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RE: Petition for a Qualified Health Claim for Macadamia Nuts and Reduced Risk of
Coronary Heart Disease (Docket No. FDA-2015-Q-4850)

Dear Dr. Johnson:

This letter responds to the qualified health claim petition submitted to the Food and Drug Administration (FDA or we) on behalf of Royal Hawaiian Macadamia Nut, Inc. on November 4, 2015. The petition was submitted pursuant to § 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(4)) and in accordance with FDA's guidance on the procedures for the submission of qualified health claim petitions ("qualified health claim procedures guidance").¹ The petition proposed a qualified health claim characterizing the relationship between consumption of macadamia nuts and reduced risk of coronary heart disease (CHD).

The petition proposed the following language for a new qualified health claim to be used on the labels or in the labeling of whole or chopped macadamia nuts that are raw, blanched, roasted, salted, and/or lightly coated and/or flavored:

Supportive but not conclusive research shows that eating 1.5 ounces per day of macadamia nuts, as part of a diet low in saturated fat and cholesterol and not resulting in increased intake of saturated fat or calories may reduce the risk of coronary heart disease. See nutrition information for fat [and calorie] content.

The petitioner provided a supplement to the petition, as requested by FDA, on November 23, 2015. The supplement provided three publications (Greer et al., 2008; Lloyd-Jones et al., 2010; Mozaffarian et al., 2015a) that were referenced but not included in the original submission, as well as clarification of two citations (Eckel et al., 2014a; Eckel et al., 2014b). FDA filed the petition for comprehensive review on December 18, 2015 and posted the petition on the Regulations.gov website for a 60-day comment period, consistent with FDA's guidance for procedures on qualified health claims.

FDA received nine comments in response to the petition, all of which supported the petition. We considered these comments in our evaluation of the petition. One of the comments discussed the benefits of macadamia nut consumption within the context of the 2015-2020 Dietary Guidelines; specifically, the recommendation of substituting unsaturated fat from nutrient dense foods for

¹ See, FDA "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements," July 10, 2003 [<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm053832.htm> (accessed January 26, 2016)].

saturated fat, as part of a healthy eating pattern. Other comments expressed support for the qualified health claim in general but did not include additional information or further evidence that would strengthen support for the petition.

This letter sets forth the results of FDA’s scientific review of the evidence for the qualified health claim requested in the petition. As explained in this letter, FDA has determined that the current evidence supports a qualified health claim for macadamia nuts – including whole or chopped macadamia nuts that are raw, blanched, roasted, salted or unsalted, and/or lightly coated and/or flavored – concerning the relationship between macadamia nuts and a reduced risk of CHD. This letter discusses the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim with respect to the consumption of macadamia nuts and a reduction in the risk of CHD.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general United States population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition.² In reviewing a qualified health claim, FDA first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.³

FDA considers the data and information provided in the petition, in addition to other written data and information available to us, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.⁴ FDA then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.⁵

In addition to individual reports of human studies, FDA also considers other types of data and information in its review, such as meta-analyses⁶, review articles⁷, and animal and *in vitro* studies. These other types of data and information may be useful to assist us in understanding the

² See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA’s interpretation of what constitutes a health claim), cert. denied, 125 S. Ct. 310 (2004).

³ See FDA, “Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final,” January 2009.

[<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm> (accessed January 26, 2016)].

⁴ For brevity, “disease” will be used as shorthand for “disease or health-related condition” in the rest of this letter except when quoting or paraphrasing a regulation that uses the longer term.

⁵ In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See *supra*, note 3.

⁶ A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

⁷ Review articles summarize the findings of individual studies.

scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications⁸ to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.⁹ If additional studies are identified, FDA evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary supplements.¹⁰ Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study.¹¹ Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, we cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a

⁸ Other examples include book chapters, abstracts, letters to the editor, and committee reports.

⁹ Certain meta-analyses may be used as part of the health claim review process. See *supra*, note 3.

¹⁰ Institute of Medicine (2005). *Dietary Supplements: A Framework for Evaluating Safety*. Chapter 7, Categories of Scientific Evidence – In Vitro Data.

¹¹ Spilker, B. 1991. *Guide to Clinical Studies*. Raven Press: New York, New York.

placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects such as age or smoking status was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and therefore are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies and then rates the strength of the total body of publicly available evidence.¹² FDA conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (i.e., the number of studies of each type and the study sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,¹³ and the overall consistency¹⁴ of the total body of evidence.¹⁵ Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship, and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of a food, regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)). In the preamble to the final rule on general principles for health claims, FDA stated that a phrase such as “eat apples to...” would constitute a reference to a substance and would satisfy the first element of a health claim. A reference to a particular food, such as apples or, in this case, macadamia nuts, is an implied claim about a substance in the food (58 FR 2478 at 2480; January 6, 1993).

