total cholesterol decreased from 243 mg/dL to 239 mg/dL (P<0.04), HDL rose from 50 to 56 mg/dL (P<0.09) and LDL fell from 180 to 158 mg/dL (NS), body weight did not change significantly during the intervention period	Pistachio nuts significantly improved the lipid profile of the hypercholesterolemia volunteers
Kris-Etherton, P M , Pearson, T A , Wan, Y , Hargrove, R L , Moriarty, K , Fishell, V and Etherton, T D	High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations	American Journal of Clinical Nutrition 1999, 70 1009-1015	Compare the risk profile of cardiovascular disease when consuming four different cholesterol lowering diets	Randomized, double-blind, crossover study	N = 22 normocholesterolemic subjects (9 men and 13 women) with BMI's 20-27	5 diets were used, Average American Diet (AAD), (34% fat, 16% SFA), AHA/NCEP step II diet (25% fat, 7% SFA), and 3 diets high in MUFA, olive oil (OO) diet (34% fat, 7% SFA), peanut oil, (PO) (34% fat, 7% SFA) and peanuts and peanut butter (PPB) (36% fat, 8% SFA).	5-twenty four-day intervention periods. There was a 4-11 day break between diets	Total-C - 10.9% (P<0.05) LDL-C -13.9% (P<0.05), TG -12.8% (P<0.05) and HDL-C (NC) for the PPB diet vs AAD control. Significant reductions in LDL-C and HDL-C for the Step I diet were also seen but T-C and TG's did not change	Peanuts and nuts, which are high in MUFA, may help provide a better lipid profile and therefore be more favorable for improving the cardio risk status

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Durak, I , Koksal, I , Kacmaz, M , Suyukkocak, S , Cimen, B M Y. and Qzturk, H S	Hazelnut supplementation enhances plasma antioxidant potential and lowers plasma cholesterol levels	Chimica Chimica Acta, 284 (1999) 113-115	To determine plasma antioxidant properties from hazelnuts	Pre-post feeding study	Thirty normocholesterolemic 18 and 19-year-old men and women Mean body wt 68.7 kg	Participants maintained a self-selected habitual diet One gram of hazelnuts per day per kg body wt was given as a supplement to their diet.	30 day intervention period	Hazelnut supplementation lowered Total-C and LDL-C by 6% and 18 9%, while HDL-C and TG levels increased 7 2% and 25 5%.	It is suggested that hazelnut supplementation may be beneficial in lower blood lipids levels and prevent atherosclerosis
Spiller, G.A , Jenkins, D A J., Bosello, O , Gates, J F , Cragen L N and Bruce, B	Nuts and plasma lipids an almond-based diet lowers LDL-C while preserving HDL-C	Journal of the American College of Nutrition, 1998, 17(3) 285-290	To compare lipid-altering effects of an almond-based diet with an olive oil-based diet, against a cheese and butter-based control diet	Randomized, controlled, parallel study	Hypercholesterolemic (baseline T-C 251 mg/dL) subjects (12 men and 13 women), mean age 53, not on any lipid lowering medications	3 diet groups, one received 100 gm raw unblanched almonds daily (20 6% fat, 5 2% SFA), the 2 nd group received 48 gm/day of olive oil, 113 gm/cottage cheese and 21 gm rye crackers (14 4% fat, 5 7% SFA), while the 3 rd group received 85 g/day cheddar cheese, 28 g butter, and 21 gm rye crackers (16 4% fat, 17 3% SFA)	One week baseline 4 week intervention	T-C (-15 2%), and LDL-C (-18 9%) levels improved significantly in the almond group vs. controls, but HDL and TG levels remained unchanged There were no significant changes in body weight after 4 weeks	Tree nuts are a beneficial replacement for saturated fats in hypolipidemic diets to improve lipid profiles

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Chisholm, A., Mann, J., Skeaff, M., Frampton, C., Sutherland, W., Duncan, A. and Tiszavari, S	A diet rich in walnuts favorably influences plasma fatty acid profile in moderately hyperlipidemic subjects	European Journal of Clinical Nutrition 1998,52 12-16	To examine the effects of walnuts on lipids, lipoproteins and triacylglycerol fatty acid in men with moderately raised cholesterol levels	Randomized cross-over study	21 men less than 65 years old with mean levels of total and LDL cholesterol of 6.58 and 4.63 mmol/L respectively with no family history of premature coronary heart disease	2 diets, low-fat and walnut diet. Subjects were counseled to consume low-fat diets, (30% fat, 12% SFA) with no nuts. The walnut diet was the low fat diet supplemented with ~78 gm/d walnuts contributing 55% fat (38% fat, 10% SFA)	One week run-in period of a lipid lowering diet then 4 weeks for each dietary intervention	Walnut diet T-C -4.0% (P<0.05), LDL-C -8.3% (P<0.01), and HDL-C +12.3% (P<0.01) vs baseline. The low fat diet also increased HDL-C by 10.1% (P<0.01) but did not impact T-C or LDL-C.	Walnuts positively influence lipid profiles thereby potentially reducing the risk of coronary heart disease even with a diet that is higher in fat.
O'Byrne, D.J., Knauff, D.A. and Shireman, R.B.	Low fat-monounsaturated rich diets containing high-oleic peanuts improve serum lipoprotein profiles	Lipids 1997 32(7) 685-695	To determine if a low fat diet high in MUFA from peanuts would result in improved serum lipid and apolipoprotein profile in postmenopausal hypercholesterolemic women	Controlled, parallel feeding study	25 healthy postmenopausal women 50-65 years with moderate hypercholesterolemia (T-C 220 - 300 mg/dL)	12 subjects consuming a low-fat (LF) diet (<30% fat) were assigned to a low fat high MUFA diet (LFMR) (26% fat, 5% SFA). 13 subjects continued to consume a LF (14% fat, 5% SFA) diet. 50-60% of the fat in the LFMR diet was from MUFA with high-oleic peanuts (35-68 g per day) the predominant source.	Seven day run-in period and 6 month diet intervention	Total-C and LDL-C in the LFMR group fell by 10% and 12%, respectively compared to baseline. TG were unchanged. Both groups had a small reduction in HDL-C but mean serum levels were not significantly different at the end of the intervention periods. Low fat group maintained their weight while LFMR trended toward a 3 kg wt loss.	The favorable lipid profiles from the LFMR - peanut diet, were under predicted by the predictive equations. Peanuts might be more advantageous than oleic or vegetable oils.

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Abbey, M., Noakes, M., Belling, G B. and Nestel, P	Partial replacement of saturated fatty acids with almonds or walnuts lowers total plasma cholesterol and low-density-lipoprotein cholesterol	American Journal of Clinical Nutrition, 1994, 59 995-999	To determine the difference between different nuts, almonds and walnuts, on plasma lipids	Sequential feeding study	16 normocholesterolemic men, mean age 41.3 years	18% of energy was provided by a daily supplement of nuts. The 1st trial period included peanuts, (50gm raw) (15.5% SFA), the 2nd trial 46 gm raw almonds, (8.2% SFA) and the 3rd trial 68 gm walnuts, (8.9% SFA)	2-week run-in prior to intervention of 3 three-week trials (3 trials)	The walnut and almond diet showed significant reduction in Total-C, 7% and 5%, respectively, and in LDL-C, 10% and 9%, respectively. There were no significant differences in total or LDL levels between the almond and walnut diets. There were no significant differences in body weight during the interventions.	The walnut and almond diet significantly improved lipid profiles and could help replace saturated fats in the public's diet.
Sabaté, J., Fraser, G E., Burke, K., Knutsen, S F., Bennett, H and Lindsted, K D	Effects of walnuts on serum lipid levels and blood pressure in normal men	New England Journal of Medicine, 1993, 328 603-607	To look at the effect on serum lipids and blood pressure when consuming a diet rich in walnuts or the NCEP diet without nuts	Controlled, single-blind, randomized, crossover design	18 men, mean age 30, BMI 23.8	2 diets, both adhered to NCEP Step I diet and contained the same foods and macronutrients composition, except, 20% of calories in the "Walnut diet" came from walnuts, 84 gm walnuts per 2500 kcals. The Step I diet had 29% fat and 9% SFA while the walnut diet had 31% fat and 6% SFA.	5 day run-in with 8 week diet intervention periods	During the walnut diet total cholesterol decreased 12%, LDL-C decreased 16.3% TG also decreased. HDL and LDL/HDL ratio also decreased. No changes in blood pressure.	Walnuts can show an improvement in lipoprotein profiles beyond that of currently recommended diets to lower cholesterol.

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Spiller, G A., Jenkins, D.J.A , Cragen, L M , Gates, J E , Bosello, O , Berra, K , Rudd, C , Stevenson, M and Superko, R	Effect of a diet high in monounsaturated fat from almonds on plasma cholesterol and lipoproteins	Journal of the American College of Nutrition, 1992, 11(2) 126-130	To determine whether plasma cholesterol, in a group already on low-fat diets could be lowered by a diet higher in total fat than the original diet	Self-controlled feeding study	26 adults (13 women), mean age 56, with mild elevated serum cholesterol (T-C >220 mg/dL)	The baseline diet (28.5% fat, 6.0% SFA) for all subjects was modified by limiting meat, fatty fish, milk products, eggs and saturated fats. Subjects consumed 100 g almonds (50 g whole, unblanched almonds, 50 g ground almonds) (36.9% fat, 4.9% SFA). Almond oil was used to replace other dietary fats (e.g. salad dressings, butter, margarine). No other nuts were permitted.	2 week baseline with 9 week intervention	Total fat intake increased from 28% en at baseline to 37% en with the almond intervention. T-C decreased 8.5% after 3 weeks and remained at this level throughout the remainder of the 9-week intervention. LDL-C decreased 13.6% at 3 weeks and also remained constant throughout the remainder of the intervention period. HDL-C, VLDL-C and TG were unchanged. Body weight was constant during the study despite an average increase of 81 calories/d.	A moderate high-fat diet high in plant foods (including almonds and possibly other nuts high in MUFA) can be effective at reducing elevated T-C.

1. Almonds

Spiller *et al.* (1992) studied the effect of feeding 100 grams of raw almonds per day to a group of 26 adult, moderately hypercholesterolemic (T-C >220 mg/dL) men and women. The subjects continued to consume their habitual low fat diet (29% of calories, 6% SFA) during a two-week baseline phase followed by a higher fat (37% of calories, 5% SFA) diet for nine weeks. The intervention diet permitted unlimited intake of grain products, fruits, vegetables, legumes, nonfat or 2% dairy products and low-fat fish. Lean beef, poultry, medium-fat cheeses, and low-fat cookies and cakes were limited to 2-3 servings per week. Subjects were not permitted to consume margarine, butter, vegetable oils, mayonnaise, most meats, shellfish, whole-fat dairy products, bakery products containing fats or oils, chips, ice cream, avocados and all nuts except almonds, which were provided. Almond oil was used to replace margarine, butter and other oils. Subjects consumed 100 g almonds (50 g whole, unblanched nuts and 50 g ground almonds) per day. Compliance was monitored by regular meetings with the investigators. Subjects collected 3-day food records during weeks 4 and 8 of the study and filled out food frequency questionnaires on a weekly basis. Fat intake increased from 28% of calories at baseline to 37% of calories during the intervention period. Most of this change was due to MUFAs, which increased from 41g/d at baseline to 62g/d during the intervention period. Serum T-C decreased significantly by 8.5% (235 mg/dL to 215 mg/dL) after 3-weeks on the experimental diet and remained at that concentration throughout the 9-week intervention. Similarly, LDL-C decreased by 13.6% (154 mg/dL to 133 mg/dL) after 3-weeks on the almond diet and also remained constant for the remainder of the study. There was no significant change in HDL-C, VLDL-C or TG concentrations. Body weight did not change during the

course of the study despite a slight increase in energy intake from 2,113 to 2,194 calories/d. The authors concluded that moderate fat diets containing whole food sources of MUFA (e.g. nuts) could be useful in reducing total cholesterol levels.

Spiller *et al.* (1998) compared three different diets that included almonds, olive oil, and cheese and butter to determine their effects on plasma lipids. Forty-five moderately hyperlipidemic healthy men and women participated in a randomized, controlled, parallel design study. Subjects consumed their usual diets during a one-week baseline period and were then randomized to one of three dietary treatments. Approximately 630 calories per day were added to the background diet in each group of which approximately 450 calories were supplied by almonds, olive oil or butter and cheese (the control diet). Each intervention lasted 4 weeks with no washout between interventions. Three-day diet records were obtained at baseline and during the fourth week of intervention.

Compliance was monitored by random 24-hour dietary recalls, 3-day diet records and random phone interviews. The almond group consumed 100 g/day of raw unblanched almonds (whole and ground), the olive oil group received 48g/day olive oil, 113 g/day of cottage cheese and 21 g/day of rye crackers and the control group was provided with 85 g/day cheddar cheese, 28g/day butter and 21 g/day rye crackers. All three diets were relatively low in total fat (14-21% of energy). The saturated fat content of the almond and olive oil diets were similar (5.3% and 5.7% of energy, respectively), but the control diet contained 17.3% SFA. All groups were required to eat a set number of whole grain products, yogurt and legumes per week. No commercial products containing fats or refined flour were allowed. Compliance was determined to be excellent. Total

cholesterol decreased significantly by 15.5% in the almond group and by 8.7% in the olive oil group compared to the controls. LDL-C decreased by 18.9% in the almond group and by 9.7% in the olive oil group compared to the control group. There were no significant changes in HDL-C or TG. Body weights did not change significantly during the study. The authors concluded, "Results suggest that the more favorable lipid-altering effects induced by the almond group may be due to interactive or additive effects of the numerous bioactive constituents found in almonds."

In a very recent study, Hyson *et al.* (2002) used a randomized, controlled, crossover design to examine the effect of whole almonds and almond oil on serum lipids. Twenty-two generally healthy, normocholesterolemic adults participated in a 12-week crossover study. Participants recorded food intake during a 7-day run-in period before being randomized to either a whole almond group or an almond oil group for 6 weeks. Subjects were then crossed over to the alternate group without a washout period. The whole almond group consumed an average of 66 grams dry-roasted nonpareil almonds per day, which provided approximately 35 grams of fat. The fat and saturated fat content of the two experimental diets were similar. Almond supplementation was based on habitual fat intake of the participants as determined by baseline food records. The almond oil period provided an average of 35 grams per day. Participants were asked to refrain from consuming any other nuts during the study. Compliance was monitored by five-day food records collected on alternative weeks and during weekly visits by a trained dietitian. Total cholesterol and LDL-C were reduced significantly from baseline, by 4.3 and 6.0%, respectively, but were not significantly different from the almond oil trial at 4.5 and

4.6%. HDL-C levels increased significantly from baseline for the whole almond compared to the almond oil trial by 4.3% and 6.8%, respectively. TG decreased significantly by 14.5% and 15.3% for the almond and almond oil groups, respectively. Although this study does not provide direct evidence that non-lipid constituents of almonds contribute to their hypercholesterolemic effect, the magnitude of change in serum lipids exceeded that predicted by the Mensink & Katan (1992) equation, which suggests that other factors may be contributing to this effect. The possibility that non-lipid components of almonds reduce the risk of CHD by mechanisms other than serum lipid lowering is also very possible. Carbohydrate intake was held constant, which may partially explain why TGs decreased in contrast to other studies in which MUFAs partially replace carbohydrate. Body weights remained stable despite the fact that the participants consumed self-selected diets. The authors concluded that almonds could easily be incorporated into a lipid lowering low fat diet designed to reduce the risk of CHD.

