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Mr. D. J. Soetaert
President
International Tree Nut Council
Nutrition Research and Education Foundation
2413 Anza Avenue
Davis, CA 95616

RE: Health Claim Petition – Nuts and Coronary Heart Disease (Docket No. 02P-0505)

Dear Mr. Soetaert:

This letter responds to the health claim petition you submitted on August 28, 2002, on behalf of the International Tree Nut Council Nutrition Research and Education Foundation. This petition requests that the Food and Drug Administration (FDA) authorize a health claim about the relationship between the consumption of nuts and the reduction of risk of coronary heart disease (CHD) on the label or in the labeling of whole or chopped nuts and certain nut-containing products. Your petition identifies peanuts and nine tree nuts (i.e., almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, pecans, pine nuts, pistachio nuts, and walnuts) as appropriate for your requested health claim. Specifically, you request that FDA authorize the following two model health claims for these nuts and certain nut-containing products:

- 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 can reduce your risk of heart disease."

FDA filed the petition for comprehensive review on December 6, 2002, in accordance with section 403(r)(4)(A)(i) of the Federal Food, Drug, and Cosmetic Act (the Act). The initial deadline for FDA's response was March 6, 2003. After mutual agreement, the deadline for the agency's response has been extended 45 days to April 20, 2003.

Before making our decision on the petition, we are providing this letter that outlines our tentative conclusions. We invite you to schedule a meeting with our scientific staff to discuss them. Specifically, this letter briefly addresses the following with regard to a health claim about CHD on the label or in the labeling of whole or chopped nuts and on nut-containing products:

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- Our tentative conclusions about how the regulatory definition in 21 C.F.R. § 101.14 for a substance might apply to a health claim about nut consumption and reduced risk of CHD;
- Our tentative conclusions about whether FDA should: 1) authorize a health claim based on significant scientific agreement, or 2) exercise enforcement discretion for a qualified health claim about the relationship between consumption of nuts and reduced risk of CHD; and
- Our tentative conclusions about the applicability of other requirements pertaining to health claims and about possible wording for a qualified health claim for: 1) whole or chopped nuts, and 2) nut-containing products.

A. How the Regulatory Definition in §101.14(a)(2) for "Substance" Might Apply to a Health Claim About Nut Consumption and Reduced Risk of CHD

In 21 C.F.R. § 101.14(a)(1), a health claim is defined as "any claim . . . that expressly or by implication . . . characterizes the relationship of any substance to a disease or health-related condition." In § 101.14(a)(2), a substance is defined as "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." In your petition, you contend that nuts are a "substance" within the meaning of § 101.14(a)(2). Specifically, your petition states that "[a]ll 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.'" (See Petition at 7). FDA considers nuts to be a category of food that varies considerably in nutrient composition rather than a specific food or a component of food. Thus, FDA does not believe that nuts clearly meet FDA's definition of "substance" under § 101.14(a)(2). However, this issue is not determinative of whether nuts may be the subject of a health claim.

A food category, such as nuts, may be the subject of a health claim provided that the claim is, at least by implication, a claim about the relationship of one or more substances common to that food category and a disease or health-related condition.¹ A category of food may be eligible for a health claim when one or more substances can serve as a "marker" for identifying the food categories which correlate to the claimed health benefit. For example, FDA has authorized a health claim for categories of foods (i.e., fruits, vegetables, and grain products) that contain fiber, particularly soluble fiber, and reduced risk of CHD. (See 21 C.F.R. § 101.77). However, because the agency could not identify a specific "substance" in this example, FDA used fiber as a "marker" to identify types of foods which correlate to reduced blood LDL-cholesterol levels, and consequently,

¹ See, e.g., Food Labeling: General Requirements for Health Claims for Food, Final Rule, 58 Fed. Reg. 2478, 2480 (Jan. 6, 1993) (citing H.R. Rep. 101-538, "Nutrition Labeling and Education Act of 1990" (June 13, 1990)).

reduced risk of CHD.² (See also 21 C.F.R. §§ 101.76 (fiber-containing grains, fruits and vegetables and cancer); 101.78 (fruits and vegetables containing vitamins A, C, or fiber, and cancer)).

FDA has consistently recognized and followed this approach, which has been articulated as follows:

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.

(*Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements* (Dec. 22, 1999) (emphasis added); see also Labeling: General Requirements for Health Claims for Food, Proposed Rule, 56 Fed. Reg. 60537 (Nov. 27, 1991) (stating that “there may be certain relationships between foods and diseases that are supported by the available evidence but that cannot be attributed to a particular nutrient”)).