The petition identified macadamia nuts as the substance that is the subject of the proposed claim. Macadamia nuts come from trees of the genus “Macadamia,” of which two important commercial species exist: *integrifolia* and *tetraphylla*. Macadamia trees are large, spreading

¹² See *supra*, note 3 [Section III.F].

¹³ Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990).

¹⁴ Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B., The environment and disease: association or causation? Proc R Soc Med 1965; 58:295-300); see also Agency for Healthcare Research and Quality, “Systems to rate the scientific evidence” (March 2002) [<http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf> (accessed January 26, 2016)], defining “consistency” as “the extent to which similar findings are reported using similar and different study designs.”

¹⁵ See *supra*, note 3 [Section III.F].

evergreen trees that typically attain a height of 30 to 40 feet and prefer a mild and moist climate. Macadamia trees are native to Australia and were introduced into Hawaii and California in the early 1880s.

Macadamia nuts have a hard seed coat enclosed in a green husk. After harvesting, the nuts are de-husked and dried, and the seed coats (or shells) are removed to yield the edible kernel, which can be roasted or eaten raw. Therefore, as the term is commonly used, macadamia nuts are the seed kernels found inside the seed coat (i.e., the hard shell that encases the kernel). Other names for the macadamia nut include Queensland nut, bush nut, maroochi nut, bauple nut, bopple nut, Gympie nut, and Hawaii nut (Bauple Museum; Hamilton and Storey, 1956).

Macadamia nuts are sold under a number of brand names in the U.S. and are commercially available in a variety of forms and flavorings, including raw, roasted, salted or unsalted, flavored (such as onion, garlic, teriyaki, and honey-roasted), chocolate covered, and chopped pieces (such as for baking). Macadamia nuts may be packaged in cans, jars, pouches, and plastic containers, and are sold separately or in combination with other nuts. All of these products are regulated as foods by FDA.

Macadamia nuts are energy dense foods containing approximately 718 calories/100 g (204 calories per 28.35 g or per ounce) (USDA National Nutrient Database for Standard Reference, Release 28, 2016). About 90% of the calories in macadamia nuts are derived from fat, 4% from protein, and 7% from carbohydrates. The lipid content of macadamia nuts consists of approximately 16% saturated fatty acids, 78% monounsaturated acids, and 2% polyunsaturated fatty acids. About half of the saturated fatty acid content is comprised of palmitic acid, while stearic acid accounts for an additional 19% of the saturated fatty acids. A one-ounce serving of macadamia nuts (e.g., a product that is packaged raw or roasted but not chocolate-covered or combined with other foods) typically provides about 31-35% Daily Value (DV) for total fat, 15-18% DV for saturated fat, and 8-10% DV for dietary fiber.

The petition stated that macadamia nuts, like other tree nuts, are nutrient dense foods that are significant sources of protein, dietary fiber, and certain micronutrients such as magnesium. The petition further noted that macadamia nuts and tree nuts are hypocholesterolemic and cardioprotective, and suggested that these beneficial characteristics may result from either a favorable ratio of unsaturated to saturated fatty acids, the dietary fiber content, or the effects of certain non-fatty acid, lipid soluble constituents (e.g., squalene, tocopherols, campesterol, stigmasterol, or beta-sitosterol).

The petition did not identify a specific substance(s) in macadamia nuts that is responsible for the purported benefit, but rather requested that macadamia nuts be the subject of the proposed claim. In the absence of an identified substance in macadamia nuts that is responsible for the purported effect, FDA considers whether the purported benefits of macadamia nuts are due to a) a substance that is unique to macadamia nuts and can only be obtained if macadamia nuts are included in diets on a daily basis at a minimally effective level; b) a substance that is also found in other foods and, therefore, the benefits can be obtained by choosing among a variety of foods that contain the substance; or c) a replacement of macadamia nuts for other foods in the diet that increase CHD risk, rather than to a biologically active substance in the macadamia nuts. In the

studies described in the petition that provided support for the qualified health claim, macadamia nuts replaced certain macronutrients (i.e., other sources of saturated fat) in the diet that increase CHD risk.

The petition did not contain sufficient scientific evidence to enable FDA to identify a biologically active substance unique to macadamia nuts or to a larger group of foods that decreases CHD risk. Further, the petition did not contain sufficient evidence for FDA to determine if the beneficial effect is simply due to the replacement of macadamia nuts for other foods that increase CHD risk.

Therefore, FDA considers macadamia nuts to be the subject of the claim for purposes of this review. As a food, macadamia nuts meet the definition of a substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified coronary heart disease (CHD) as the disease or health-related condition that is the subject of the proposed claim. The agency concludes that CHD is a disease and therefore the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food, food ingredient, or a food component whose use at levels necessary to justify the 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 Act.