Jenkins *et al.* (in press) studied the dose-response of almonds with respect to blood lipids using a randomized, crossover design study among 27 hyperlipidemic men and women (mean baseline LDL-C= 4.32 mmol/L). Three one-month diet interventions were separated by 2-week washout periods. During the experimental periods muffins with graded levels of almonds were incorporated into iso-energetic diets. All muffins provided similar amounts of saturated fatty acids and PUFA, but contained increasing levels of MUFA from the almonds. Three different levels of each supplement were given based on estimated energy requirements of the participants. Fifty grams of almonds were

provided to subjects with energy requirements below 1600 kcal, 75g/d almonds for those between 1600 and 2400 kcal/d, and 100 g/d almonds for participants over 2400 kcal/d. The mean half dose of almonds was 37g/d and the full dose was 73 g/day. Participants followed self-selected low fat diets to which these supplements were added.

Approximately 50% of subjects habitually followed the NCEP Step 2 diet before the study and the remainder followed such a diet one month prior to the start of the study. The participants were counseled to make allowances in food intake to account for the supplements and were asked not to consume any nuts or nut products. Compliance was assessed using 7-day diet histories, and a check of supplements consumed or returned. Electronic food scales were used by participants to weigh foods during the 7-day diet histories. Compliance of supplements was judged to be good and there were no significant changes in body weight across the trials. There were no significant changes in baseline lipids after consuming the control diet (muffins without almonds) except that TG levels increased by 10.4%. Both the half and full-dose almond diets significantly reduced T-C from baseline by 3.1 and 5.6%, respectively. LDL-C decreased by 4.4 and 9.4%, and apoB decreased 3% and 7.3% respectively, while HDL-C increased by 4.6 and 3.8%, respectively. These data show that each 7 g/d of almonds reduced LDL -C by about 1%. This study demonstrates that almonds can reduce CHD risk in diets that are already low in saturated fats. The possibility that non-lipid components of almonds (e.g. vegetable protein, phytosterols, flavonoids) contribute to their lipid-lowering effects was discussed. The authors conclude, "Almonds used as snacks in the diets of hyperlipidemic subjects reduce CHD risk factors probably in part related to the non-fat (protein and fiber) components of the nut."

Sabaté (submitted for publication) also studied the dose response of almond consumption and serum lipids in a randomized, crossover, controlled feeding study with 27 healthy adult men and women. Participants were normo- or moderately hypercholesterolemic (between the 15th and 90th percentile for T-C) with normal TGs (<250 mg/dL) and BMIs less than 30. A baseline Western diet with 34% of calories from fat was fed during a two-week run in period. Subjects were randomized to either a Step I diet (30% of energy from fat; 8.2% SFA), a low almond diet which contained approximately 34 g almonds per 2000 kcal (35% fat; 8% SFA) or a high almond diet which provided about 68 g almonds per 2000 kcal (39% fat; 7.7% SFA). Subjects were weighed two times per week and energy content of the diets was adjusted as necessary to maintain constant body weight. Four weeks dietary interventions were employed with no washout between treatments. All meals were prepared at the research facility. Breakfasts and dinners were eaten at a metabolic kitchen Sunday through Friday and Saturday meals were consumed off-site. Compliance was monitored by assessing plasma fatty acid concentrations at the end of each study period, by obtaining dietary records from participants and by the presence of study personnel at all meals. Compliance with the study design was judged excellent. A significant dose response trend was seen for T-C, LDL-C and the LDL/HDL ratio with respect to the almond content of the diet. Compared to the Step I diet (no almonds) the low almond diet lowered T-C by 0.05 mmol/L (1.9 mg/dL) (NS) and the high almond diet lowered it by 0.24 mmol/L (9.3 mg/dL) ($P \leq 0.01$). Changes in LDL-C resulting from the low and high almond diet compared to the Step I diet were 0.01 mmol/L (0.39 mg/dL) (NS) and 0.26 mmol/L (10.1 mg/dL) ($P \leq 0.01$), respectively. There were no significant changes in HDL-C compared to the Step I diet although the low almond diet lowered it

slightly (0.01 mmol/L; 0.39 mg/dL) while the high almond diet raised HDL-C slightly (0.02 mmol/L; 0.78 mg/dL). The difference between HDL-C on the low and high almond diets was significant ($P \leq 0.01$). Both almond diets lowered T-C and LDL-C significantly compared to the baseline diet. The authors concluded that every 28-30 g serving of almonds substituted for an equal number of calories results in a decrease of 4-5 mg/dL in serum T-C and LDL-C.

A very recent study by Yi *et al.* (submitted for publication) examined the effect of supplementation with almonds on serum lipids among 85 adult normo- and moderately hypercholesterolemic subjects. Average initial total cholesterol concentration among the hypercholesterolemic subjects was less than 300 mg/dL. Thirteen of the hyperlipemic subjects had a history of taking cholesterol-lowering drugs and this treatment was continued during the study. The participants consumed their usual diet (34% calories from fat, 10% SFA) but added a supplement of 75 grams of almonds per day in the form of 50 grams whole roasted almonds and 25 grams of raw chipped almonds in bread for a period of 4 weeks. The almond-containing diet provided 42% energy as fat and 9.4% as SFA. Based on blood samples taken at baseline, in the middle and at the end of the intervention period, T-C decreased 7.6% ($P < 0.05$), LDL-C decreased 8.9% (NS) and HDL-C decreased 2.8% (NS) among all participants. Similar data for the 42 hyperlipidemic volunteers were: T-C -9.6% ($P < 0.001$), LDL -14.3% ($P < 0.001$) and HDL -3.7% (NS). Three-day diet records showed that almond supplementation resulted in an increase in total calories (192/d), protein (15.7 g/d), total fat (28.4 g/d) and MUFA (23.4

g/d) while saturated fat was unchanged. Body weight remained stable throughout the experiment despite an increase in energy intake due to supplementation with almonds.

2. Macadamia nuts

Curb *et al.* (2000) conducted a controlled, randomized crossover design feeding study that compared the effect of a high MUFA diet from macadamia nuts, an AHA Step I diet, and an Average American Diet (AAD) on serum lipids. Thirty healthy adult men and women (most of whom did not meet clinical standards for hypercholesterolemia) consumed each diet for 30 days. A 6-day run-in period was used to help screen for compliance issues. No washout period between trials was used because other studies suggest carryover between diets would not be a factor under these experimental conditions. The AAD diet provided 37% energy as fat and 14% as SFA, the Step I diet contained 30% energy as fat and 7% SFA while corresponding values for the macadamia nut diet were 37% and 6% of calories, respectively. Thirty-four grams of finely ground macadamia nuts per 1000 kilocalories were used in the macadamia diet. Average intake of Macadamia nuts was 115.6 grams per day (personal communication from the author). Breakfasts and dinners were eaten at the study site, and participants were provided with a prepared lunch that was consumed off-site. There were no significant weight changes despite the fact that participants were permitted to consume additional foods furnished at the study site. T-C decreased significantly for both the macadamia diet (4.9%) and the Step I diet (4%) compared to the AAD. LDL-C levels also significantly decreased 6.9% and 4.6% from the macadamia diet and Step I diet, respectively. TG's were down 9.6% for the macadamia, but increased 7.8% for the Step I diet. HDL-C decreased 4.5% on the

macadamia diet compared to a 5.9% decrease on the Step I diet vs. the AAD. There was a favorable change in the LDL/HDL ratio despite the reduction in HDL-C due to the macadamia nut diet.

3. Hazelnuts

Durak *et al.* (1999) studied the effect of hazelnut supplementation on plasma lipid levels among 30 healthy male and female students age 18-19 years. The usual diet was supplemented with hazelnuts (1 gram/ kg body weight) for 30 days. The nutrient content of the diets was not reported. T-C decreased by 6% ($P<0.005$), LDL-C by 18.9% ($P<0.0005$) and HDL-C concentrations increased by 7.2% ($P<0.05$). Plasma TG increased by 25.5% ($P<0.001$) as a result of the supplementation, but the final value was still in the normal range (95.6 mg/dL). Body weight did not change significantly during the supplementation period. This study did not control the basal diet or collect dietary information, but asked participants to continue their habitual diet along with hazelnut supplementation. Although this study did not employ a rigorous design, the results are consistent with those of other studies that demonstrate nuts are effective in reducing the risk of CHD.

4. Pecans

Morgan *et al.* (2000) reported that pecans lowered LDL-C in normolipemic subjects. This study used a randomized, controlled design to compare a pecan diet to a self-selected diet. Nineteen healthy men and women with normal lipid levels completed the 8-week study. They were randomly assigned to either a control group or the pecan group.

The control group consumed a self-selected diet without nuts for 8 weeks. Participants in the pecan group consumed a similar diet but were provided with 68 grams of pecan meat per day. The pecans contributed 44 grams of fat (including 29 grams of MUFA) per day. There was no significant difference in the SFA content of the two diets. Each participant met with a nutritionist biweekly and kept 3-day food diary records every 2 weeks. Compliance was monitored by participant interviews, reviewing food records and inspecting pecan ration boxes. Serum lipids were not significantly different between the groups at baseline. T-C increased in the control group but decreased by 10.7% in the pecan group. LDL-C levels decreased by 6% from baseline in the pecan group and increased among controls. HDL-C increased by 6.2% and 5.0% in the pecan and control groups, respectively after 8 weeks. There were no significant changes in TG. Body weight remained unchanged even though energy intake increased in the pecan group. This study supports the contention that simply adding nuts (e.g. pecans) to one's current diet has the potential to reduce the risk of CHD.

Rajaram *et al.* (2001) used a randomized, crossover design to examine the effect of feeding pecans on serum lipids. Twenty-three healthy adult men and women with normal to moderately high serum cholesterol concentrations were randomized into one of two experimental diets for 4 weeks after consuming a typical American diet (34% energy as fat) for a 2-week run-in period. The experimental diets were a Step I regimen (28% of calories from fat, 8% SFA) and a pecan enriched diet (40% fat, 8% SFA) in which 20% of the calories from the Step I diet were replaced with pecans. The pecan diet provided 40% of calories from fat and contained 72 grams of pecans per 2,400 calories. There was

no washout between treatments because previous experience showed that blood lipids would stabilize in less than 4 weeks. Morning and evening meals Sunday through Friday were consumed at the study site with lunches and Saturday meals prepared to take out. All pecans were eaten at the study site. Homogenates of the menus were prepared and analyzed for 18 different days over both diet trials. Compliance, which was determined to be greater than 95%, was monitored by participant diaries, the presence of study personnel at mealtimes and assessment of plasma fatty acids at the end of each intervention period. Blood lipids were significantly reduced with the pecan diet compared with the Step I diet. The pecan diet resulted in a decrease in T-C and LDL-C by 6.7 and 10.4%, respectively. HDL-C increased 5.6% compared to the Step I diet. TG levels also significantly decreased from the Step I diet by 11.1%. Body weight did not change. The authors concluded, "Nuts such as pecans that are rich in monounsaturated fat may therefore be recommended as part of prescribed cholesterol-lowering diet of patients or habitual diet of healthy individuals."

5. Peanuts

O'Byrne, *et al.* (1997) examined the effect of low fat-MUFA rich diets containing high-oleic acid peanuts on blood lipids in 36 free-living hypercholesterolemic women. The experimental group consisted of 20 postmenopausal women who had traditionally consumed a typical American diet (34% energy as fat, 11% as saturated fat) who were placed on a peanuts-rich low-fat diet high in MUFA (26% fat, 5% SFA) (LFMR diet). Sixteen hypercholesterolemic women who already followed a low-fat diet (17% fat, 5% SFA) were used as a low-fat (LF) comparison cohort group. Volunteers completed

seven-day diet records prior to the beginning of the study. Total fat was less than 30% of energy and saturated fat less than 10% in both the LF and LFMR groups. Participants in the LFMR group received prepackaged daily portions of peanuts (36-68 gm/d). This amount would replace 1 ounce of cooked lean meat and 3-4 servings of fat in the diet. Compliance was monitored by collecting seven consecutive days of food records each month and through monthly telephone interviews. Both groups reduced energy intake compared to the baseline diet. There was a trend toward weight loss in the last month of the study for the LF group, and the LFMR group experienced a weight loss of approximately 3 kg that occurred throughout the study period. T-C and LDL-C levels decreased by 10 and 12%, respectively among the LFMLR group and TG levels remained unchanged. T-C and LDL-C were unchanged in the LF group, but TG rose by 14%. HDL-C was modestly reduced in both groups, but there was a trend toward beneficial changes in the LDL/HDL ratio in the LFMLR group. The authors concluded, "...free-living postmenopausal women can achieve improved serum lipid and apolipoprotein levels on a self-selected LF diet high in MUFA."

Kris-Etherton *et al.* (1999) conducted a randomized, crossover feeding study that compared high MUFA diets supplied by peanut and peanut butter (PPB), peanut oil (PO) or olive oil (OO) with an AHA/NCEP Step II diet and an Average American Diet (AAD). All participants were healthy normocholesterolemic adult men and women. Each diet was fed for 24 days with an interval of 4-11 days between trials. The authors noted that plasma lipids stabilize within 2-3 weeks so that a washout period was not necessary to prevent a carryover effect, but was used to reduce the burden of compliance. Twenty-two

participants completed all 5-diet periods and 2 subjects finished 4 of the 5 periods. Participants ate breakfast and dinner on weekdays at the study site and were furnished with lunch and weekend meals by the research staff. Compliance was monitored with daily dietary assessment questionnaires. The Step II diet provided 25% of calories from fat compared to 34-36% for the other three diets. The PPB, PO, and OO diet had the same saturated fat and cholesterol content as the Step II diet but provided 17-21% of energy from MUFAs compared to 12% for the Step II diet. The high-MUFA diets lowered T-C by 10% and LDL-C by 14%. This response was comparable with that observed for the Step II diet. TG concentrations were 13% lower in subjects consuming the high-MUFA diets and were 11% higher with the Step II diet than with the AAD. The high-MUFA diets did not lower HDL-C whereas the Step II diet lowered it by 4% compared with the AAD. The authors concluded that the OO, PI, and PPB diets would decrease CVD risk by an estimated 25%, 16%, and 21%, respectively, whereas the Step II diet would do so by only 12%.

6. Pistachio nuts

Edwards *et al.* (1999), studied the effect of pistachio nuts on lipid levels in 10 healthy men and women with moderate hypercholesterolemia. A randomized, crossover design study with two 3-week interventions was employed. Blood lipids were determined at baseline and on days 5 and 7 of the third week of each treatment. Half of the subjects were initially randomized to the pistachio diet (39% energy as fat, 16% SFA) and crossed over to their habitual diet (37% fat, 23% SFA) for the remainder of the 6-week study. The difference between SFA between the two diets was statistically significant ($P < 0.01$).