Your petition echoes the agency’s thinking by stating that “[t]he exact mechanism by which nuts reduce the risk of CHD cannot be definitively attributed to a single component.” (Petition at 15). Indeed, your petition provides some evidence based on studies conducted with a variety of nuts that one or more substances in these nuts may be effective in lowering LDL-cholesterol levels. FDA believes that the food category of nuts could be the subject of a health claim about reduced risk of CHD because most nuts have a good ratio of unsaturated fat to saturated fat and contain other substances that may reduce the risk of CHD, such as dietary fiber and phytosterols. The fact that nuts can achieve an LDL-cholesterol lowering effect by increasing the overall dietary ratio of unsaturated to saturated fatty acids when used to replace other foods with lower ratios is not, in and of itself, a sufficient basis for a health claim. If simply replacing a food component known to increase risk of CHD (such as saturated fat) were enough, even substances with no bioactive component could qualify for a health claim. Such an approach would render health claims meaningless because the claim would not be based on any intrinsic value of the food substance for which the claim was made, but rather on altering the dietary pattern to reduce intake of saturated fat. However, because your petition provides some evidence that nuts may be effective in lowering LDL-cholesterol independent of the effect of replacing saturated fat with unsaturated fat, FDA tentatively concludes that the majority of the nuts identified in your petition could be the subject of a health claim about reduced risk of CHD, as discussed below.

² See *id.* at 2563, 2572-73.

B. Evaluation of a Health Claim for Nuts Based on Significant Scientific Agreement

Section 403(r)(3)(B)(i) of the Act (21 U.S.C. § 343(r)(3)(B)(i)) and FDA's current regulations provide that FDA may issue a regulation authorizing a health claim only when the agency "determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence." (21 U.S.C. § 343(r)(3)(B)(i), 21 C.F.R. 101.14(c)). FDA reviewed your petition based on this standard.

For the following reasons, FDA tentatively concludes that there is not significant scientific agreement that consumption of nuts may reduce the risk of CHD:

- **Assessment of Intervention Studies.** Most of the 19 intervention trial reports submitted with the petition involved relatively high doses of nuts (e.g., greater than two servings of nuts per day), and all but one of the studies were of short duration (3-9 weeks). We consider that consumption of these high doses might be impractical for many consumers to sustain, and if they could be sustained, they might contribute to other risk factors for CHD (e.g., weight gain). Six of the intervention trials did use nut daily consumption levels of approximately 50 g or less (Jenkins, et al., 2002; Sabaté et al., unpublished; Iwamoto et al., 2002; Almario et al., 2001; Zambon et al., 2000; and O'Byrne et al., 1997). Of these six trials, three were consistent in not finding statistically significant effects of nuts on reducing LDL-cholesterol (Jenkins et al., 2002; Sabaté et al., unpublished; and Zambon et al., 2000). With the other three trials with 50 g nuts per day or less that did report significant lowering of LDL-cholesterol, FDA questions the reliability of extrapolating these data to the general U.S. population. One of these trials was in a population that started with low LDL-cholesterol levels (Iwamoto et al., 2002); in a separate study the significant effect on LDL-cholesterol was observed only when nuts were added to an extremely low fat (19% of energy) and low calorie (1600 kcal/day) diet (Almario et al., 2001). In the third trial (O'Byrne et al., 1997) the interpretation of the LDL-cholesterol lowering effect of nuts was confounded by a decrease in total fat consumption and accompanying weight loss which have been independently shown to lower LDL-cholesterol.
- **Assessment of Observational Studies.** Observational studies submitted with the petition describe an association between the intake of nuts and the incidence of and mortality resulting from CHD. These included four large U.S. cohort studies (Physicians' Health Study, Adventist Health Study, Nurses' Health Study, and Iowa Women's Health Study), and a smaller French cross-sectional study. FDA believes that these data suggest an association between nut consumption and reduced incidence of and mortality from CHD, but that the data are not conclusive.

- Assessment of Significant Scientific Agreement on Walnuts – CHD Health Claim By Groups of Qualified Experts.

FDA also considered the findings of outside experts that reviewed the science underlying the statement that walnuts may reduce the risk of CHD. One group of experts was convened by the Life Sciences Research Office (LSRO) and prepared a report for the California Walnut Commission. Three other experts in the field of nutrition and CHD were retained by FDA to independently review a petition submitted on behalf of the California Walnut Commission.

Both the LSRO and FDA groups of experts raised concerns and criticisms with respect to a relationship between walnuts and reduced risk of CHD. These concerns are also applicable to the other nuts that are the subject of this petition. Specifically, the LSRO report cited the lack of intervention studies using low doses of walnuts and the need for trials of extended duration essential for critical evaluation of the sustainability of the health-beneficial outcomes and evidence of adverse effects (e.g., body weight gain and gastrointestinal intolerance). The outside experts retained by FDA also noted the short duration of the trials, in addition to the high amount of walnuts consumed in order to show a positive benefit.