FDA evaluates whether the substance is “safe and lawful” under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the substance, which is either a food or an ingredient that is the source of the substance, is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (21 CFR 101.70(f)).

Macadamia nuts are the substances that are the subject of the qualified health claim requested in the petition. The petition stated that macadamia nuts, like other tree nuts and peanuts, are nutritious foods that are well recognized by U.S. consumers. As an indication that macadamia nuts are safe and lawful and a familiar component of the American diet, the petition cited recent production data from the USDA Economics, Statistics and Market Information System that provided information about macadamia nuts, as well as other harvestable tree nuts, with respect to acreage, yield per acre, production (in-shell), season-average grower price, and other factors (USDA 2014). As previously mentioned, a wide variety of macadamia nut products are commercially available, including raw, roasted, salted, chopped, chocolate-covered, macadamia nut flour, macadamia nut butter and macadamia nuts sold in other flavors and in combination

with other nuts, ingredients, and foods. FDA agrees that macadamia nuts are a component of the U.S. food supply that provides nutritive value to the diet.

The petition also acknowledged that, as a tree nut, macadamia nuts would be among the category of foods most likely to cause severe allergic reactions in certain individuals, and cited a study in which the authors reviewed the literature on this topic and described two case reports of patients who developed anaphylaxis from eating macadamia nuts (De Knop et al., 2010). However, the petition further noted that, in evaluating a health claim petition, FDA previously indicated that it does not consider the allergenic potential of a food or food component to be a determining factor in deciding whether or not a substance is safe. For example, FDA stated in its final rule authorizing a health claim on the association between soy protein and reduced risk of CHD (64 FR 57700) that “FDA does not believe that, because some persons may have allergic reactions to a food, it is unsafe” (64 FR 57700 at 57707). Moreover, the petition stated it was unaware of any populations – including pregnant and lactating women and children younger than three years of age – that must receive special consideration as a result of the proposed claim with respect to allergenicity of macadamia nuts. Although these groups were previously advised to avoid tree nuts in order to minimize early exposure to potential allergens, the petition noted that the American Academy of Pediatrics (AAP) no longer suggests in its policy statement that foods containing macadamia nuts should be avoided during pregnancy, lactation or early childhood, as insufficient data exist for continuing this recommendation.

The principal fatty acid in macadamia nuts is oleic acid, an omega-9 monounsaturated fatty acid which comprises about 58% of the total lipid content. Unsaturated fatty acids (i.e., the combined amounts of mono- and polyunsaturated fatty acids) account for about 80% of the total lipid content in macadamia nuts. In the 2002 Macronutrient Dietary Reference Intake Report (IOM, 2002), the Institute of Medicine (IOM) reviewed safety data for dietary unsaturated fatty acids and found insufficient evidence of adverse effects on which to set a Tolerable Upper Intake Level (UL) for either the omega-6 polyunsaturated fatty acids (PUFAs) or the omega-9 monounsaturated fatty acids (MUFAs). Lacking safety data upon which to base a UL, the IOM established an “upper boundary” for an Acceptable Macronutrient Distribution Range (AMDR) for omega-6 polyunsaturated fatty acids based on the approximate highest intake levels for individuals in North America. Since high intakes of linoleic acid (the major dietary source of PUFAs) create a pro-oxidant state that may predispose to several chronic diseases including CHD and cancer, the IOM estimated an AMDR of 5-10 percent of energy for omega-6 PUFAs. Thus, an upper boundary for linoleic acid was set at 10 percent of energy.

According to the IOM (2002), there are limited data on the association between omega-9 MUFAs and chronic disease risk, and on any adverse health effects that may result from a high intake of omega-9 MUFAs. Therefore, the IOM did not establish an AMDR for omega-9 MUFAs, but noted that the consumption of MUFAs (which are not essential in the diet) will be practically limited by the AMDRs that have been established for total fat and other types of fatty acids.

Although the evidence concerning a reduction in TC and LDL-C as a result of macadamia nut consumption is limited, the lowest intake level that showed a significant reduction in TC and LDL-C levels was 41g/2,000 kcal/day, or about 1.5 ounces/day (Griel et al., 2008). The amount

of PUFAs in 1.5 ounces of macadamia nuts is about 0.6 grams. According to the 2007-2010 NHANES, the 95th percentile of PUFA intake for all individuals is 27.4 g/day, which exceeds the sum of the median intake of PUFAs from all foods (15.9 g/day) plus the PUFAs from 1.5 ounces of macadamia nuts (0.6 g). Because the 99th percentile of intake was used to set the upper boundary of the AMDR for PUFAs, FDA concludes that consuming 1.5 ounces of macadamia nuts per day falls within the margin of safe intake for PUFAs.