There was no washout between diet periods. The pistachio diet was based on habitual diet with 20% of calories replaced by roasted, unsalted pistachio nuts. The pistachio supplement replaced high fat snacks or other sources of fat in the habitual diet. Three-day food records were kept before the beginning of the study, and compliance was monitored by one-day food records collected weekly. T-C decreased from 243 to 239mg/dL ($P<0.04$), HDL-C increased from 50 to 56 mg/dL ($P<0.09$) and LDL-C and TGs were unchanged. Pistachio feeding significantly reduced the T-C/HDL-C and LDL-C/HDL-C ratios ($P<0.01$ and $P<0.02$, respectively). Body weight did not change during the study. The authors concluded, "Results suggest that eating pistachio nuts instead of other dietary fat calories can improve lipid profiles, thereby decreasing coronary risk."

7. Walnuts

Sabaté *et al.* (1993) studied the effect of adding walnuts to an NCEP Step I diet on lipid levels and blood pressure using a randomized, crossover design. Eighteen healthy normal to moderately hypercholesterolemic adult men were randomly assigned to one of two diets after a five-day run-in period. The macronutrient content of both diets met Step I criteria (approximately 30% calories from fat, <300 gm cholesterol). The experimental diet contained 84 gm of walnuts per 2,500 calories (substituted for portions of fatty foods) and 6% SFA. The Step I diet provided 9% of energy as SFA. Breakfasts and dinners were eaten at the study site, and lunches were prepared for take out. The participants kept daily diaries to record any deviation from the diet. Body weight was measured biweekly during the intervention period. Each diet was randomly assigned and followed for 4 weeks with no washout between the experimental diet periods. Dietary

compliance was excellent as determined by ongoing analysis of serum cholesterol esters. There was no evidence of carryover between the two diet periods based on T-C and LDL-C values. The walnut diet resulted in decreases in T-C (12.4%), LDL-C (16.3%), and TG (8.3%) compared to the reference diet. HDL-C levels decreased by 4.9% during the walnut diet, but the LDL/HDL ratio was significantly ($P < 0.001$) lower. There were no significant changes in blood pressure between the two groups. The authors concluded that, "... incorporating moderate quantities of walnuts into the recommended cholesterol-lowering diet while maintaining the intake of total dietary fat and calories decreases serum lipid levels of total cholesterol and favorably modifies the lipoprotein profile in normal men."

Sixteen normocholesterolemic adult men completed a free-living study conducted by Abbey *et al.* (1994) in which almonds and walnuts replaced a portion of saturated fat in habitual diets. A 2-week run-in period was used to familiarize volunteers with recording dietary information. A background diet designed to match the usual Australian diet provided 18% of fat-calories from meat, dairy, oils and spreads and an additional 18% of fat-calories from a supplement composed of 59 g raw peanuts, 40 g coconut cubes, and 50 g confectionary bar. The reference diet was consumed without modification for the first 3 weeks of the study, supplemented with 84 g raw almonds per day for the second 3 weeks and with 68 g of walnuts per day for the final 3-week treatment. The reference diet contained twice as much SFA (16% of energy) as the almond and walnut diets (8% SFA). All nuts were supplied in bulk and weighed out by the participant on electronic scales provided by the investigators. Participants kept food records for three consecutive

days during each separate diet and recorded fat sources daily. Participants were interviewed four times during each treatment and a dietitian reviewed diet records. Total fat intake remained constant for all three treatments although fat composition differed due to the different supplements. Compared to the reference diet there was a significant reduction in plasma lipids with both almond and walnut supplementation. T-C for the almond and walnut diets decreased by 7 and 5%, respectively compared to the reference diet. LDL-C also decreased with almond and walnut supplementation by 10 and 9%, respectively. There were no significant differences between the almond and walnut diet in either T-C or LDL concentrations. HDL-C and TG did not change with either nut supplement compared to the reference diet. Although the lack of randomization in this study may have affected the results, the authors concluded that the addition of reasonable amounts of almonds or walnuts to a typical diet could result in a significant reduction in serum lipids of 7-10%, which would be expected to reduce the risk of CHD by about 14%.

Chisholm *et al.* (1997) used a randomized, crossover design to determine the effect of walnuts on blood lipids in a group of 22 healthy, moderately hyperlipidemic adult men. A standard lipid lowering diet was consumed during a one-week run-in period after which subjects were randomized to either a walnut diet (38% energy as fat, 10% SFA) or a low fat reference diet (30% fat, 12 % SFA) for 4 weeks. Subjects were then switched to the alternate diet for an additional 4 weeks. The diets were individually designed based on estimated energy requirements. All meals were eaten at home and dietary counseling was provided to the individuals. The reference low fat diet was 30% of energy from fat,

none of which came from nuts. Both experimental diets provided 30% calories from fat. The walnut diet included 78 g shelled walnuts per day. The participants received detailed dietary counseling and sample meal plans along with recipes to meet calorie and fat objectives. At the end of both the low fat and the walnut diet, T-C and LDL-C were lower by 4.0 and 8.3%, respectively, but the decrease was statistically significant only for walnuts. T-C and LDL-C levels for the walnut diet were lower than for the low fat diet, but not significantly so. HDL-C concentrations increased significantly for both the walnut diet (12.3%) and the lowfat diet (10.1%). Saturated fat and dietary cholesterol were higher in the low fat diet, while the walnut diet was higher in total fat and polyunsaturated fat. Both diets met recommendations for macronutrient intakes based on NCEP. Compliance on the walnut diet was shown to be good based on linoleic acid and oleic acid levels in plasma TGs. Energy intake during the walnut diet increased, which suggested that at least part of the walnuts supplemented, rather than replaced other dietary components. Nevertheless, mean body weight remained constant for both diet groups. Apo B concentrations were lower in the walnut diet compared to the low-fat treatment, and there was a trend towards lower LDL-C and higher HDL-C, but no other significant differences were reported.

Zambon *et al.* (2000) studied the effect of walnuts substituted for dietary MUFA on lipid profiles. Forty-nine adult, moderately hypercholesterolemic men and women completed this randomized, crossover feeding study. The subjects were randomly assigned to either a control group (31% energy as fat, 7% SFA), or a walnut group (33% fat, 6% SFA) for 6 weeks and then changed to the alternate group. A washout period was not used because

dietary-induced lipoprotein changes stabilize in less than 4 weeks. The diets were individually designed based on estimated energy requirements. These free-living subjects were provided with detailed dietary information. The control diet was a Mediterranean-type diet with no nuts allowed. The walnut diet was similar to the Mediterranean diet except that walnuts replaced part of the olive oil in the diet as well as other fatty foods. Prepackaged raw shelled walnuts were prescribed in 41 to 56 g amounts based on estimated energy so that they contributed approximately 18% total energy and 35% of total fat. Compliance was monitored by unannounced 24-hour diet recalls weekly, by counting empty walnut packages during clinic visits, and by analyzing the fatty acid component of LDL lipids. Forty-nine individuals completed the study with 100% compliance (defined as less than 20% deviation from instructions on nutrient or walnut intake). T-C decreased from baseline by 9% on the walnut diet and by 5% on the control diet. Similarly, LDL-C concentrations decreased by 11.2% and 5.6%, and HDL-C decreased by 1% and 4.8% on the walnut and control diets, respectively. TG decreased by 7.8 on the walnut diet and 2% on the control diet. Body weight remained stable throughout the experiment. The authors concluded that, “Substituting walnuts for part of the monounsaturated fat in a cholesterol-lowering Mediterranean diet further reduced total and LDL-C levels in men and women with hypercholesterolemia.

An additional study conducted by Almario *et al.* (2001) examined the effect of walnut consumption on lipoproteins and hyperlipidemia in men and women using a non-randomized, sequential design. Volunteers followed four different diets in free-living conditions. The diets were a habitual diet (HD) (11% energy as SFA), a habitual diet

with walnuts (HDW) (10% SFA), a low fat diet that contained 20% energy as fat and 8% SFA (LFD) and the low fat diet (8% SFA) with walnuts (LFDW). The HD diet was fed for 4 weeks while all other dietary treatments were fed for 6 weeks. The participants did not receive nutrition education during the first 2 periods (HD and HDW) in order to avoid influencing habitual dietary intake. However, at the beginning of the LFD, intensive group and individual nutritional education was provided which continued every 2-3 weeks during remainder of the study. During the second and fourth intervention, the diets were supplemented with 48g walnuts (which provided 30 g of fat). T-C decreased significantly with the LFDW diet compared to the HD (9.8%) and the LFD (7.7%). LDL-C levels decreased on the LFDW by 9.8% compared to the HD and by 12.2% compared to the LFD. In addition, the LFDW diet lowered small-density LDL-C by 27.5% compared to the LFD. Compared to the HD, HDL-C decreased by 11% on the LFDW, by 12.5% on the LFD and by 4.7% on the HDW. Body weight did not change during the course of the study despite the fact that energy intake increased with walnut supplementation. There was an energy deficit with the low fat diet that resulted in a 1.3 kg weight loss. Because T-C and LDL-C were lowered even more with the LFDW than with the LFD, it may be that the nuts provide an additional independent action rather than just replacing saturated fats with MUFAs and PUFAs. The authors concluded, "Walnut supplementation may beneficially alter lipid distribution among various lipoprotein subclasses even when total plasma lipids do not change. This may be an additional mechanism underlying the antiatherogenic properties of nut intake."

Iwamoto *et al.* (2002) examined the effect of feeding 43-57 g/d of walnuts to 40 normocholesterolemic Japanese men and women using a randomized, controlled, single blind, crossover design. Subjects consumed a typical Japanese diet (reference diet) during a 5-day run-in period before being randomized to either a walnut diet (24% energy as fat, 7% SFA) or continuing the reference diet (26% fat, 5% SFA) for 4 weeks. Participants were then switched to the alternate diet for an additional 4-weeks. The reference diet contained approximately 25% energy from fat and was devoid of nuts, nut butters and nut oils. Energy intake was controlled (10.0 to 11.1 MJ for men and 8.37 to 9.20 MJ for women), and walnuts were added to the diet at the expense of fatty foods such as meat and visible fat (e.g. oils, margarine and butter). The reference and experimental diets were similar in percent energy from protein, carbohydrates, total fat and dietary fiber. All foods were provided to the subjects. Lunches were distributed for consumption during the day, and all other foods were consumed on-site. T-C was reduced by 3.8% in men ($P<0.05$) and by 4.9% in women ($P<0.01$) by the walnut diet. LDL-C was reduced by the walnut diet by 11.0% in women ($P<0.01$) but did not change significantly in men ($P=0.13$). However, the LDL/HDL ratio was significantly reduced in both genders ($p<0.05$) because HDL-C did not change significantly among men or women. TG also remained unchanged by the walnut diet. Body weight decreased by 1.3 kg for men and by 0.1 kg for women during the course of the study, but was not related to dietary treatment. The authors concluded, "Incorporating moderate quantities of walnuts into the average Japanese diet while maintaining the intake of total dietary fat and energy decreases serum total cholesterol concentrations and favorably modifies the lipoprotein profile in Japanese, particularly in women." [Note: this study was published earlier in a

different journal (Iwamoto, *et al.* 2000) and later retracted (Iwamoto *et al.*, 2000a) because it contained inadequate attribution to statements published by Sabaté *et al.* (1993). The notice of retraction did not call into question the validity of the results presented.]

8. Additional, suggestive studies

In addition to the studies that meet FDA's criteria for consideration of SSA, summarized above, several additional studies are consistent with the hypothesis that increased consumption of nuts reduces the risk of CHD. These studies include human feeding studies using almonds and walnuts along with other sources of MUFA and PUFA (Berry *et al.*, 1991; Berry *et al.*, 1992), mixed nuts (with the exception of peanut butter) as part of a whole food diet (Bruce *et al.*, 2000), nuts as part of a plant-based diet including whole grains and raisins (Bruce *et al.*, 1997), almonds, cashew nuts and peanuts as part of a diet rich in fruits and vegetables (Jenkins *et al.*, 1997), and almonds and walnuts in a high fish/vegetable diet (Singh *et al.*, 1992). These studies were not designed to provide evidence that nuts, *per se* reduce the risk of CHD, and it is not possible to attribute the beneficial effects of these diets specifically to nuts. Nevertheless, these studies provide additional evidence that nuts, when fed in a variety of dietary contexts, can contribute to a reduced risk of CHD.

9. Summary of Dietary Intervention Studies

The totality of dietary intervention studies provides very consistent evidence that feeding reasonable amounts of tree nuts and/or peanuts significantly reduces total and LDL-

cholesterol in both normo- and moderately hypercholesterolemic individuals when fed under a variety of conditions. This effect is seen when nut-containing diets are compared to the AAD (i.e. containing more than 30% of energy as fat) as reported by Sabaté *et al.* (submitted for publication), Hyson *et al.* (2002), Yi *et al.* (submitted for publication), Jenkins *et al.* (in press), Almario *et al.* (2001), Rajaram *et al.* (2001), Morgan *et al.* (2000), Curb *et al.* (2000), Edwards *et al.* (1999), Kris-Etherton *et al.* (1999), Durak *et al.* (1999), Spiller *et al.* (1998), Chisholm *et al.* (1998) and Abbey *et al.* (1994). In addition, nuts were shown to be hypocholesterolemic when compared to low-fat regimens (LF) including the National Cholesterol Education Program Step I and Step II diets as reported by Sabaté *et al.* (submitted for publication), Jenkins *et al.* (in press), Iwamoto *et al.* (2002) Almario *et al.* (2001), Rajaram *et al.* (2001), Curb *et al.* (2000), Kris-Etherton *et al.* (1999), Chisholm *et al.* (1998), O'Byrne *et al.* (1997), Sabaté *et al.* (1993) and Spiller *et al.* (1992). Taken together these studies provide strong evidence that feeding nuts reduces the risk of CHD across a broad range of dietary fat intakes.

One mechanism by which nuts may reduce T-C and LDL-C is by replacing SFA in the diet. Seven of the intervention studies summarized in Table 6 reported a significant hypocholesterolemic effect when nuts were fed in diets which had a difference of more than 2% energy from SFA compared to the control diets (Almario *et al.*, 2001; Curb 2000 *et al.*, (macadamia nut diet vs. AAD); Edwards *et al.*, 1999; Kris-Etherton *et al.*, 1999 (MUFA-containing diets vs. AAD); Spiller *et al.*, 1998; Abbey *et al.*, 1994; Sabaté *et al.*, 1993). However, 10 intervention studies reported lipid-lowering effects of nuts when fed in diets with similar SFA contents ($\leq 1\%$ of energy difference) compared to non-nut-

containing diets (Sabaté *et al.*, submitted for publication; Jenkins *et al.*, in press; Yi *et al.*, submitted for publication; Hyson *et al.*, 2002; Rajaram *et al.*, 2001; Zambon *et al.*, 2000; Morgan *et al.*, 2000; Curb *et al.*, 2000 (macadamia nut diet vs. Step I); Kris-Etherton *et al.*, 1999 (MUFA-containing diets vs. Step II); O'Byrne *et al.*, 1997). These data strongly suggest that the mechanism by which nuts reduce T-C and LDL-C is not limited to their ability to substitute for SFA in the diet, and that one or more lipid and/or non-lipid components are exerting a positive effect.