- Authoritative Statements

FDA also considered whether there are any relevant authoritative statements from a scientific body of the U.S. Government or the National Academy of Sciences. FDA did not find any such authoritative statements that consumption of nuts may reduce the risk of heart disease.

In summary, based on consideration of the totality of publicly available scientific evidence, assessment of the evidence by qualified experts, and a review of authoritative statements from scientific bodies of the U.S. Government and the National Academy of Sciences, FDA tentatively concludes that although there is some scientific evidence to support a health claim about nut consumption and reduced risk of CHD, the evidence is not conclusive.

C. Evaluation of a Qualified Health Claim About Consumption of Nuts and Reduced Risk of CHD.

For claims that do not meet the significant scientific agreement standard, FDA considers whether to exercise enforcement discretion for qualified health claims about the relationship between the substance and the disease. After reviewing the scientific evidence in your petition and other relevant scientific evidence, FDA tentatively concludes that there is a basis for a qualified health claim for nuts and reduced risk of CHD. This tentative conclusion is based on consideration of the fact that there is some scientific evidence to support a health claim about nut consumption and reduced risk of CHD, but the evidence is not conclusive. The mechanism by which nuts appear to lower LDL- and total-cholesterol is not known and is probably multi-factorial. One factor is

probably the lipid profile of nuts, as most nuts are high in unsaturated fatty acids and relatively low in saturated fatty acids.

D. Other Requirements Pertaining to Health Claims and Possible Wording for a Qualified Health Claim

A qualified health claim on the label or in the labeling of whole or chopped nuts or nut-containing products would need to comply with the health claim general requirements in § 101.14, except where FDA finds a justification for enforcement discretion, as discussed below. In addition, the following discussion states the agency's tentative conclusions about how a product that is essentially only nuts would be defined compared to a product that contains nuts and significant amounts of other ingredients, including the separate criteria that each category of products would need to satisfy in order to be eligible for the qualified health claim.

Definitions for distinguishing products that are essentially only nuts from products containing nuts and significant amounts of other ingredients. FDA tentatively concludes that the following definitions should apply:

- 1) "Whole or chopped nuts". This category would include whole or chopped nuts (regardless of size) that are raw, blanched, roasted, salted, and/or lightly coated and/or flavored, provided that any fat or carbohydrate added in the coating or flavoring meets the definition of an insignificant amount in 21 C.F.R. § 101.9(f)(1).
- 2) "Nut-containing products". Many products in the food supply (e.g., breakfast cereals, main dishes, snacks, cookies, brownies, candies, and desserts) contain nuts in varying amounts in combination with significant amounts of other ingredients. The "nut-containing products" category would include nut-containing foods other than whole or chopped nuts as defined above.

Petition's proposal for a minimum content of nuts per RACC. Your petition proposed that a minimum of 7.1 g nuts per reference amount customarily consumed (RACC) be required as part of the eligibility criteria for a food to bear a health claim about nut consumption and reduced risk of CHD. The petition further indicated that 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 g / 4 servings per day = 7.1 g/serving). FDA tentatively concludes that there are insufficient data to establish this amount, or any other, as the minimum daily effective dose of nuts that is associated with reduced risk of CHD. That a minimum daily effective dose cannot presently be established does not, however, necessarily preclude a qualified health claim about nuts and reduced risk of CHD.

Disqualifying nutrient levels (§101.14(a)(4)).

- 1) Based on consideration of recent USDA food composition data (*see* USDA's Nutrient Database for Standard Reference (NDB-SR), Release 15), it appears that the majority of nuts cited in the petition do not exceed the saturated fat disqualifying levels in § 101.14(a)(4). However, whole and chopped nuts do not meet the limit for total fat per RACC, per label serving size, or per 50 g. FDA believes, however, that an appropriately qualified claim about consumption of nuts might assist consumers in maintaining healthy dietary practices, provided that the label bears a disclosure statement about total fat that complies with § 101.13(h). (*See* § 403(r)(3)(A)(ii) of the Act (21 U.S.C. § 343(r)(3)(A)(ii)). With regard to nuts that exceed saturated fat disqualifying levels, FDA tentatively concludes that it would not assist consumers in maintaining healthy dietary practices to allow a health claim about CHD on these nuts.
- 2) For nut-containing products, FDA agrees with the position in your petition that these products should not exceed disqualifying nutrient levels for health claims.

Criteria for CHD health claims that the food shall meet all the nutrient content requirements of §101.62 for a "low saturated fat," "low cholesterol," and "low fat" food.