The amount of MUFAs in 1.5 ounces of macadamia nuts is about 25 grams. According to the 2007-2010 NHANES, the median intake of MUFAs from all foods for all individuals is 26.9 grams and the 95th percentile of MUFA intake for all individuals is 46.7 g/day. Since macadamia nuts presumably constitute a relatively small part of the American diet (the utilized production of macadamia nuts is less than that of other tree nuts, such as almonds and walnuts [USDA/ERS 2016]), we would not expect macadamia nuts to contribute a significant amount of MUFAs to the daily diet. Further, as previously noted, the IOM has not established an AMDR for MUFAs as there is little evidence that excessive consumption may adversely affect health. Consequently, FDA concludes that, under the preliminary requirement of 21 CFR 101.14(b)(3)(ii), the use of macadamia nuts at a level of 1.5 ounces per day is safe and lawful.

II. The Agency's Consideration of a Qualified Health Claim

FDA has identified the following disease endpoints to use in identifying CHD risk reduction for purposes of a health claim evaluation: the incidence of coronary events (e.g., myocardial infarction or ischemia), cardiovascular death, coronary artery disease, and atherosclerosis. In addition, the following surrogate endpoints have been identified by FDA for evaluating CHD risk reduction for the purposes of a health claim: high blood pressure, blood (serum or plasma) concentrations of total cholesterol (TC), and blood (serum or plasma) concentrations of low density lipoprotein cholesterol (LDL-C).¹⁶ These disease and surrogate endpoints were used to evaluate the potential effects of macadamia nuts on CHD risk.

The petition cited 74 publications as evidence to substantiate the relationship for the proposed claim (see Docket # FDA-2015-Q-4850) including five human intervention studies evaluating the relationship between macadamia nut consumption and CHD risk. In addition, the petition cited 27 review articles; 8 meta-analyses; 4 opinion papers/letters to the editor; 8 publications from federal agencies or professional associations; 3 articles on the chemical composition of macadamia nuts; and 19 observational and intervention studies that did not evaluate the substance/disease relationship (see Appendix 1).

A. Assessment of Background Materials

“Background materials” here refers to review articles, meta-analyses, opinion papers, and reports from federal agencies and non-profit associations. Although useful for background information, these materials do not contain sufficient information on the individual studies that they reviewed

¹⁶ National Heart, Blood and Lung Institute (NHLBI), Heart and Blood Vessel Diseases [http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html] and National Cholesterol Education Program, U.S. Department of Health and Human Services, 2001 [<http://www.nhlbi.nih.gov/files/docs/resources/heart/atp-3-cholesterol-full-report.pdf>]. Accessed January 26, 2016.

and, therefore, FDA could not draw any scientific conclusions from this information. For example, FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., nutrient composition of the experimental diets). Similarly, the lack of detailed information on studies summarized in these materials prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the background materials supplied by the petitioner did not provide information from which scientific conclusions can be drawn regarding the substance/disease relationship claimed by the petitioner.

B. Assessment of Intervention Studies

FDA evaluated five individual intervention studies that were designed to investigate the relationship between consumption of macadamia nuts and risk of CHD. Of the five intervention studies reviewed and evaluated, scientific conclusions could not be drawn from two of these studies (Garg et al., 2003; Hiraoka-Yamamoto et al., 2004).¹⁷ The study by Garg et al. (2003) was a single arm study with no control group. Without a control group, it cannot be determined whether changes in the endpoints of interest are due to macadamia nuts or due to unrelated and uncontrolled extraneous factors (Spilker, 1991). The study by Hiraoka-Yamamoto et al. (2004) lacked an identifiable control group and did not report statistical analyses between treatments. Conducting a statistical analysis of a relationship is critical because it provides a basis for comparing individuals who consumed macadamia nuts and those who did not consume macadamia nuts to determine whether there was an actual reduction in the risk of CHD.¹⁸ When appropriate statistical tests are not performed on the specific substance/disease relationship, it cannot be determined whether there is a significant difference between the experimental groups. Based on the above reasons, scientific conclusions could not be drawn from these two studies about the relationship between macadamia nut consumption and the reduced risk of CHD.

There were three intervention studies available (Colquhoun et al., 1996; Curb et al., 2000; Griel et al., 2008) from which scientific conclusions could be drawn about the relationship between consumption of macadamia nuts and reduced risk of CHD. These studies are discussed below.