The totality of dietary intervention studies also demonstrates that nuts have beneficial effects on serum lipids when introduced into the diet with varying degrees of rigor. This fact suggests that a very straightforward message to consumers (e.g. "Diets containing one ounce of nuts per day can reduce your risk of heart disease.") could have important public health benefits because it is simple, easy to accomplish, and utilizes foods that are readily available and well-liked. Six studies used prepared diets fed to subjects in supervised environments so that compliance and composition of the diet were tightly managed: Sabaté *et al.*, submitted for publication; Iwamoto *et al.*, 2002; Rajaram *et al.*, 2001; Curb *et al.*, 2000; Kris-Etherton *et al.*, 1999; Sabaté *et al.*, 1993). Three studies simply provided the subjects with nuts and asked that they be consumed as part of a self-selected diet without further modifications (Yi *et al.*, 2002; Morgan *et al.*, 2000; Durak *et al.*, 1999). The remainder of the studies summarized in Table 6 asked participants to incorporate nuts that were provided by the investigators into prescribed diets that were monitored by a variety of techniques (e.g. serum fatty acid changes, food diaries,

interviews). The hypocholesterolemic effect of nuts was seen in *all* of these studies, which gives strong credence to the contention that SSA has been achieved.

Many of the studies summarized in Table 6 also show that the addition of nuts to the diet has a favorable to neutral effect on serum HDL-C concentrations. Nut consumption increased the concentration of this biomarker in response to feeding almonds (Hyson *et al.*, 2002; Jenkins *et al.*, in press), pecans (Rajaram *et al.*, 2001; Morgan *et al.*, 2000), hazelnuts (Durak *et al.*, 1999) and walnuts (Chisholm *et al.*, 1998). One study reported a decrease in HDL-C resulting from consumption of macadamia nuts (Curb *et al.*, 2000) and another for walnuts (Sabaté *et al.*, 1993), but the LDL/HDL ratio was favorably affected by addition of these nuts to the diet so that the overall impact on CHD risk remained favorable. The remaining studies in Table 6 reported no change in HDL-C or did not measure this parameter.

There are no known published intervention studies that examine the effect of feeding Brazil nuts, cashew nuts or pine nuts on serum lipids. However, like the nuts discussed in this section, they are rich sources of unsaturated fatty acids and contain other potentially cardioprotective factors (e.g. magnesium, copper, protein, folate, vitamin B₆). Therefore, these nuts would be expected to be hypocholesterolemic based on their nutrient composition. In addition, the observational data discussed earlier pertain to nuts generally, and provide sufficient evidence that the proposed claim should apply to all nuts.

F. Statements from Public Health and Professional Organizations

Several public health and governmental organizations have published dietary guidelines and other statements corroborating the conclusion that consumption of reasonable amounts of nuts, as part of a healthy diet, can have a favorable effect on serum lipids. In addition, these guidelines attest to the fact that frequent consumption of nuts can be recommended as part of a diet designed to manage the risk of CHD. Brief summaries of these statements are provided below.

1. The American Heart Association

The American Heart Association (AHA) recently published revised dietary guidelines (Krauss *et al.* 2000). A guideline entitled, “Desirable Cholesterol Profile,” states, “Limit foods high in saturated fat and cholesterol; and substitute unsaturated fat from vegetables, fish, legumes, **nuts.**” (emphasis added)

The AHA Nutrition Committee explained its rationale for this position”

In conjunction with an energy intake suitable for maintaining a normal body weight, a diet high in unsaturated fat and low in saturated fat can be a viable alternative to a diet that is very low in total fat, particularly in individuals with an atherogenic dyslipidemia characterized by low HDL cholesterol, elevated triglycerides, and small dense LDL. This dietary approach entails replacing saturated fat calories with unsaturated fat calories rather than carbohydrate calories. A diet high in unsaturated fat may provide up to 30% of calories from monounsaturated and polyunsaturated fat, <10% of calories from saturated fat, and <300 mg/d of cholesterol. **As noted above, there is now clear evidence that total and LDL cholesterol levels are reduced comparably by replacement of saturated fat with either unsaturated fat or carbohydrate during weight maintenance conditions.** (emphasis added) Moreover, a diet relatively high in unsaturated fat can prevent or attenuate the decrease in HDL cholesterol and the increase in triglycerides that can occur in some individuals’ response to a high-carbohydrate, low-fat diet. These latter

effects may confer additional cardio protective effects beyond LDL cholesterol lowering. Implicit to recommending a high unsaturated fat diet is that a healthy body weight be achieved and maintained.

2. U.S. Department of Health and Human Services

The U.S. Department of Health and Human Services health objectives for the nation entitled, "*Healthy People 2010*" notes the health benefits of increasing intake of unsaturated fats in the diet of Americans. This document states,

The major vegetable sources of monounsaturated fatty acids include nuts, avocados, olive oil, canola oil, and high-oleic forms of safflower and sunflower seed oil. The major sources of polyunsaturated fatty acids are vegetable oils, including soybean oil, corn oil, and high-linoleic forms of safflower and sunflower seed oil and a few nuts, such as walnuts.

Substituting monounsaturated and polyunsaturated fatty acids for saturated fatty acids can help lower health risks. (emphasis added)

3. The Life Sciences Research Office

The Life Sciences Research Office (LSRO) recently published an extensive review of the literature pertaining to the effect of walnuts and other nuts on the risk of CHD (Feldman, 2002). This report provided an in-depth analysis of the available intervention trials and observational studies involving walnuts as well as an overall assessment of the literature for almonds, macadamia nuts, pistachio nuts, pecans, peanuts and studies with mixed nuts.

The report concluded that walnuts lower blood cholesterol in humans when consumed as part of a heart-healthy diet, and do not cause a net gain in body weight when they are eaten as a replacement for other foods. In addition, large prospective observational studies all demonstrated a dose response-related inverse association between daily

consumption of small amounts of nuts (including walnuts) and relative risk of CHD and CVD. Finally, the report concluded that the human clinical intervention studies suggest that walnuts reduce the risk of CHD, but that definitive conclusions cannot be drawn without additional data and longer-term studies. This report discussed the concept of significant scientific agreement, but did not conclude specifically whether LSRO believes this standard has been met. This report was undertaken primarily to evaluate walnuts, and its conclusions were based largely on studies designed to evaluate this food. INCNREF believes that consideration of the totality of evidence (i.e. data from tree nuts and peanuts generally in addition to walnuts) adds further credence to the contention that nuts, as a group, reduce the risk of CHD, and that the LSRO report is entirely consistent with this conclusion.

4. National Institutes of Health

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) recently updated recommendations for cholesterol testing and management from the National Cholesterol Education Program (2001). This document is a thorough, evidence-based report that describes the recommended approaches to reduce the risk of CHD in the United States. This report states, “ATP III affirms the validity of lifestyle changes as first-line therapy for primary prevention [of CHD]. It places priority on LDL-lowering modification because of the identification of LDL cholesterol as the primary target of therapy; however, ATP III also urges the use of a broad approach to lifestyle changes for CHD risk reduction in primary prevention.”

The ATP III report contained two “evidence statements” that confirm the hypocholesterolemic properties of unsaturated fatty acids:

Evidence statements: Monounsaturated fatty acids lower LDL cholesterol relative to saturated fatty acids (A2, B2). Monounsaturated fatty acids do not lower HDL cholesterol nor raise triglycerides (A2, B2).

Evidence statements: Linoleic acid, a polyunsaturated fatty acid, reduces LDL cholesterol levels when substituted for saturated fatty acids in the diet (A1, B1). Polyunsaturated fatty acids can also cause small reductions in HDL cholesterol when compared with monounsaturated fatty acids (B2). Controlled clinical trials indicate that substitution of polyunsaturated fatty acids for saturated fatty acids reduces risk for CHD (A2, B2).

The ATP III report also makes specific recommendations to include nuts as alternatives for other foods in its TLC Sample Menus (see Appendix B). The specific dietary recommendations regarding nuts are also presented in Table 7.

Table 7
Specific Dietary Recommendations Regarding Nuts in the ATP III Report

TLC Sample Menu	Alternative recommendation for nuts
Traditional American Cuisine	“For a higher fat alternative, substitute 1/3 cup of unsalted peanuts, chopped (to sprinkle on the frozen yogurt) for 1 cup of the rice.”
Lacto Ovo Vegetarian Cuisine	“For a higher fat alternative, substitute ½ cup unsalted almond slices for ½ cup of the kidney beans in the salad.”
Southern Cuisine	“For a higher fat alternative, substitute ¼ cup of unsalted almond slices for the corn on the cob. Sprinkle the almonds on the rice.”

The “evidence statements” in the ATP III report as well as specific examples on how nuts can be included into healthy diets provide compelling support for the contention that nuts, all of which contain substantial amounts of mono- and/or polyunsaturated fatty acids, reduce the risk of CHD.

G. Significant Scientific Agreement (SSA)

FDA’s “Guidance for Industry, Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements” (1999) enumerates the criteria used by the agency to determine whether a causal relationship exists between a dietary factor and a disease. Such a causal relationship is essential for FDA to conclude that SSA has been achieved. An assessment of the data summarized in this document using these criteria (provided below) strongly supports the contention that there is a causal relationship between the consumption of nuts and reduced risk of CHD, and that the SSA standard has been met.

1. Strength of the association

Analyses of the totality of epidemiologic data (summarized in Table 5) including the four largest and best designed epidemiologic databases available, show that regular consumption of tree nuts and/or peanuts results in a reduced risk of CHD of approximately 30 to 50%. (Albert *et al.*, 2002; Fraser *et al.*, 1992; Fraser *et al.*, 1997; Hu *et al.*, 1998; Kushi *et al.*, 1996). In addition, all of the clinical trials summarized in Table 6 found significant reductions in serum T-C and/or LDL-C of up to 15.2% and 18.9%, respectively. The size of the relative risks from the observational studies and the

magnitude of the hypocholesterolemic effect exhibited by the intervention studies demonstrate that there is a strong, causal association between nut consumption and risk of CHD.

2. Consistency of the association

There were no studies identified in the literature that failed to support the hypothesis that nuts can reduce the risk of CHD. As noted above, all of the observational studies summarized in Table 5 found strong, inverse correlations between the consumption of tree nuts and peanuts and incidence of CHD. In addition, all 19 dietary intervention studies summarized in Table 6 demonstrated that increased consumption of nuts significantly reduced the risk of CHD based on lowered serum T-C and/or LDL-C. In addition, nine of these studies reported favorable effects on HDL-C and/or the HDL/LDL ratio (Sabaté *et al.*, submitted for publication, Chisholm *et al.*, 1998; Curb *et al.*, 2000, Durak *et al.*, 1999; Hyson *et al.*, 2002; Jenkins *et al.*, in press; Morgan *et al.*, 2000; Rajaram *et al.*, 2001; Sabaté *et al.*, 1993). Six additional studies (Berry *et al.*, 1991; Berry *et al.*, 1992; Bruce *et al.*, 1997; Bruce *et al.*, 2000; Jenkins *et al.*, 1997; Singh *et al.*, 1992) provided suggestive, but less definitive evidence that increased consumption of nuts reduces the risk of CHD. Therefore, the available literature is extremely consistent that nuts can reduce the risk of CHD.

3. Independence of the association

The independence of the association between nuts and reduced CHD risk is evidenced by the strong and consistent results of multivariate analyses of the epidemiologic databases

that were used to correct for many potential confounding variables. In addition, the independence of this association was repeatedly demonstrated by the dietary intervention studies that provided nuts to human subjects in controlled settings – especially those with very rigorous protocols (Sabaté *et al.*, submitted for publication; Rajaram *et al.*, 2001; Curb *et al.*, 2000; Kris-Etherton *et al.*, 1999; Sabaté *et al.*, 1993). These studies provide strong evidence that the observed effects on CHD-incidence and serum biomarkers reported in the literature are due to consumption of nuts, and not to some other factor.

4. Dose-response relationship

Evidence of a dose-response relationship was reported in three of the four major epidemiologic studies (Albert *et al.*, 2002; Fraser *et al.*, 1992; Hu *et al.*, 1998). In addition, Sabaté *et al.* (submitted for publication) and Jenkins *et al.* (in press) reported a dose-response relationship with respect to serum lipids among subjects fed two different amounts of almonds. Furthermore, a meta-analysis of 16 dietary intervention studies conducted for INCNREF confirms that a dose-response relationship exists for nuts and CHD biomarkers. The details of this study are discussed in section V below and the complete report is provided in Appendix C. In conclusion, available data provide strong evidence of a dose-response relationship between consumption of tree nuts and/or peanuts and reduced risk of CHD.

5. Temporal relationship

The temporal correctness of the relationship between consumption of nuts and CHD is convincingly demonstrated by the prospective observational data and by the controlled intervention studies.

6. Effect of dechallenge

There are no epidemiologic studies that specifically addressed whether subjects who reduced consumption of nuts had increased risk of CHD. However, studies that employed a crossover design showed that removal of nuts from the diet resulted in a loss of their beneficial effect on serum lipids (Sabaté *et al.*, submitted for publication; Almario *et al.*, 2001; Chisholm *et al.*, 1998; Curb *et al.*, 2000; Edwards *et al.*, 1999; Iwamoto *et al.*, 2002; Jenkins *et al.*, in press; Kris-Etherton *et al.*, 1999; Rajaram *et al.*, 2001; Sabaté *et al.*, 1993; Zambon *et al.*, 2000).

7. Specificity

The data summarized in this document demonstrate that increased consumption of nuts reduces the risk of CHD. Other studies suggest that increased consumption of nuts may have beneficial effects on cancer (Herbert *et al.*, 1998; Jain *et al.*, 1999; Trichopoulos *et al.*, 1985), blood pressure (Appel *et al.*, 1997; Sacks *et al.*, 2001) and weight control (McManus *et al.*, 2001). The fact that increased consumption of nuts may have additional benefits beyond reduction of CHD is fortunate from a public health perspective, but beyond the scope of this petition.

8. Biological plausibility

The dietary intervention studies that show favorable effects on serum lipids clearly demonstrate a plausible (in fact highly likely) biological mechanism for the protective effect of nuts on the risk of CHD. As discussed earlier, nuts contain a variety of non-lipid substances that may contribute to their cardioprotective effects (Hu *et al.*, 2001; Dreher and Maher, 1996; Kris-Etherton *et al.*, 2001; Sabaté *et al.*, 1999), but evidence relating to the favorable effects of these foods on serum biomarkers alone is sufficient to demonstrate biological plausibility.

9. Overall Conclusion Regarding SSA

The data discussed above on the ability of nuts to reduce the risk of CHD clearly demonstrate that the SSA standard has been achieved. Evidence supporting this conclusion is derived from several recent review papers, compelling observational data, consistent dietary intervention studies and thorough assessments of the literature by public health and governmental organizations including the American Heart Association and the National Heart Lung Blood Institute. In conclusion, INCNREF respectfully submits that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that eating nuts can reduce the risk of CHD. INCNREF strongly urges FDA to authorize the proposed claim based on the strength of the totality of available evidence.

IV. DIETARY CONSIDERATIONS

Data from the 1994-1996 Continuing Survey of Food Intake by Individuals (CSFII) and the 1988-1994 National Health and Nutrition Examination Survey (NHANES) can be used to compare the nutrient intake of nut consumers with that of their non-nut eating counterparts. These data are useful to analyze, “the potential effect of the use of the proposed claim on food consumption,” as stipulated in 21 CFR § 101.70 (f). The results of this analysis suggest that individuals who choose to consume one ounce of nuts per day would benefit from a more nutrient dense diet without increasing body weight, or consuming excessive amounts of fat or saturated fat. Additional details of this analysis are provided below.