- 1) Whole and chopped nuts do not meet the definition of a "low saturated fat" or "low fat" food. However, because most nuts have a good ratio of unsaturated fat to saturated fat and contain other potentially beneficial substances, they may be useful in maintaining healthy dietary practices, as long as the saturated fat content of the nut is not so high as to exceed disqualifying levels for health claims. Thus, FDA might not object to use of a health claim about CHD on whole or chopped nuts that do not exceed saturated fat disqualifying levels, provided that disclosure about saturated fat in addition to total fat is made as part of the claim statement in accordance with the requirement in 21 C.F.R. § 101.13(h) that the food bear the following statement: "See nutrition information for total fat and saturated fat content." (*See* § 403(r)(3)(A)(ii) of the Act (21 U.S.C. § 343(r)(3)(A)(ii)).
- 2) For nut-containing products, FDA recognizes that it might be difficult for products to include nuts in meaningful amounts and still meet the definition of a "low fat" food. Consequently, FDA might not object to these products bearing the qualified health claim if they are otherwise eligible, provided that disclosure about total fat is made as part of the claim statement. However, FDA tentatively concludes that these products should still be required to meet the

definitions of a "low saturated fat" and "low cholesterol" food to be consistent with current dietary guidance for reducing risk of CHD and with the other CHD health claims authorized by FDA.

10% nutrient contribution requirement (§101.14 (e)(6)).

- 1) Not all whole or chopped nuts meet the requirement under 21 C.F.R. § 101.14(e)(6) that a food contain 10 percent or more of the Reference Daily Intake or the Daily Reference Value for vitamin A, vitamin C, iron, calcium, protein, or fiber per RACC prior to any nutrient addition. A primary aim of this provision is to prevent health claims on foods of minimal nutritional value. However, a review of recent food composition data (NDB-SR, Rel. 15, *supra*) suggests that eight of the ten types of nuts identified in the petition meet this requirement, and the other two nuts come very close to meeting it. For example, walnuts contain about 9% of the Daily Value for protein and about 8% of the Daily Value for dietary fiber per RACC. In addition, most nuts have a good ratio of unsaturated fat to saturated fat and contain other potentially beneficial substances that may be useful in maintaining healthy dietary practices. Consequently, FDA might not object to a qualified health claim of the type described herein on labels and in labeling of nuts that do not exceed saturated fat disqualifying levels.
- 2) For nut-containing products, FDA agrees with the position in your petition that these products should still be required to meet the 10% nutrient contribution requirement.

Context of a Total Daily Diet. FDA's health claim regulations require that a health claim enable the public to comprehend the information provided and to understand the relative significance of such information in the context of a total daily diet. (See 21 C.F.R. § 101.14(d)(2)(v); § 403(r)(3)(B)(iii) of the Act (21 U.S.C. § 343(r)(3)(B)(iii)). For health claims pertaining to CHD that are authorized by regulation (e.g., health claims about fruit, vegetables and grain products that contain fiber, particularly soluble fiber, and risk of CHD (21 C.F.R. § 101.77)), FDA requires information relative to a total diet low in saturated fat and cholesterol because this is an essential part of dietary guidance for reducing risk of CHD. We consider this important to a qualified claim about nuts and reduced risk of CHD.

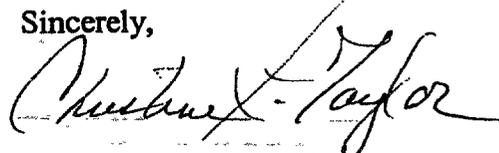
Other general requirements for health claims. A qualified health claim in the labeling of whole or chopped nuts or on nut-containing products would need to meet all other general requirements for a health claim, except for the requirement that the claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation.

In summary, we have considered the scientific evidence submitted with your petition and, as appropriate, have also considered other pertinent scientific evidence. Our tentative conclusion is that there is not significant scientific agreement about the science underlying the statement that nuts may reduce the risk of CHD. However, the science provides evidence for a qualified health claim for whole or chopped nuts that do not exceed saturated fat disqualifying levels, and for certain nut-containing products, provided that the health claim is appropriately worded so as not to mislead consumers. FDA proposes the following qualified claim for discussion at our meeting:

"Nuts [including *name of specific nut*], as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. FDA evaluated the data and determined that, although there is scientific evidence supporting the claim, the evidence is not conclusive. See nutrition information for total fat and saturated fat content."

We look forward to meeting with you to discuss our tentative conclusions and your response. Please contact Ms. Brenda Adams at (301) 436-2373 to schedule a meeting.

Sincerely,



Christine L. Taylor, Ph.D.

Director

Office of Nutritional Products, Labeling,
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Center for Food Safety
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cc: Guy H. Johnson, Ph.D.
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