Griel et al. (2008) conducted a randomized, crossover,¹⁹ controlled-feeding study of high methodological quality in U.S. adults (n = 24). Subjects were recruited with LDL-C between the 25th and 90th percentile (101-175 mg/dL; baseline mean LDL-C = 134 ± 21 mg/dL). Participants were provided the following two controlled diets (5 weeks each): a macadamia nut diet (33% energy total fat; 7% energy saturated fatty acids [SFA], 18% energy MUFA) and an average American diet (33% energy total fat; 13% energy SFA, 12% energy MUFA). The dose of macadamia nuts provided on the macadamia nut diet was 1.5 oz/day for participants consuming

¹⁷ In this section, significant flaws in the reports of intervention studies from which scientific conclusions could not be drawn are generally discussed. Such studies may have other flaws in addition to those specifically mentioned.

¹⁸ See *supra*, note 3 [Section III. D].

¹⁹ In a crossover intervention study, all subjects in the intervention group “cross over” to the control group, and vice versa, after a defined time period. See *supra*, note 3 [Section III. B]. In other words, during the second phase of the study, the groups switch so that the subjects who had been in the intervention group follow the control diet, and the subjects who had been on the control diet receive the intervention.

2,100 kcal/day, or approximately 18% of energy. The macadamia nut diet significantly lowered TC and LDL-C compared with the average American diet ($P < 0.05$).²⁰

The study by Curb et al. (2000) was a moderate quality randomized, crossover, controlled-feeding study in U.S. adults ($n = 34$) with normal to high blood cholesterol levels (baseline TC ranged from 157-272 mg/dL; baseline LDL-C = 134 ± 30 mg/dL). There were three 30-day diet periods during which participants consumed the following diets: macadamia nut diet (37% energy total fat; 9% energy SFA, 21% energy MUFA), average American diet (37% energy total fat; 16% energy SFA, 14% energy MUFA), and Step-1 diet (30% energy total fat; 9% energy SFA, 14% energy MUFA).²¹ The dose of macadamia nuts provided on the macadamia nut diet was 34 g/1,000 kcal or a mean intake of 116 g (~31% of energy).²² Compared to the average American diet, the macadamia nut diet resulted in a significant decrease in TC and LDL-C ($P < 0.01$ and $P < 0.05$, respectively). There were no significant differences in TC and LDL-C when comparing the macadamia nut diet and Step-1 diet.

Colquhoun et al. (1996) conducted a moderate quality 12-week, 3-period study in Australian adults ($n = 14$) who were normo- to hypercholesterolemic (TC ranged from 155-309 mg/dL; baseline LDL-C = 160 ± 31 mg/dL). All participants started with the 4-week pre-entry phase where dietary intake was assessed prior to any dietary modification. This phase was representative of an average American diet, consisting of 37% of energy as total fat, 16% energy SFA, and 14% energy MUFA. Participants were then randomized to two 4-week diet periods. The macadamia nut diet consisted of 42% of energy from total fat, 11% energy SFA, and 31% energy MUFA. Macadamia nuts provided 20% of energy on the macadamia nut diet. The lower fat (high carbohydrate) diet consisted of 21% energy total fat, 9% energy SFA, and 8% energy MUFA. There were no significant differences in TC and LDL-C when comparing the macadamia nut diet and low-fat diet. Compared to the diet representative of a typical American diet, consumption of the macadamia nut diet resulted in significantly lower TC and LDL-C ($P < 0.01$).

C. Assessment of Observational Studies

There were no available observational studies that evaluated the relationship between macadamia nut consumption and reduced risk of CHD.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the number of studies and number of subjects per group, whether the body of scientific evidence supports a health claim relationship for the U.S. population or a target subgroup, whether study

²⁰ For the outcome of a study to demonstrate a statistically significant difference between groups, P must be <0.05 . See *supra*, note 3 [Section III. F].

²¹ Step 1 diets were created by the National Cholesterol Education Program and promoted by the American Heart Association (NIH publication No. 94-2920). A Step 1 diet contains 30 percent of daily energy from total fat, 8-10 percent from saturated fat, ~55 percent from carbohydrate, ~15 percent from protein, and contains no more than 300 mg per day of dietary cholesterol.

²² Dose was not provided in the study, but rather as a personal communication between petitioner and study author.

results supporting the proposed claim have been replicated,²³ and the overall consistency²⁴ of the total body of evidence.²⁵ Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

As discussed in Section II, the evidence for a relationship between macadamia nut consumption and reduced risk of CHD is based on three intervention studies (Colquhoun et al., 1996; Curb et al., 2000; Griel et al., 2008). All three studies were small (14-34 subjects per study), randomized controlled trials that were of moderate or high methodological quality. The studies were conducted in individuals with baseline TC and LDL-C that ranged from normal to high. Consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.²⁶ All three studies reported a benefit of the macadamia nut consumption in reducing TC and LDL-C, when compared to an average American diet that was lower in monounsaturated fat and higher in saturated fat. Two of these studies (Colquhoun et al., 1996; Curb et al., 2000) also compared the macadamia nut diet to a lower fat diet (lower in monounsaturated fat and lower or equal in saturated fat) and found comparable effects on TC and LDL-C between the diets. Although there was some credible evidence demonstrating a beneficial effect of macadamia nuts on lowering TC and LDL-C, only three studies representing a total sample size of 72 subjects were evaluated, and only one of these studies (Griel et al., 2008) was of high methodological quality.