A. Micronutrients

Table 8 provides data on the micronutrient intake of 9,221 adult men and women from the USDA 1994-96 CSFII⁴.

Nut consumers were defined as individuals who reported consumption of one or more obvious sources of nuts (e.g. whole or chopped nuts, snacking nuts) on one or both days of the dietary survey. Products with small amounts of nuts (e.g. ice cream, baked goods) or nuts in confectionary products were not included. Detailed information about the analysis of CSFII data is presented in Appendix D.

⁴ CSFII data were provided by Matthew Robinson, Kraft Foods North America, East Hanover, NJ 07936.

Table 8
Mean Daily Nutrient Intake of Women and Men Aged 20 and Older by Nut/Nut Butter Consumption

Nutrient	Nut Consumers (n=1,264) (nuts eaten at least once during the two days of the survey)	Non-Nut Consumers (n=7,975) (no nuts eaten on either survey day)
Protein (g)	82.5 ± 0.9**	76.9 ± 0.9
Vitamin A (RE)	1,141 ± 40**	974 ± 17
Vitamin E (TE)	10.5 ± 0.2**	7.9 ± 0.1
Vitamin C (mg)	104 ± 2.9**	94.0 ± 1.8
Thiamin (mg)	1.72 ± 0.02**	1.58 ± 0.02
Riboflavin (mg)	2.03 ± 0.03**	1.78 ± 0.02
Niacin (mg)	25.5 ± 0.04**	22.3 ± 0.02
Vitamin B ₆ (mg)	1.95 ± 0.03**	1.78 ± 0.02
Folate (µg)	302 ± 8**	246 ± 6
Vitamin B ₁₂ (µg)	5.24 ± 0.21	5.17 ± 0.26
Calcium (mg)	856 ± 14**	729 ± 11
Phosphorous (mg)	1,378 ± 16**	1,192 ± 13
Magnesium (mg)	335 ± 5**	262 ± 2
Iron (mg)	17.0 ± 0.03**	15.0 ± 0.02
Zinc (mg)	12.6 ± 0.03**	11.1 ± 0.02
Copper (mg)	1.47 ± 0.02**	1.18 ± 0.01
Selenium (µg)	116 ± 1.9**	104 ± 1.3

CSFII, 1995-1996, 2 days Mean is sample-weighted and standard error is estimated by linearization method of SUDAAN

**P<0.01 by t-test, nuts or nut butters vs non-consumer

The data in Table 8 show that nut consumers have more nutrient dense diets than non-nut consumers. All of the nutrients examined, with the exception of Vitamin B₁₂, were present in significantly greater amounts in the diets of nut-consumers compared to non-consumers. This difference suggests that nuts are contributing nutrients directly to the diet, and that nut-consumers may tend to choose more nutrient dense foods than non-nut consumers. These data are consistent with USDA's observation (Lino, 2000) that nut-consumers had a significantly higher modified Healthy Eating Index than non-nut consumers.

B. Energy/body weight

Data from the CSFII survey presented in Table 9 show that energy intake is slightly higher among nut consumers compared to non-consumers but that Body Mass Index (BMI) is lower.

Table 9
Mean Daily Energy Intake and Body Mass Index of Women and Men Aged 20 and Older by Nut/Nut Butter Consumption

Parameter	Nut Consumers (n=1,264) (nuts eaten at least once during the two days of the survey)	Non-Nut Consumers (n=7,975) (no nuts eaten on either survey day)
Energy (Kcal)	2,186 ± 28**	1,980 ± 22
Body Mass Index	25.7 ± 0.1*	26.1 ± 0.01

CSFII, 1995-1996, 2 days. Mean is sample-weighted and standard error is estimated by linearization method of SUDAAN
*P<0.05, **P<0.01 by t-test, nuts or nut butters vs. non-consumer

Body Mass Index data from the CSFII survey must be interpreted with caution because they are based on self-reported weight and height information. While there is no reason to expect differences in reporting error between nut and non-nut consumers, this fact cannot be verified with the existing database. In order to overcome this limitation, data from the 1988-1994 NHANES survey were analyzed to examine the relationship between nut consumption and BMI. Participants in the NHANES surveys are examined directly by study investigators so the limitation of self-reported data is avoided.

Regression analysis was conducted for 1,598 nut consumers aged 20 or above (total population 15,577) in the 1988-1994 NHANES database.⁵ The model was sample weighted and controlled for gender, age, race-ethnicity, and smoking using SUDAAN. The sample includes those participants 20 years and over with complete and reliable

⁵ NHANES data were provided by Matthew Robinson, Kraft Foods North America, East Hanover, NJ 07936.

intake records, excluding pregnant and lactating women and participants with missing information or measurements. BMI was significantly ($P = 0.003$) negatively associated with nut intake among this sample ($R^2 = 0.035$; β Coefficient = -0.76). These data provide additional confirmation that nut consumers tend to be leaner than their non-nut consuming counterparts.

An inverse relationship between nut intake and BMI has also been observed in large epidemiologic studies. Fraser *et al.* (1992) reported a statistically significant negative association between consumption of nuts and the Quetelet index of obesity in a sample of 31,208 Seventh-Day Adventists. Hu *et al.* (1999) also reported a negative association between nut consumption and obesity (as measured by BMI) among 86,016 participants in the Nurses' Health Study. There was no apparent association between BMI and nut consumption in the Physicians' Health Study (Albert *et al.*, 2002). BMIs by quartile of nut consumption (ranging from rarely/never to two or more times per week) were 24.9, 24.9, 25.0 and 24.7 among this cohort of 21,454 male physicians. Although the paper did not report the statistical significance of these data, it is clear from inspection that nut intake was not associated with increased BMI.

Further evidence that feeding nuts is not associated with increased body weight is provided by many of the dietary intervention trials reviewed in Table 6. Two studies reported a tendency for weight loss in the group fed nuts (Iwamoto *et al.*, 2002; O'Byrne *et al.*, 1993). Eleven studies (Abbey *et al.*, 1994; Almario *et al.*, 2001; Chisholm *et al.*, 1998; Curb *et al.*, 2000; Edwards *et al.*, 1999; Hyson *et al.*, 2002; Jenkins *et al.*, in press;

Morgan *et al.*, 2000; Spiller *et al.*, 1998; Spiller *et al.*, 1992 and Yi *et al.*, 2002) reported no weight gain during the course of nut feeding – even if nuts were provided in a free-feeding situation. None of the intervention studies reported a weight gain in subjects who had been fed nuts compared to non-nut fed controls.

Alper and Mattes (2002) recently reported the effect of “chronic” peanut consumption on weight gain in a group of 15 healthy, normal weight adults using a randomized, cross-over design. The subjects were provided with 500 Kcal/day peanuts (89 g or 3.1 oz) under three experimental conditions: a “free-feeding” trial (FF) where participants were given peanuts without dietary guidance; an “addition” phase (ADD) where subjects were asked to add peanuts to their customary diet; and a “substitution” period (SUB) during which peanuts replaced an equal amount of other fats in the diet. Participants in the SUB group did not gain weight during the experiment. Participants in the FF group gained 1.0 kg during the eight-week intervention, which was considerably less than the predicted weight gain of 3.6 kg based on the additional calories provided. Similarly, subjects in the ADD group gained only 0.6 kg compared to a theoretical prediction of 1.4 kg. Part of this difference was attributable to dietary compensation for a portion of the extra calories provided by peanuts. In addition, resting energy expenditure was significantly higher after consumption of peanuts although physical activity levels did not change. The authors concluded, “Despite being energy dense, peanuts have a high satiety value and chronic ingestion evokes strong dietary compensation and little change in energy balance.” The amount of peanuts provided in this study (500 Kcal/d) is approximately three times the amount that would be specified in the proposed claim. Extrapolation of

the data in this study to reflect one ounce per day suggests that weight gain would probably have been statistically insignificant.

Fraser *et al.* (2002) also reported that feeding nuts to human subjects had minimal effects on body weight. Eighty-one subjects were provided with 320 Kcal of raw or dry-roasted almonds per day (54.3 g or 1.9 oz.) in a randomized, crossover study. Subjects were provided with almonds, but were given no specific dietary instructions. After six months of consuming the almond supplement, male subjects gained a “biologically insignificant” 0.65 kg ($P < 0.01$) and the women gained 0.11 kg ($P = 0.79$). Only subjects in the lowest tertile of baseline BMI gained weight during the almond phase of the study, and women in the highest baseline BMI tertile actually lost weight with almond supplementation.

The authors concluded, “Incorporating a modest quantity (76 kJ) of almonds in the diet each day for six months did not lead on average to statistically or biologically significant changes in body weight and did increase the consumption of unsaturated fats.”

There are several possible explanations why nut consumption is not associated with an increased BMI in free-living individuals. People who eat nuts may tend to engage in higher levels of physical activity than non-nut consumers. Hu *et al.* (1998) reported that nut consumption was associated with greater incidence of “vigorous exercise” among 86,016 nurses. Fecal fat loss due to incomplete mastication of nuts or other factors may result in a loss of available energy. Levine *et al.* (1980) reported that subjects fed whole peanuts excreted 17.8% of fat in the stool. In addition, Zemaitis and Sabaté (2001) reported that diets containing 10 and 20% of energy from almonds resulted in an increase

in fecal fat of 4.6 and 5.9 g, respectively compared to subjects consuming an almond free diet. In addition, metabolic effects of unsaturated fatty acids or other components of nuts may increase resting energy expenditure (REE) resulting in less fat deposition (Alper and Mattes, 2002).

Another reason that eating nuts is not associated with obesity in free-living individuals may be due to their effect on satiety. Kirkmeyer and Mattes (2000) demonstrated that nuts and other energy-dense foods enhance satiety ratings and affect subsequent food intake after a preload. In addition, McManus *et al.* (2001) reported that subjects fed a moderate fat, weight-reduction diet containing almonds, cashew nuts, hazelnuts, macadamia nuts, pecans, pistachio nuts, walnuts, peanuts, peanut butter and olive oil were significantly more likely to remain compliant at 18 months than subjects fed a low fat, high carbohydrate diet. This increased adherence to a weight loss regimen was attributed largely to increased palatability of the foods in the moderate fat diet.

In conclusion, the available data demonstrate that nut consumption among free-living individuals is not associated with higher BMIs as compared to non-nut consumers despite the fact that they are energy-dense foods. These data further support that individuals who are advised that consuming one ounce of nuts per day can reduce their risk of heart disease are unlikely to experience increased body weight.

C. Fat/Saturated fat

Data from the CSFII survey presented in Table 10 demonstrate that percent of calories from fat is slightly higher among nut consumers compared to non-consumers, but the intake of saturated fat is the same in both groups.

Table 10
Percent of Calories from Total Fat and Fatty Acids for Women and Men Aged 20 and Older by Nut/Nut Butter Consumption

Fat Type	Nut Consumers (n=1,264) (nuts eaten at least once during the two days of the survey)	Non-Nut Consumers (n=7,975) (no nuts eaten on either survey day)
Total Fat	34.5 ± 0.3**	32.9 ± 0.1
Monounsaturated	13.6 ± 0.1**	12.5 ± 0.1
Polyunsaturated	7.5 ± 0.1**	6.7 ± 0.0
Saturated	10.9 ± 0.1	11.0 ± 0.1

CSFII, 1995-1996, 2 days. Mean is sample-weighted and standard error is estimated by linearization method of SUDAAN
*P<0.05, **P<0.01 by t-test, nuts or nut butters vs non-consumer

Although the data in Table 10 show that the fat intake of nut consumers is greater than that of non-nut consumers, this difference is due almost exclusively to unsaturated fats. Furthermore, the percent of energy contributed by total fat, monounsaturated fats and polyunsaturated fats of nut-consumers is well within the upper guidelines specified by the National Cholesterol Education Program (NCEP) in the ATP III report (National Cholesterol Education Program, 2001) of 35%, 20% and 10%, respectively. Therefore, INCNREF believes that the available dietary data do not suggest that nut consumption is associated with excessive intakes of dietary fat.

The data in Table 10 also show that the percent calories from saturated fat is identical among nut and non-nut consuming individuals. This result is consistent with the fact that even though nuts do not meet the definition of “low-saturated fat” they provide relatively modest amounts of this constituent to the diet. Most nuts contain ≤ 2 grams saturated fat per serving and are therefore eligible to make “no cholesterol” claims under 21 CFR § 101.62 (d).

Current intake of saturated fat exceeds the most recent NCEP maximum guideline of 7% of energy. However, the fact that nut eaters do not consume more saturated fat than non-nut eaters suggests that more prominent sources of this constituent (e.g. red meat) should be the focus of dietary guidance to meet NCEP recommendations. The available dietary data do not suggest that nut consumption is associated with excessive intakes of dietary saturated fat.

In summary, with respect to dietary considerations, available data demonstrate that nut-consumers have a diet that is higher in nutrient density, slightly higher in calories (but nut consumption is associated with a lower BMI), slightly higher in total fat (from unsaturated fats) and similar in saturated fat compared to non-nut consumers. This information clearly shows that nuts can make a valuable contribution to a diet designed to reduce the risk of CHD – a fact that is reflected by the sample menus provided in the ATP III report (National Cholesterol Education Program, 2001).

V. EFFECTIVE DOSE

A meta-analysis of 16 nut-feeding trials was recently conducted for INCNREF⁶ and is appended to this petition. This analysis consisted of 454 individual observations from both normo- and moderately hypercholesterolemic men and women. The overall results of the study are presented in Table 11.

Nut consumption resulted in a significant decrease in T-C and LDL-C when expressed as change in mg/dL, mmol/L and percent. In addition, feeding nuts resulted in a small, but statistically significant increase in HDL-C when expressed as percent change. There was no change in the concentration of HDL-C expressed as mg/dL or mmol/L. There were also significant improvements in the LDL/HDL and T-C/HDL ratios when expressed as absolute or percentage changes. These data provide further confirmation that nuts as a whole reduce the risk of CHD as suggested by the individual intervention studies.

The results of nut feeding on serum lipids stratified by baseline T-C are presented in Table 12. As expected, these data show that subjects with higher baseline T-C concentrations experienced a greater reduction in T-C and LDL-C after consuming nuts compared to normocholesterolemic individuals. The highest baseline T-C group (>250 mg/dL) experienced a decrease in T-C and LDL-C of 6.4% and 8.9%, respectively.

⁶ Meta-analysis conducted by Nutrition Impact LLC. The full report is provided in Appendix C.

Table 11
Overall Effects of Nut Consumption on Blood Lipids

Variable	Mean (95% CI)
Number of Observations	454
Total Cholesterol Difference, mg/dL	-10.5 (-12.3, -8.7)
Total Cholesterol Difference, mmol/L	-0.27 (-0.316, -0.224)
Total Cholesterol Difference, %	-4.6 (-5.4, -3.8)
LDL-Cholesterol Difference, mg/dL	-9.7 (-11.5, -8.2)
LDL-Cholesterol Difference, mmol/L	-0.25 (-0.296, -0.211)
LDL-Cholesterol Difference, %	-6.4 (-7.7, -5.1)
HDL-Cholesterol Difference, mg/dL	0.39 (-0.16, 0.98)
HDL-Cholesterol Difference, mmol/L	0.01 (-0.004, 0.025)
HDL-Cholesterol Difference, %	1.5 (0.2, 2.7)
LDL/HDL Difference	-0.23 (-0.275, -0.178)
LDL/HDL Difference, %	-6.4 (-8.1, -4.7)
T-C/HDL Difference	-0.24 (-0.300, -0.182)
T-C/HDL Difference, %	-4.7 (-5.8, -3.5)

Values in bold are significantly different from zero ($p < 0.05$)

Corresponding reductions for normocholesterolemic ($T-C \leq 200$ mg/dL) subjects were 3.2% for T-C and 5.5% for LDL-C. Subjects with baseline T-C > 200 mg/dL but ≤ 250 mg/dL had an intermediate response. There were no significant changes in HDL-C when expressed as change in concentration or percent among the subjects stratified for baseline

cholesterol, however all subsets experienced beneficial changes in the ratios of HDL/LDL and T-C/HDL. These data show that nut consumption results in statistically significant reductions in T-C and LDL-C among both normo- and moderately hypercholesterolemic individuals, with a greater response among subjects at greater risk of CHD.