Based on the above, FDA concludes that there is consistent but limited scientific evidence for a relationship between macadamia nut consumption and reduced risk of CHD, when macadamia nuts are substituted for other sources of saturated fat in the diet.

IV. Other Enforcement Discretion Factors

A qualified health claim on the label or in the labeling of whole or chopped macadamia nuts is required to meet all applicable statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. Factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims about macadamia nuts and reduced risk of CHD are discussed below.

A. Qualifying Level of Macadamia Nuts to Achieve the Claimed Effect

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for

²³ See *supra*, note 13.

²⁴ See *supra*, note 14.

²⁵ See *supra*, note 3[Section III.F].

²⁶ See *supra*, note 3 [Section III.F] and note 12.

“high” has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (21 CFR 101.14(d)(2)(vii)).

While evidence is limited from studies that demonstrated a reduction in TC and LDL-C when macadamia nuts were substituted for other sources of saturated fat in the diet, the lowest intake level of macadamia nuts that resulted in a significant reduction in blood levels of TC and LDL-C was 42.5 g/2100 kcal/day, or 1.5 ounces/2100 kcal/day (Griel et al., 2008). In the absence of dose response data on the effect of lower daily intake levels of macadamia nuts on TC and LDL-C levels, FDA finds that there remains uncertainty as to the lowest daily macadamia nut intake level necessary to reduce CHD risk. Therefore, FDA intends to consider exercising enforcement discretion for the use of the qualified health claim when the claim specifies 1.5 ounces as the daily dietary intake necessary to achieve the claimed effect.

B. Low Fat, Low Saturated Fat, and Low Cholesterol Criteria for CHD-Related Health Claims

FDA has required that foods bearing CHD-related health claims be low in saturated fat as defined by 21 CFR 101.62(c)(2) and low in cholesterol as defined by 21 CFR 101.62(d)(2) (see 21 CFR 101.75, 101.77, 101.81, 101.82, and 101.83). In addition, most currently authorized CHD-related health claims require that the food meet the definition of a low fat food (21 CFR 101.62(b)(2) (see authorized claims in 21 CFR sections 101.77, 101.81, 101.82, and 101.83). Whole or chopped macadamia nuts contain no cholesterol but they do not meet the definition of a “low saturated fat” or “low fat” food. However, because macadamia nuts have a favorable ratio of unsaturated fat to saturated fat (5:1) and contain other potentially beneficial substances such as dietary fiber and phytosterols, a qualified health claim about macadamia nuts and reduced risk of CHD might assist consumers in maintaining healthy dietary practices. In addition, FDA concurs with the current 2015-2020 Dietary Guidelines for Americans that nuts in general are nutrient dense foods that can serve as protein sources and contribute to a healthy U.S.-style eating pattern.

Thus, even though macadamia nuts are not low in total fat and saturated fat, FDA intends to consider the exercise of its enforcement discretion for a CHD-related qualified health claim based on the consumption of whole or chopped macadamia nuts, including raw, blanched, roasted, salted or unsalted, and/or lightly coated and/or flavored macadamia nuts. As explained in Section C below, FDA may authorize a health claim for a food even though a nutrient(s) in the food exceeds the disqualifying level, if such a claim will assist consumers in maintaining healthy dietary practices.

C. Disqualifying Nutrient Levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)), a food may not bear a health claim if the food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in 21 CFR 101.14(a)(4), unless FDA establishes an alternative level. Section 101.14(e)(3) applies to all health claims regardless of types of diseases and health-related conditions. The disqualifying nutrient levels vary for individual foods, meal products, and main dishes.

The disqualifying level for sodium is 480 mg sodium per Reference Amount Customarily Consumed (RACC), or per 50 g of a food product if the RACC is 30 g or less. Although raw macadamia nuts contain only about 2 mg of sodium per 50 g, some commercially available macadamia nut products are salted. However, the USDA Nutrient Database lists the sodium content as 176 mg per 50 g of product for dry roasted macadamia nuts with salt added, and we are not aware of any commercially available macadamia nut product that exceeds the disqualifying level for sodium. The disqualifying level for cholesterol (60 g per RACC or per 50 g of food product if the RACC is 30 g or less) is not relevant to this qualified health claim as macadamia nuts are a plant product and therefore do not contain cholesterol.