Table 12

Effects of Nut Consumption on Blood Lipids at Various Starting Total Cholesterol Levels

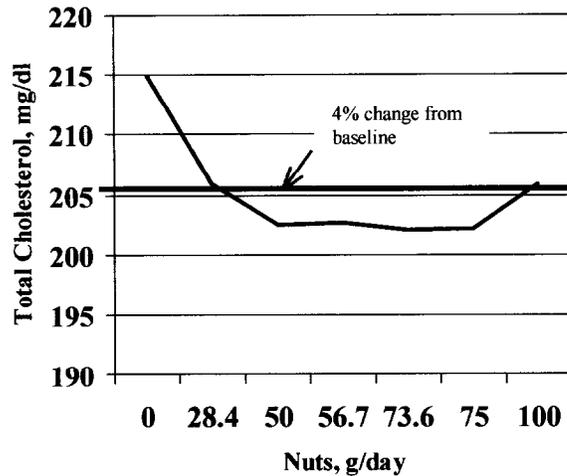
Variable	Baseline total cholesterol ≤ 5.2 mmol/L ¹	Baseline total cholesterol > 5.2 and ≤ 6.5 mmol/L	Baseline total cholesterol > 6.5 mmol/L
Number of Subjects	181	166	107
Total Cholesterol Difference, mg/dL	-5.5² (-8.0, -3.1)	-11.3 (-13.9, -8.4)	-17.9 (-22.3, -13.5)
Total Cholesterol Difference, mmol/L	-0.14 (-0.205, -0.080)	-0.29 (-0.357, -0.215)	-0.46 (-0.573, -0.347)
Total Cholesterol Difference, %	-3.2 (-4.8, -1.7)	-4.9 (-6.1, -3.7)	-6.4 (-7.9, -4.8)
LDL-Cholesterol Difference, mg/dL	-6.2 (-8.4, -3.9)	-8.9 (-11.7, -6.5)	17.1 (-21.3, -13.2)
LDL-Cholesterol Difference, mmol/L	-0.16 (-0.217, -0.101)	-0.23 (-0.301, -0.167)	-0.44 (-0.548, -0.340)
LDL-Cholesterol Difference, %	-5.5 (-8.2, -2.9)	-5.8 (-7.6, -4.1)	-8.9 (-10.9, -6.8)
HDL-Cholesterol Difference, mg/dL	0.39 (-0.51, 1.2)	0.39 (-0.62, 1.2)	0.78 (-0.51, 2.0)
HDL-Cholesterol Difference, mmol/L	0.01 (-0.013, 0.030)	0.01 (-0.016, 0.030)	0.02 (-0.013, 0.052)
HDL-Cholesterol Difference, %	1.9 (-0.3, 4.1)	1.1 (-0.7, 3.0)	1.3 (-1.1, 3.6)
LDL/HDL Difference	-0.17 (-0.248, -0.094)	-0.21 (-0.292, -0.134)	-0.34 (-0.444, -0.235)
LDL/HDL Difference, %	-5.5 (-8.7, -2.2)	-5.7 (-8.1, -3.4)	-9.0 (-11.7, -6.3)
T-C/HDL Difference	-0.15 (-0.246, -0.055)	-0.26 (-0.362, -0.167)	-0.36 (-0.481, -0.236)
T-C/HDL Difference, %	-3.3 (-5.6, -1.2)	-4.8 (-6.7, -3.0)	-6.6 (-8.8, -4.5)

¹ Baseline total cholesterol levels are ≤ 200 mg/dL, > 200 mg/dL but ≤ 250 mg/dL, and > 250 mg/dL, respectively

² Values are means and 95% Confidence Intervals. Values in bold are significantly different from zero ($p < 0.05$)

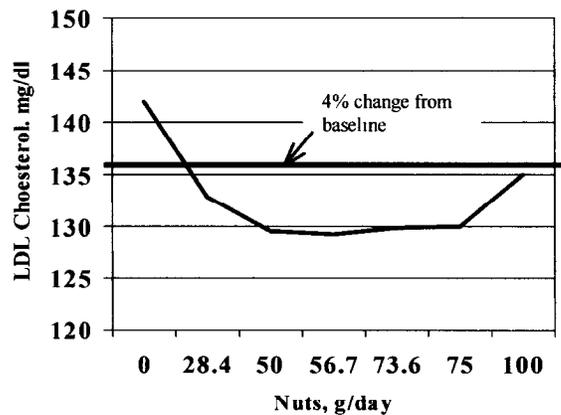
Regression analysis was used to determine the predicted response of serum lipids to different amounts of dietary nuts. These data are presented for T-C in Figure 2 and for LDL-C in Figure 3.

Figure 2
 Predicted Total Cholesterol Concentration by Nut Intake



Cholesterol values predicted by models generated by General Linear Model procedures in SAS
 Total Cholesterol, mg/dl = 205.1 + Study Effect + 0.8095*Age + 0.5036*Body Mass Index - 0.4037*Nut Amount + 0.0031*Nut Amount²
 Linear effect. p = 0.0004, Quadratic effect. p = 0.0084

Figure 3
 Predicted LDL-Cholesterol Concentration by Nut Intake



Cholesterol values predicted by models generated by General Linear Model procedures in SAS
 LDL Cholesterol, mg/dl = 122.5 + Study Effect + 0.7698*Age + 0.6755*Body Mass Index - 0.4233*Nut Amount + 0.0035*Nut Amount²
 Linear effect. p < 0.0001, Quadratic effect. p = 0.0011

The data in Figures 2 and 3 show that feeding one ounce of nuts results in a predicted decrease of 4.1% for T-C and 6.5% for LDL-C compared to baseline, respectively. These decreases are similar in magnitude to those achieved by feeding soy protein, sterol/stanol esters, β -glucan soluble fiber from whole oats or soluble fiber from psyllium seed husks at the minimum daily dose specified in the health claim regulations pertaining to these substances (21 CFR §§ 101.82, 101.83, 101.81). FDA stated in the preamble to the final rule for the psyllium health claim (63 FR 8103, 8109, February, 18, 1998) that reductions of serum T-C and LDL-C as low as 4% are significant and sufficient to authorize a health claim,

Similarly, there is no basis to require that the qualifying criteria for a substance associated with risk of CHD be based on the amount of that substance to elicit a 5 percent reduction in blood total- and LDL-cholesterol levels. The data on psyllium seed husk suggests that the magnitude of the effect on blood lipids for intakes of about 10 g/d of psyllium seed husk ranges from 4 to 6 percent for blood total-cholesterol and about 4 to 8 percent for LDL-cholesterol levels in conjunction with diets low in saturated fat and cholesterol (Ref. 7). Although modest in size, these are clinically significant reductions in blood lipids and translate to a reduced risk of CHD for individuals with hypercholesterolemia...

The regression analysis presented in Figures 2 and 3 also suggests that no additional benefit with respect to CHD risk would be obtained by eating more than approximately 50g nuts per day. However, all levels of nut consumption studied would result in a net benefit compared to non-nut consumers.

In summary, a meta-analysis of 16 nut dietary intervention data sets demonstrates that feeding one ounce of nuts per day is sufficient to elicit a clinically significant reduction in serum CHD biomarkers that would be expected to reduce the risk of CHD. Therefore,

INCNREF proposes that one ounce of nuts per day be used as the minimum effective dose in determining the nature of the food eligible to bear the proposed health claim.

VI. NATURE OF THE FOOD ELIGIBLE TO BEAR THE CLAIM

INCNREF requests that nut-containing products with at least 7.1 g nuts per RACC and \leq 20 mg cholesterol per RACC (or per 50 grams for products with small RACCs) be eligible to bear the proposed health claim. Straight nut products (products that consist essentially only of nuts) including raw or blanched whole or chopped nuts, roasted nuts and nuts lightly coated with non-fat ingredients would be excluded from the total fat disqualifier level, and Brazil nuts, cashew nuts and macadamia nuts would also be excluded from the saturated fat disqualifier level. All formulated products (i.e. those with significant amounts of non-nut ingredients) would be subject to the general health claim requirements in 21 CFR § 101.14.

A. Minimum content of nuts per RACC

As noted above (see section V) one ounce of nuts per day is sufficient to lower T-C and LDL-C by amounts FDA has deemed sufficient to authorize other health claims.

INCNREF proposes that a minimum of 7.1 g nuts per RACC be required for a food to bear the claim. This amount is based on the premise that consumers should have the flexibility to consume the minimum effective dose by eating up to four servings of nut-containing foods per day ($28.4 \text{ g} \div 4 \text{ servings/d} = 7.1 \text{ g/serving}$).

FDA has traditionally considered that a typical daily food consumption pattern is composed of three meals and a snack per day (58 FR 2302, 2379, January 6, 1993). This dietary pattern was used to define the minimum content criterion for three CHD-related health claims: soy protein (64 FR 57700 at 57713); β -glucan soluble fiber from whole oats (62 FR 3584 at 3592); and soluble fiber from psyllium seed husks (63 FR 8103 at 8109). INCNREF believes the following reasons justify the use of the same consumption pattern for the proposed health claim for nuts.

1. Provide consumers with dietary flexibility

Consumers may often choose to consume the minimum effective dose of one ounce of nuts per day as a single serving of a straight nut product. However, the availability of a wide range of nut-containing products with smaller amounts of nuts per serving would provide a greater selection of foods to choose from and would allow new products to be targeted to different meal occasions (e.g. breakfast, snacks). This flexibility would help health conscious consumers with different lifestyles to eat nuts regularly. For example, Sabaté *et al.* (2001) report that as many as 7% of the U.S. population are vegetarian, and that the trend is increasing. Finally, increased availability of nut-containing products would help to avoid the dietary monotony that could result if the number of eligible products were unnecessarily limited.

2. Allow the development of innovative nut-containing products

A marketplace survey⁷ suggests that relatively few currently available nut-containing products qualify for the proposed claim.⁸ An important factor limiting the number of such products is that many have a small RACC (e.g. ready-to-eat cereals, snack foods). The smaller the RACC, the more difficult it would be for manufacturers to incorporate 7.1 g of nuts into a serving of product (i.e. 7.1 g nuts would constitute approximately 25% by weight of a product with a one-ounce RACC). In addition, the quantity of nuts that can be added to foods is limited by economic considerations, organoleptic characteristics and physical properties. Nevertheless, ready-to-eat cereals, bar-type products (e.g. meal replacements, granola bars, energy bars) and formulated snacks (e.g. trail mix-type products, nut-popcorn mixtures) are among the product categories that have the potential to be reformulated to qualify for the proposed claim at 7.1 g per serving. The new claim would provide an important incentive for food manufactures to develop and market such products. However, this incentive would be severely diminished if a higher level of nuts were required.

3. Increase nut intake among the general population

The regression analysis discussed in section V above suggests that even small amounts of nuts would be expected to have a public health benefit. For example, according to this analysis 7.1 g of nuts per day would result in a decrease in T-C and LDL-C of 1.3 and 2.0%, respectively. Therefore, consumers who are not making a conscious effort to eat

⁷ Survey of grocery stores in the Kalamazoo, MI area conducted by Johnson Nutrition Solutions LLC, August 5, 2002.

⁸ The eligibility of existing products could not be precisely determined without knowledge of the products formulation, but the position of nuts in relation to other ingredients and overall product characteristics were used to estimate whether such products contain ≥ 7.1 g nuts per serving.

more nuts, but do so simply because more nut-containing products are available may also experience a reduction in CHD risk.

4. Increase consumer awareness of the health benefits of nuts

Use of the proposed claim on a wide variety of nut-containing products would increase consumer understanding about the benefits of eating nuts and help ensure that their public health potential is realized. Restricting use of the claim by increasing the amount of nuts that products must contain to qualify would have the opposite effect.

In conclusion, we agree with FDA's rationale of using four servings per day to determine the eligibility of products to bear previously authorized health claims, and recommend that the same approach be applied to the proposed claim. Although nut-containing products contain fat, the dietary data presented earlier in this document suggest that the consumption of one ounce of nuts per day is not associated with excessive fat or saturated fat intake. Furthermore, the fat provided by the nuts in such foods is unsaturated, and is necessary for the cardioprotective effect. In addition, eligibility for the claim by all products with significant amounts of non-nut ingredients would be limited by the general health claim criteria specified in 21 CFR § 101.14. INCNREF believes establishing a minimum level of 7.1 g nuts/RACC is both reasonable and necessary to take full advantage of the proposed claim as a public health opportunity.

B. Total fat content

Public health authorities have long recommended a low-fat, high carbohydrate diet as a means to reduce the risk of CHD. Such recommendations were made explicitly in the fourth edition of the Dietary Guidelines for Americans (U.S. Department of Agriculture, U.S. Department of Health and Human Services, 1995), which stated, “Choose a diet low in fat, saturated fat, and cholesterol.” Similar recommendations were a cornerstone of the second report of the National Cholesterol Education Program (1994).

However, evolving science regarding the cardioprotective role of unsaturated fats has caused these (and other) public health recommendations to be updated. For example, the fifth edition of the Dietary Guidelines for Americans (U.S. Department of Agriculture, U.S. Department of Health and Human Services, 2000) modified the previous “low fat” guideline to, “Choose a diet that is low in saturated fat and cholesterol and **moderate in total fat**”(emphasis added). In addition, the latest report of the National Cholesterol Education Program (ATP III) increased the upper recommended level of total dietary fat from 30 to 35% of calories in order to accommodate up to 10% of calories from polyunsaturated fatty acids and up to 20% of calories from monounsaturated fatty acids (National Cholesterol Education Program, 2001).

The majority of currently authorized CHD-related health claims (21 CFR §§ 101.75, 101.77, 101.81) require that foods meet the “low-fat” definition (21 CFR §101.62 (b)(2)) in order to be eligible to make the claim. However, FDA has recognized the need for several important exceptions to this policy. For example, the agency initially proposed

that foods eligible to make the soy-CHD claim be required to be low in fat, but eliminated this requirement because total fat intake is not directly related to CHD, and because the inherent fat content of soybeans would have prevented many products made from whole beans from making the claim (64 FR 57700 at 57717). In addition, the agency chose not to impose a low-fat criterion on products eligible to make the sterol/stanol ester health claim because fat is the only vehicle capable of delivering these cardioprotective substances which were deemed to have important public health significance (65 FR 54686 at 54708). FDA also noted that this policy was consistent with the fifth edition of the Dietary Guidelines for Americans, which recommends “moderate” rather than “low” fat diets.