The disqualifying level for total fat is above 13.0 g per RACC or per 50 g of a food product if the RACC is 30 g or less. The RACC for nuts is 30 g (21 CFR 101.12(b)); therefore, the disqualifying total fat level for macadamia nuts is 13 g total fat per 50 g of macadamia nuts. According to the USDA Nutrient Database for Standard Reference, Release 28 (USDA/ARS) the total fat content of raw macadamia nuts is 37.9 g total fat/50 g, which exceeds the health claim disqualifying level.

The disqualifying level for saturated fat is above 4.0 g per RACC or per 50 g of food product if the RACC is 30 g or less. As stated above, because the RACC for nuts is 30 g (21 CFR 101.12(b)), the disqualifying level of saturated fat for macadamia nuts is 4 g saturated fat per 50 g of macadamia nuts. According to the above referenced USDA Nutrient Database, the saturated fat content (i.e., the total saturated fatty acid content) of raw macadamia nuts is 6.03 g saturated fat /50 g, which exceeds the health claim disqualifying level for saturated fat.

In addition, the credible evidence that is available, and on which we are relying, suggests that consumption of macadamia nuts may only be effective in lowering TC and LDL-C when they replace other sources of saturated fat and calories in the diet. Therefore, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that the qualified health claim include the phrase “and not resulting in increased intake of saturated fat or calories” in the qualified health claim to reflect the state of the science supporting this claim, and to assist consumers in understanding the relative significance of this claim in the context of the total daily diet.

As previously mentioned, the general requirements for health claims also provide for FDA to authorize a health claim for a food despite the fact that a nutrient in the food exceeds the disqualifying level, based on a finding that such a claim will assist consumers in maintaining healthy dietary practices. In such cases, the label must also bear a disclosure statement that complies with §101.13(h), highlighting the nutrient that exceeds the disqualifying level (21 CFR 101.14(e)(3)). FDA believes that an appropriately worded qualified health claim about consumption of macadamia nuts could assist consumers in maintaining healthy dietary practices, based on the suggestive evidence of a relationship between macadamia nuts and a reduced risk of CHD. Furthermore, FDA concurs with the current 2015-2020 Dietary Guidelines for Americans that dietary patterns characterized by the regular consumption of nuts (among other foods) may be associated with beneficial cardiovascular disease health outcomes. Thus, FDA intends to consider the exercise of its enforcement discretion for a qualified health claim for whole or chopped macadamia nuts if the disclosure statement (i.e., “See nutrition information for total fat

and saturated fat”) is placed immediately adjacent to and directly beneath the claim, with no intervening material, in the same size, typeface, and contrast as the claim itself.

FDA does intend to consider, as a factor in the exercise of its enforcement discretion for macadamia nuts labeled with a macadamia nut and CHD qualified health claim that such foods not exceed the disqualifying nutrient levels.

D. 10 Percent Minimum Nutrient Content Requirement

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the Daily Value (DV) of certain nutrients per RACC (21 CFR 101.14(e)(6)). The purpose of this requirement is to prevent the use of health claims on foods with minimal nutritional value. The specific nutrients listed in 21 CFR 101.14(e)(6) are vitamin A, vitamin C, iron, calcium, protein, and fiber.²⁷ For the purpose of this health claim, the agency intends to exercise its enforcement discretion with respect to 21 CFR 101.14(e)(6) for the qualified health claim to be used on food labels where the food contains 10 percent or more of the DV for vitamin D or potassium, in addition to the nutrients currently listed (i.e., vitamin A, vitamin C, iron, protein, fiber) per RACC prior to any nutrient addition.

FDA has previously exempted certain foods from the 10 percent minimum nutrient content requirement when it has determined that such exemptions could assist consumers in maintaining healthy dietary practices. For example, we considered a qualified health claim for walnuts and a reduced risk of CHD even though walnuts did not meet the 10 percent minimum nutrient content requirement.²⁸ We also allowed authorized health claims for dietary noncariogenic carbohydrate sweeteners and dental caries (21 CFR 101.80) and for plant sterol/stanol esters and risk of coronary heart disease (21 CFR 101.83) for certain foods that did not meet the 10 percent minimum nutrient content requirement of 21 CFR 101.14(e)(6).

Although macadamia nuts do not meet the 10 percent minimum nutrient content required by section 21 CFR 101.14(e)(6) for foods bearing a health claim, macadamia nuts contain about five percent of the DV per RACC for protein and about nine percent of the DV per RACC for dietary fiber (USDA Nutrient Database for Standard Reference, Release 28). FDA intends to consider exercising enforcement discretion as to section 21CFR101.14(e)(6) because the content of dietary fiber in macadamia nuts is very close to the 10 percent DV level. In addition, macadamia nuts contain about 30 percent of the DV per RACC for thiamin (an excellent source of this nutrient) and about nine percent of the DV per RACC for magnesium (USDA Nutrient Database for Standard Reference, Release 28), which is close to being a good source of magnesium.