INCNREF believes that similar reasoning should be applied to the proposed health claim for nuts. The evolution in scientific understanding about the cardioprotective effects of unsaturated fat is fundamental to this proposed claim. Unlike other CHD-related claims, the health benefit of nuts is *dependent* on fat. This basic premise dictates that foods not be required to meet the definition of low fat in order to qualify for the claim. The fat content of 7.1 g of common nuts ranges from 3.2 to 5.3 grams. Because “low-fat” foods are limited to 3g per RACC, imposition of this criterion would prevent all non-meal-type products from making the claim. INCNREF believes that the public health benefits of the proposed claim clearly justify waiving this requirement.

C. Cholesterol content

All of the CHD-related health claims that have been authorized to date require that eligible foods be low in cholesterol as defined by 21 CFR § 101.62 (d). Like all plant-based foods, nuts do not contain cholesterol. INCNREF believes that nut-containing formulated products should be required to contain ≤ 20 mg cholesterol per RACC (or per 50 g if the RACC is 30 g or less or two tablespoons or less) according to 21 CFR § 101.62(d)(2)(ii)(A) in order to be eligible to make the proposed claim.

D. Saturated fat content

Numerous studies have shown that dietary saturated fat can increase concentrations of serum T-C, LDL-C and HDL-C (National Cholesterol Education Program, 2001). This well-known fact has prompted FDA to require that foods bearing CHD-related health claims be low in saturated fat according to 21 CFR § 101.62(c)(2) (see 21 CFR §§ 101.75, 101.77, 101.81, 101.82 and 101.83). However, this criterion is not necessary, or appropriate, to define the nature of foods eligible to bear the proposed claim for nuts. In fact, to do so would be contrary to FDA's public health mission.

1. The saturated fat in nuts is overshadowed by unsaturated fat with respect to cardioprotective effects.

As noted Table 3, the fat content of nuts is predominantly composed of unsaturated fatty acids. The unsaturated fat content of common nuts ranges from 71-88% of total fat with an average of 81.9%. This high percentage of unsaturated fatty acids ensures that whole

nuts are hypocholesterolemic because it more than compensates for the relatively small amount of saturated fat that accompanies it.

Eligibility of foods to bear the proposed claim is based on their content of whole nuts. This criterion ensures that the nut-derived saturated fat content of such products will *always* be overshadowed by the unsaturated fat that accompanies it. A requirement that nut-containing foods be low in saturated fat in order to bear the claim would severely restrict the very component of such foods that contributes to their cardioprotective effect, and would inappropriately limit the scope of foods eligible to provide this important public health information.

2. Nuts are moderate sources of saturated fat that can easily be incorporated into a “heart healthy” diet.

None of the nuts that are the object of the proposed claim meets the definition of low saturated fat. However, nuts are moderate sources of saturated fat compared to many other foods, and can easily fit into a low saturated fat diet. The saturated fat content of the nuts that are the object of the proposed claim is presented in Table 13.

According to 21 CFR § 101.62(c)(2)(i), foods must contain 1 g or less saturated fat per RACC and not more than 15% of total calories from saturated fat in order to be considered “low” in this nutrient. All but one of the common tree nuts meet the 15% of total calories criterion, but none meets the absolute weight definition. Nevertheless, the

Table 13
Saturated Fat Content of Tree Nuts and Peanuts

Nut	Saturated Fat (g/1 oz. serving)	Calories (per 1 oz. serving)	Percent Calories as Saturated Fat
Almonds	1.1	164	6.0
Brazil nuts	4.6	185	22.3
Cashew nuts	2.4	160	13.5
Hazelnuts	1.3	178	6.6
Macadamia nuts	3.4	204	15.0
Peanuts	1.9	161	10.6
Pecans	1.8	196	8.2
Pine nuts	2.2	160	12.4
Pistachio nuts	1.5	158	8.5
Walnuts	1.7	185	8.3

saturated fat content of nuts (average 2.2 g/serving) is modest, and comparable to other “healthy” dietary sources of this component as shown in Table 14.

Table 14
Saturated Fat Content of “Healthy” Foods

Food	Serving Size	Saturated Fat (g/serving)
Nuts (average value)	1 ounce	2.2
Reduced fat (2%) milk	1 cup	2.9
Roasted chicken breast	½ breast	2.1
Cooked halibut	3 ounces	2.6
Cooked extra lean ground beef	3 ounces	5.4
Olive oil	1 tablespoon	1.8
Avocado	1 cup (sliced)	3.6

As noted previously, nuts can easily be incorporated into a balanced diet that contains an appropriate amount of saturated fat. The National Heart, Lung, Blood Institute (National Cholesterol Education Program, 2001) has made specific recommendations to include nuts as alternatives for other foods in its TLC Sample Menus (see Appendix B). In

addition, USDA's publication, "The Food Guide Pyramid" (1992) specifies that a one ounce serving of nuts is equivalent to 3 ounces of cooked lean meat, poultry or fish with respect to meeting Pyramid recommendations. Finally, The Dietary Guidelines for Americans (U.S. Department of Agriculture, U.S. Department of Health and Human Services, 2000) recommend that consumers choose 2 to 3 servings per day from the food group that contains nuts. These public policy recommendations clearly support the fact that one ounce of nuts per day can be an appropriate part of a heart-healthy diet.

3. Dietary intake data show that nut eaters and non-nut eaters have similar amounts of saturated fat in their diets.

As discussed above (see section IV), U.S. food consumption data show that the percent of calories from saturated fat in the diets of nut consumers and non-consumers is similar. Because nuts do not appear to add saturated fat to the diet of free-living individuals, a requirement to restrict eligibility of the proposed claim to low-saturated fat products would be unnecessary and overly restrictive.

4. The disqualifier level for saturated fat will help ensure appropriate use of the proposed claim.

As discussed below, the saturated fat disqualifier level will prevent the proposed claim from being used on formulated nut-containing products with inappropriate levels of saturated fat.

In summary, despite the fact that nuts do not meet the definition of “low-saturated fat”, they are only minor sources of this dietary component, and can easily fit into a heart healthy diet. INCNREF believes that the health benefits of including nuts in the diet more than outweigh the nutritionally benign amount of saturated fat they provide, and we respectfully request that FDA not require foods to meet the definition of “low-saturated fat” in order to be eligible to make the proposed claim.

VII. EXEMPTIONS TO GENERAL HEALTH CLAIM PROVISIONS

A. Total Fat Disqualifier Level

As noted previously, unsaturated fatty acids are now recognized by public health authorities as having the ability to reduce the risk of CHD (National Cholesterol Education Program, 2001; U.S. Department of Agriculture, U.S. Department of Health and Human Services, 2000; Krauss *et al.* 2000). In addition, evidence presented in this petition demonstrates that consumption of one ounce of nuts per day can reduce the risk of CHD, and that the unsaturated fat content of these foods contributes significantly to this effect. In other words, the cardioprotective effect of nuts *depends* on their contribution of fat to the diet.

The dietary analysis presented in section IV of this document provides ample evidence that nut-consumers do not receive excessive amounts of dietary fat, and that such foods can easily contribute to a diet designed to reduce the risk of CHD.

Despite their health benefits, all straight nut products exceed the disqualifier level for total fat as defined in 21 CFR § 101.14 (a)(4). Therefore, INCNREF respectfully requests an exemption from this requirement for whole and chopped raw or blanched nuts, roasted nuts and nuts lightly coated with non-fat components (e.g. honey roasted nuts, sugared snack nuts). This exemption is necessary because straight nut products are popular sources of nuts in the American diet, and would be important foods for consumers who choose to reduce their risk of CHD by regularly eating nuts. As noted previously, a marketplace survey found that there are very few formulated nut-containing products currently available that would qualify for the proposed claim. Therefore, authorization of the claim without an exemption to the total fat disqualifier level for straight nut products would greatly restrict consumers' exposure to important public health information and severely restrict the number of products eligible to make the claim. In addition, failure to provide an exemption to the fat disqualifier level would create consumer confusion if certain nut-containing products were able to make the proposed claim but straight nut products were not. In practical terms, the proposed claim can only be viable as a public health measure if FDA grants the requested fat disqualifier level exemption.

FDA granted such an exemption for products making the sterol/stanol ester health claim. The agency cited four criteria it considered in making this decision (65 FR 54686 at 54709). These criteria were: whether the disease in question is of public health significance; whether the absence of an exemption from the disqualifier level would severely limit the number of foods that would qualify to bear the claim; whether there is

evidence that the population to which the health claim is targeted is not at risk for the disease; and whether there are other public health reasons for granting the exemption.

FDA concluded that sterol/stanol ester-containing foods should be granted the requested exemption because CHD is a significant public health concern, because lack of an exemption would severely limit the foods that would qualify for the claim and because sterol/stanol ester-containing products have a significant potential to benefit public health by virtue of the fact that they can lower serum T-C and LDL-C without adversely affecting HDL-C. The agency also justified the exemption by concluding that, “...current scientific evidence does not indicate that diets high in unsaturated fat are associated with CHD...”, and cited the 2000 Dietary Guidelines for Americans which states, “Choose a diet that is low in saturated fat and cholesterol and **moderate in total fat**” (emphasis added).

INCNREF believes that all of the criteria used by FDA to justify the total fat disqualifier level exemption for sterol/stanol ester-containing foods also apply to the proposed claim for nuts, and we respectfully request that the exemption be granted.

Products which make the proposed claim that exceed the fat disqualifier level would be required to bear the disclosure statement, “See nutrition information for fat content” as specified in 21 CFR § 101.13(h). This statement would alert consumers to the fact that such foods contain fat and would also call attention to additional nutrition information that can help them make informed dietary choices.

INCNREF also believes that the total fat disqualifier level *should* be applied to all products other than the straight nut products listed above. This restriction is necessary to ensure that formulated nut-containing products that would be inappropriate candidates for the proposed claim (e.g. confectionary products, ice cream) are prevented from using it.

B. Saturated Fat Disqualifier Level

INCNREF also requests that FDA grant an exemption from the saturated fat disqualifier level for Brazil nuts, macadamia nuts and cashew nuts. The saturated fat content of all other straight nut products falls within this value. The primary rationale for such an exemption is that the saturated fat contained in nuts is of little nutritional significance, and it should not prevent such foods from making a health claim according to the rationale for disqualifier levels set forth in section 403(r)(3)(A)(ii) of the Federal Food, Drug, and Cosmetic Act:

if the food for which the claim is made does not contain, as determined by the Secretary by regulation, any nutrient in an amount which increases to persons in the general population that risk of a disease or health-related condition which is diet related, taking into account the significance of the food in the total daily diet, except that the Secretary may by regulation permit such a claim based on a finding that such a claim would assist consumers in maintaining healthy dietary practices and based on a requirement that the label contain a disclosure of the type required by subparagraph (2)(B).

INCNREF believes that the nuts in question do not, “contain...a nutrient in an amount which increases to persons in the general population the risk of a disease...” On the contrary, data presented in this document strongly suggest that nuts, “...would assist consumers in maintaining healthy dietary practices...” As discussed in section V of this document, the saturated fat contained in nuts does not contribute to CHD because it is

always overshadowed by the unsaturated fat that accompanies it, and that unsaturated fat is necessary for the beneficial effect. Furthermore, data from the CSFII database presented in Table 10 show that there is no difference in saturated fat intake between nut consumers and non-nut consumers. This finding suggests that nuts replace other sources of saturated fat when eaten by free-living individuals.

In addition, even though the saturated fat in these three nuts is overshadowed by the unsaturated fat they contain, they are minor constituents of the diet. Per capita consumption of macadamia nuts is only 0.07 pounds/year (1.3% of per capita consumption of all nuts excluding nut butters) (U.S. Department of Agriculture, Economic Research Service, 2002). Consumption of Brazil nuts and cashew nuts represents only about 8% of total nut intake.

We are concerned that consumer confusion will result if not all nuts are able to make the proposed claim. Consumers are not generally aware of FDA's disqualifier levels, and it would be very difficult to explain why some nuts are "healthy" and others are not – especially when the scientific evidence suggests they are all beneficial. The eligibility of all common nuts to make the claim will provide a clear and simple public health message to consumers, and avoid the need for complex explanations that may undermine the credibility of the claim.

Products which make the proposed claim that exceed the saturated fat disqualifier level would be required to bear the disclosure statement, "See nutrition information for

saturated fat content” as specified in 21 CFR § 101.13(h). This statement would help alert consumers to the fact that such foods contain a modest amount of saturated fat per serving, and would also call attention to additional nutrition information that can help them make informed dietary choices.

INCNREF, therefore, respectfully requests that FDA grant an exemption from the saturated fat disqualifier level for Brazil nuts, cashew nuts and macadamia nuts.

INCNREF also believes that the saturated fat disqualifier level *should* be applied to all products other than the three nuts listed above. This restriction is necessary to ensure that formulated nut-containing products that would be inappropriate candidates for the proposed claim (e.g. confectionary products, ice cream) are prevented from using it.

C. 10% DV Nutrient Contribution Requirement

Foods must contain at least 10% DV of protein, dietary fiber, calcium, iron, vitamin A or vitamin C per RACC in order to bear a health claim unless otherwise exempt by regulation (21 CFR § 101.14 (e)(6)). The agency explained the rationale for this requirement in the preamble to its final rule on the general principles concerning approval of health claims (58 FR 2478, 2521, January 6, 1993), which states, “ Thus, FDA finds merit in the suggestion that foods bearing health claims should be those consistent with dietary guidelines, and that the value of health claims should not be trivialized or compromised by their use on foods of little or no nutritional value.”

Since the initial rulemaking for health claims, FDA has proposed to exempt certain fruits and vegetables as well as many enriched grain products from the 10% DV nutrient contribution requirement (60 FR 66206, 66214, December 21, 1995). The agency's proposal states, "Moreover, diets high in fruits, vegetables and grain products have been associated with various specific health benefits, including lower occurrence of coronary heart disease...and therefore, are exactly the types of foods that should be included in the diet to reduce the risk of specific diet-related diseases." FDA further stated that it would consider providing additional exemptions from the 10% DV requirement if it were provided with sound justification to do so. Indeed, the agency granted such a request for salad dressings to bear the sterol/stanol ester claim. In so doing FDA explained (65 FR 54686 at 54711), "...the minimum nutrient content requirements of §101.14(e)(6), while important, are outweighed by the public health importance of communicating the cholesterol-lowering benefits from consumption of plant sterol/stanol esters."

Brazil nuts and walnuts do not meet a literal reading of the 10% DV rule based on the most recent USDA nutrient composition data (USDA, 2001) as shown in Table 15. However, these foods are clearly not "foods of minimal nutritional value." Brazil nuts contain 16% DV of magnesium and 18% DV of thiamin per serving, and walnuts are a significant source of magnesium. In addition, both nuts contain substantial amounts of

Table 15
Nutrient Content of Nuts per RACC

Nut	Protein (g per 30g RACC)	Dietary Fiber (g per 30g RACC)	Iron (mg per 30g RACC)
Almonds	6.4*	3.5*	1.3
Brazil nuts	4.3	1.6	1.0
Cashew nuts	5.5*	1.0	2.0*
Hazelnuts	4.5	2.9*	1.4
Macadamia nuts	2.4	2.6*	1.1
Peanuts	7.7*	2.6*	1.4
Pecans	2.8	2.9*	0.8
Pine nuts	7.2*	1.4	2.8*
Pistachio nuts	6.2*	3.1*	1.2
Walnuts	4.6	2.0	0.9

*Indicates 10% or greater of the DRV/RDI per 30g RACC

unsaturated fats, which favorably affect CHD biomarkers. Furthermore, dietary guidelines published after FDA's health claim regulations were issued have recommended nuts as part of a balanced diet. NHLBI's ATP III report (National Cholesterol Education Program, 2001) makes specific recommendations for the use of nuts in heart-healthy diets (see Appendix B), and the Dietary Guidelines for Americans (USDA/USDHHS, 2000) state that nuts are good sources of unsaturated fat that, "do not raise blood cholesterol." The Dietary Guidelines also recommend that consumers choose two to three servings per day from the food group that contains nuts. In conclusion, nuts are materially different from the "jelly bean"-type foods that prompted FDA to initiate the 10% DV requirement, and have substantial public health benefits. We therefore respectfully request that an exemption from this requirement be granted for Brazil nuts and walnuts.

VIII. PROPOSED MODEL HEALTH CLAIM

Model statements for the proposed health claim are as follows:

“Diets containing one ounce of nuts per day can reduce your risk of heart disease.”

“Eating a diet that includes one ounce of nuts daily can reduce your risk of heart disease.”

INCNREF believes these model statements accurately reflect the scientific information that demonstrates daily consumption of one ounce of nuts can reduce the risk of CHD by lowering serum T-C and LDL-C while having no effect (or possibly a slight beneficial effect) on HDL-C. No other qualifications are necessary because a low-fat diet is not necessary for the beneficial effect, and dietary survey information shows that free-living individuals who eat nuts do not consume any more saturated fat than non-nut consumers. In addition, while some studies show that nut consumers tend to have a lower BMI than non-nut consumers, the totality of available data convincingly show that consuming nuts is NOT associated with a higher BMI, and that including one ounce of nuts in the diet is unlikely to contribute to obesity.

INCNREF further believes that these model statements provide sufficient information to help consumers attain a total dietary pattern that will reduce their risk of CHD. The model statements include the specific amount of nuts necessary to achieve the desired effect, and advise consumers to “include” nuts in the current diet rather than add them to currently consumed foods.

IX. DETERMINATION OF COMPLIANCE

As noted in section VI above, foods will be required to have a minimum of 7.1g of nuts per RACC in order to be eligible to bear the proposed claim. In cases where the claim appears on straight nut products (e.g. whole or chopped nuts, roasted nuts), compliance will be obvious because the RACC for such products is 30 g, and the weight of non-nut ingredients is insignificant. However, for products that are composed primarily of non-nut ingredients (e.g. breakfast cereals, formulated snacks), compliance with the claim will not be obvious. Furthermore, there are no AOAC approved methods that would allow FDA to determine the nut content of such products analytically.

INCNREF proposes that information supplied by the manufacturer be used to establish compliance when the claim is used on formulated foods that are not composed primarily of nuts. This approach is similar to that used to determine the eligibility of products to bear the health claim for soy protein and CHD (21 CFR § 101.82 (c)(2)(ii)(B)). This provision requires manufacturers to maintain records such as, "... recipes or formulations, purchase orders for ingredients...", or any other information that reasonably substantiates the claim. In addition, INCNREF proposes that manufacturers choosing to make the claim be required to maintain records sufficient to substantiate the claim for as long as the products are marketed, and to provide these records, on written request, to FDA.

X. REQUEST FOR INTERIM FINAL RULE

FDA has the authority under Section 403(r)(7) of the Federal Food, Drug, and Cosmetic Act to issue an interim final rule a for health claim if such action is necessary for public health. INCNREF believes that the three criteria specified by the act that enable FDA to take this approach have been satisfied:

A. “Enable consumers to develop and maintain healthy dietary practices.”

The scientific evidence demonstrates that eating nuts is a healthy dietary practice. As noted earlier, recent review papers conclude that regular consumption of nuts is associated with a decrease in the incidence of CHD by 30-50% (Fraser, 1999; Kris-Etherton *et al.*, 2001; Sabaté, 1999). Furthermore, authoritative bodies including the National Heart, Lung and Blood Institute of the National Institutes of Health (National Cholesterol Education Program, 2001) have recommended nuts as part of a heart healthy diet. The proposed claim would provide an important new opportunity to educate consumers and would serve as an ongoing reminder about this healthy practice.

B. “Enable consumers to be informed promptly and effectively of important new knowledge regarding nutritional and health benefits of food.”

Packages of nuts have not been permitted to provide information on their cardioprotective benefits, which has restricted the dissemination of this information and failed to provide an incentive for the food industry to develop and market additional products containing nuts. As a result, consumers are generally unaware of the health benefits of this food. Not a single consumer (out of a sample of 1,001) mentioned nuts when asked the

question, “What, if anything, are you eating more of to ensure that your diet is healthy?” (Food Marketing Institute, 2002). Nevertheless, consumer research suggests that the public is likely to respond to the proposed claim because nuts are well-liked foods⁹, and “heart health” was identified as a meaningful message based on importance, believability and ability to motivate¹⁰.

C. “Ensure that scientifically sound nutritional and health information is provided to consumers as soon as possible”

A tentative final rule would shorten the length of time necessary to provide information on the cardioprotective properties of nuts in labeling by approximately one year. As noted earlier, a 30% reduction in CHD incidence could result in a yearly savings of 138,000 lives, prevent 600,000 hospitalizations, and reduce direct health care costs by \$16 billion based on statistics compiled by the American Heart Association (2000).

In conclusion, INCNREF believes that all three conditions for an interim final rule have been met. FDA took this approach for the sterol/stanol esters health claim (65 FR 54686 at 54713), and we believe the public health rationale to do the same for nuts is even more compelling.

⁹ Consumer Attitude, Awareness and Usage Study conducted by The Sterling-Rice Group, Boulder, CO 80302, Consumer Research conducted for Kraft Foods, Inc (2002)

¹⁰ Consumer Research conducted for Kraft Foods, Inc (2002)

XI. ENVIRONMENTAL IMPACT ASSESSMENT

INCNREF chooses to avail itself of the categorical exclusion with respect to an environmental impact assessment provided by 21 CFR § 25.32(p). Accordingly, an environmental impact assessment is not required for this submission.

XII. CONCLUSION

Based on the totality of evidence included in this petition, INCNREF respectfully requests that FDA issue an interim final rule authorizing the use of the proposed claim. The scientific data clearly demonstrate that the consumption of one ounce of nuts per day would reduce the risk of CHD. In addition, consumers would be likely to respond to such a message because they like the taste of nuts and identified “heart healthy” as a meaningful claim based on importance, believability and ability to motivate. Approval of the proposed claim is consistent with (if not mandated by) FDA’s public health mission. We look forward to the agency’s timely response to this important matter.

XIII. PROPOSED REGULATORY TEXT

§ 101. _____ Health claims: nuts and risk of coronary heart disease (CHD).

(a) *Relationship between diets that include nuts and the risk of CHD.* (1) Cardiovascular disease means diseases of the heart and circulatory system. Coronary heart disease (CHD) is one of the most common and serious forms of cardiovascular disease and refers to diseases of the heart muscle and supporting blood vessels. High blood total cholesterol and low density lipoprotein (LDL) cholesterol levels are associated with increased risk of developing coronary heart disease. High CHD rates occur among people with total cholesterol levels of 240 milligrams per deciliter (mg/dL) (6.21 millimole per liter (mmol/l)) or above and with LDL cholesterol levels of 160 mg/dL (4.13 mmol/l) or above. Borderline high-risk blood cholesterol levels range from 200 to 239 mg/dL (5.17 to 6.18 mmol/l) for total cholesterol, and from 130 to 159 mg/dL (3.36 to 4.11 mmol/l) for LDL cholesterol.

(2) Populations with moderate intakes of total fat composed predominantly of unsaturated (i.e. monounsaturated and polyunsaturated) fatty acids from nuts, certain vegetable oils, fish and other foods that include abundant amounts of fruits and vegetables tend to have a low incidence of CHD.

(3) Scientific evidence demonstrates that diets that include nuts can reduce the risk of CHD.

(b) *Significance of the relationship between diets that include nuts and the risk of CHD.*

(1) CHD is a major public health concern in the United States. It accounts for more deaths than any other disease or group of diseases. Early management of risk factors for CHD is a major public health goal that can assist in reducing risk of CHD. High blood total and LDL cholesterol are major modifiable risk factors in the development of CHD.

(2) Scientific evidence establishes that including nuts in the diet helps to lower blood total and LDL cholesterol levels.

(c) *Requirements – (1) General.* All requirements set forth in § 101.14 shall be met, except as set forth in this paragraph.

(2) *Specific requirements – (i) Nature of the claim.* A health claim associating diets that include nuts with reduced risk of CHD may be made on the label or labeling of a food described in paragraph (c)(2)(iii) of this section, provided that:

(A) The claim states that diets that include nuts “can” or “may” reduce the risk of heart disease;

(B) In specifying the disease, the claim uses the terms “heart disease” or “coronary heart disease”;

(C) In specifying the substance, the claim uses the term “nuts” and/or one or more of the following names including common variations thereof: almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, peanuts, pecans, pine nuts, pistachio nuts, or walnuts;

(D) The claim does not attribute any degree of risk reduction for CHD to diets that include nuts;

(E) The claim does not imply that consumption of diets that include nuts is the only recognized means of achieving a reduced risk of CHD; and

(F) The claim specifies that the daily intake of nuts that is necessary to reduce the risk of CHD is one ounce.

(ii) *Nature of the substance – Nuts.* Tree nuts from one or more of the following species: almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, pecans, pine nuts, pistachio nuts, or walnuts; and peanuts.

(iii) *Nature of the food eligible to bear the claim.* (A) The food product shall contain at least 7.1 grams of nuts as described in paragraph (c)(2)(ii) per reference amount customarily consumed (RACC), as determined by reference to § 101.12. FDA will assess whether the required amount of nuts is present for products other than those specified in paragraph (c)(2)(iii)(C) based on information identified and supplied by manufacturers, such as recipes or formulations, purchase orders for ingredients, or any other information that reasonably substantiates the amount of nuts in the product. Manufacturers must maintain records sufficient to substantiate the required amount of nuts for as long as the products are marketed, and must provide these records, on written request, to FDA.

(B) The food contains 20 mg or less of cholesterol per RACC and per 50 g if the RACC is 30 g or less or 2 tablespoons or less (for dehydrated foods that must be reconstituted before typical

consumption with water or a diluent containing an insignificant amount, as defined in § 101.9(f)(1), of all nutrients per RACC, the per 50-g criterion refers to the “as prepared” form); and

(C) The food must meet the limit for total fat in § 101.14 (a)(4), except for nuts (including whole, chopped and any other physical form) that are raw, blanched, roasted, salted, and/or lightly coated and/or flavored with a safe and suitable coating and/or flavoring that does not add a significant amount of fat (as used in this paragraph, “safe and suitable” means an ingredient that conforms to the definition in § 130.3(d), and “not ... significant” means an amount of fat that may be expressed as zero in accordance with § 101.9(c)(2)) provided the label of the food bears a disclosure statement that complies with § 101.13(h); and

(D) The food must meet the limit for saturated fat in § 101.14 (a)(4), except,

(1) Brazil nuts, (including whole, chopped and any other physical form) that are raw, blanched, roasted, salted, and/or lightly coated and/or flavored with a safe and suitable coating and/or flavoring that does not add a significant amount of fat (as used in this paragraph, “safe and suitable” means an ingredient that conforms to the definition in § 130.3(d), and “not ... significant” means an amount of fat that may be expressed as zero in accordance with § 101.9(c)(2)) are not required to meet the limit for saturated fat provided the label of the food bears a disclosure statement that complies with § 101.13(h); and

(2) Cashew nuts and macadamia nuts (including whole, chopped and any other physical form) that are raw, blanched, roasted, salted, and/or lightly coated and/or flavored with a safe and suitable coating and/or flavoring that does not add a significant amount of fat (as used in this paragraph, “safe and suitable” means an ingredient that conforms to the definition in § 130.3(d), and “not ... significant” means an amount of fat that may be expressed as zero in accordance with § 101.9(c)(2)) are not required to meet the limit for saturated per 50 g provided the label of the food bears a disclosure statement that complies with § 101.13(h); and

(E) The food must meet the minimum nutrient contribution requirement in §101.14 (e)(6) except that Brazil nuts and walnuts (including whole, chopped and any other physical form) that are raw, blanched, roasted and/or, salted are not required to meet this requirement; and

(F) The exemptions established by paragraphs (c)(2)(iii)(C), (D) and (E) of this section apply only to nuts within the scope of those paragraphs. Other foods that include nuts as an ingredient are not exempted from any provisions of § 101.14(a)(4) and (e)(6).

(d) *Optional information.* (1) The claim may state that the development of heart disease depends on many factors and may identify one or more of the following risk factors for heart disease about which there is general scientific agreement: A family history of CHD; elevated blood total and LDL cholesterol; excess body weight; high blood pressure; cigarette smoking; diabetes; and physical inactivity. The claim may also provide additional information about the benefits of exercise and management of body weight to help lower the risk of heart disease.

(2) The claim may state that the relationship between intake of diets that include nuts and reduced risk of heart disease includes the intermediate link of “blood cholesterol” or “blood total and LDL cholesterol.”

(3) The claim may include information from paragraphs (a) and (b), which summarize the relationship between diets that include nuts and the risk of CHD and the significance of the relationship.

(4) The claim may include information from the following paragraph on the relationship between nuts and the risk of CHD: The scientific evidence establishes that diets moderate in fat, containing predominantly monounsaturated and polyunsaturated fatty acids, and low in saturated fat, are associated with reduced risk of CHD. Public health authorities have concluded that such diets are equally effective in reducing the risk of CHD as low-fat, high-carbohydrate diets that are also low in saturated fat. Recommended cholesterol intakes are 300 mg or less per day. Scientific evidence demonstrates that diets that contain one ounce of nuts per day are associated with lower blood total and LDL cholesterol levels.

(5) The claim may state that diets that include nuts are consistent with “Nutrition and Your Health: Dietary Guidelines for Americans,” U.S. Department of Agriculture (USDA) and Department of Health and Human Services (DHHS), Government Printing Office (GPO).

(6) The claim may state that individuals with elevated total and LDL cholesterol should consult their physicians for medical advice and treatment. If the claim defines high or normal blood total and/or LDL cholesterol levels, then the claim shall state that individuals with high blood cholesterol should consult their physicians for medical advice and treatment.

(7) The claim may include information about the number of people in the United States who have heart disease. The sources of this information shall be identified, and it shall be current information from the National Center for Health Statistics, the National Institutes of Health, or “Nutrition and Your Health: Dietary Guidelines for Americans,” U.S. Department of Agriculture (USDA) and Department of Health and Human Services (DHHS), Government Printing Office (GPO).

(e) *Model health claims.* The following model health claims may be used in food labeling to describe the relationship between diets that include nuts and reduced risk of heart disease:

- (1) Diets containing one ounce of nuts per day can reduce your risk of heart disease.
- (2) Eating a diet that includes one ounce of nuts daily may reduce your risk of heart disease.

XIV. CERTIFICATION

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,

**INTERNATIONAL TREE NUT COUNCIL RESEARCH
AND EDUCATION FOUNDATION**

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