²⁷ We note that the final rule entitled “Food Labeling: Revision of the Nutrition and Supplement Facts Labels” (81 Fed. Reg. 33742; May 27, 2016) changed the mandatory declaration of vitamins and minerals as a percent of the RDI in 21 CFR 101.9(c)(8) from vitamin A, vitamin C, calcium, and iron to vitamin D, calcium, iron, and potassium. Therefore, vitamin D and potassium are now nutrients of public health significance. We plan to address, as appropriate and as time and resources permit, the impact of the changes in nutrient declarations in the final rule to other regulations, such as 21 CFR 101.14(e)(6), in separate rulemaking actions (see 81 Fed. Reg. 33742 at 33751).

²⁸ <http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072910.htm>

V. Conclusions

Based on FDA's consideration of the scientific evidence submitted with your petition and the recommendations of the 2015-2020 Dietary Guidelines for Americans, FDA concludes that the current scientific evidence, though limited, is appropriate for consideration of a qualified health claim regarding the consumption of macadamia nuts and reduced risk of CHD, and the claim proposed by the petitioner is appropriately worded so as not to mislead consumers. This language and supporting scientific evidence is consistent with a qualified health claim the agency exercises enforcement discretion over with respect to the consumption of walnuts and reduced risk of CHD. Therefore, FDA intends to consider exercising its enforcement discretion for the following qualified health claim as proposed by the petitioner:

“Supportive but not conclusive research shows that eating 1.5 ounces per day of macadamia nuts, as part of a diet low in saturated fat and cholesterol and not resulting in increased intake of saturated fat or calories may reduce the risk of coronary heart disease. See nutrition information for fat [and calorie] content.”

FDA intends to consider exercising its enforcement discretion for the above qualified health claim when all factors for enforcement discretion identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that would support significant scientific agreement, would no longer support the use of the above qualified health claim, or that may raise safety concerns about the substances that are the subject of the claims.

Sincerely,

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Center for Food Safety
and Applied Nutrition

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Appendix 1

Human Intervention Studies

Colquhoun et al., 1996
Curb et al., 2000
Garg et al., 2003
Griel et al., 2008
Hiraoka-Yamamoto et al., 2004

Review Articles

Blomhoff et al., 2006
Bray et al., 2002
Burton-Freeman et al., 2000
Coates et al., 2007
Davis et al., 2008
Dreher et al., 1996
Fraser et al., 1999
Hooper et al., 2011
Hu et al., 1999
Jackson et al., 2014
Jakobsen et al., 2009
Kelly et al., 2006
King et al., 2008
Kris-Etherton et al., 2008
Martinez-Gonzalez et al., 2011
Mukuddem-Petersen et al., 2005
Natoli et al., 2007
Ros et al., 2006
Ros et al., 2009
Ros et al., 2010
Rudkowska et al., 2007
Sabate et al., 1993
Sabate et al., 1994
Sabate et al., 2003
Skeaff et al., 2009
Vadivel et al., 2012
Vinson et al., 2012

Meta-analyses

Chowdhury et al., 2014
Flores-Mateo et al., 2013
Kass et al., 2012
Mensink et al., 1992

Mensink et al., 2003
Mozaffarian et al., 2010
Rosanoff et al., 2013
Siri-Tarino et al., 2010

Publications from Federal Agencies or Professional Associations

Dietary Guidelines for Americans, 2000
Dietary Guidelines for Americans, 2010
Eckel et al., 2014a
Eckel et al., 2014b
Greer et al., 2008
Jacobson et al., 2015
Lloyd-Jones et al., 2010
Mozaffarian et al., 2015a

Opinion Papers/Letters to the Editor

Astrup et al., 2011
Liebman et al., 2014
Mozaffarian et al., 2015b
Willett et al., 2014

Articles on the Chemical Composition of Macadamia Nuts

De Knop et al., 2010
Maguire et al., 2004
Moodley et al., 2007

Observational and Intervention Studies Not Evaluating the Substance/Disease Relationship

Albert et al., 2002
Bao et al., 2013
Bes-Rastrollo et al., 2006
Bes-Rastrollo et al., 2009
Cassady et al., 2009
Ellsworth et al., 2001
Fernandez-Montero et al., 2013
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Hu et al., 1998
Iwamoto et al., 2002
Jaceldo-Siegl et al., 2014
Kushi et al., 1996
Luu et al., 2015
Mennella et al., 2015

Mozaffarian et al. 2011
O'neil et al., 2010
O'neil et al., 2011
Wien et al. 2003