



OCT 7 2002

Food and Drug Administration
College Park, MD

Sheila G. West, Ph.D.
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Dear Dr. West:

This letter is in response to your letter dated September 20, 2002, in which you support the health claim petition submitted by the California Walnut Commission.

We appreciate your interest in the issues raised in the health claim petition. We have forwarded your letter to the Dockets Management Branch (HFA-305) for inclusion in the administrative record under Docket No. 02P-0292. Your letter will be considered by the agency in its deliberations on what action to take on the California Walnut Commission's health claim petition.

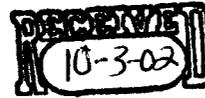
Sincerely,

James E. Hoadley, Ph.D.
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Office of Nutritional Products, Labeling
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September 20, 2002

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To Whom it May Concern:

I am writing to support the Health Claim Petition submitted by the California Walnut Commission requesting that FDA approve "for use in the labeling of foods comprising whole and chopped walnuts, health claims communicating that diets including walnuts can reduce the risk of coronary heart disease" (Docket # 02P-0292). As an academic scientist, my research examines the vascular effects of various dietary interventions. I believe that this petition provides consistent evidence that nuts, and walnuts in particular, promote cardiovascular health. Evidence for this claim is drawn from well-designed, randomized clinical studies and from observational studies linking increased nut consumption to lower risk of cardiovascular disease. I believe the consistency of these findings provides strong support for the cardiovascular benefits of walnuts, and that the scientific evidence from these studies is fairly presented in this petition.

In weighing the merits of a functional food health claim, it is important to identify plausible bioactive agents that could explain the apparent cardioprotective effects. Walnuts contain several critical nutrients that have been shown to promote vascular function and lower cholesterol in animal and in vitro studies. For example, walnuts provide a rich source of alpha-linolenic acid (ALA), one of the few plant derived omega-3 fatty acids. Although flaxseed contains higher concentrations, flax is not commonly consumed in the typical American diet. The USDA nutrient database shows that walnuts have high levels of ALA (9.1 g / 100g of walnuts). The cardiovascular benefits of consuming ALA have been summarized in detail in this petition and in the Life Sciences Research Office (LSRO) report recently published in the *Journal of Nutrition*.

The American Heart Association has recommended fish consumption (2 servings per week) as a way to increase intake of omega-3 fatty acids, thereby promoting cardiovascular health. However, there are two critical concerns about recommending fish as a primary dietary source of omega-3 fatty acids. First, the biomass of marine fish is not enough to support recommended intake of omega-3's for the world's population. Indeed, many scientists are concerned about severe declines and poor recovery of marine fish stocks in oceans around the world (e.g.

Hutchings, 2000). Because walnuts are a concentrated source of an important and protective omega-3 fatty acid (ALA), they represent a renewable resource that may augment fish as a source of omega-3 fatty acids in the diet. For vegetarians or others who do not consume fish, plant sources take on an even greater importance.

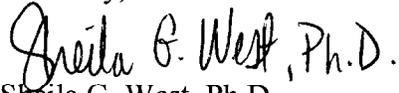
In addition, although fish consumption is the commonly recommended strategy for increasing omega-3 intake, there is some concern about the health effects of methyl-mercury, an environmental toxin that accumulates in the tissues of fish (Storelli, Stuffer, & Marcotrigiano, 2002). Two large and well designed epidemiologic studies (Rissanen, Voutilainen, Nyssonen, Lakka, & Salonen, 2000; Salonen, Seppanen, Nyssonen, Korpela, et al, 1995) have shown that fish consumption was not protective against cardiovascular disease when mercury exposure (as documented in hair samples) was also high. Rissanen and colleagues (2000) summarized their findings as follows, "Our data provide further confirmation for the concept that fish oil-derived fatty acids reduce the risk of acute coronary events. However, a high level of methyl mercury content in fish could attenuate this protective effect." Presumably, walnuts are not subject to the same mercury contamination that is present in many fish. In making this argument, it is critical to acknowledge that the specific omega-3 fatty acids contained in fish (DHA and EPA) are not found in walnuts. However, walnuts do contain high levels of their precursor molecule, ALA. Taken together with data summarized in this petition on the cardiac benefits of ALA, walnuts appear to be a safe and appropriate source of dietary omega-3 fatty acids.

Walnuts are also a rich source of the amino acid L-arginine, the precursor for the potent vasodilator nitric oxide. The most compelling data from clinical studies of L-arginine show improvements in vascular function (Clarkson, Adams, Powe, Donald, et al, 1996) and increases in pain-free walking time (Maxwell, Anderson, & Cooke, 2000) among adults with peripheral vascular disease. The usual intake of L-arginine in the American diet is approximately 5.4 grams per day (Visek, 1986). The USDA nutrient database shows that a 100 gram serving of walnuts provides almost ½ this amount (2.3 g of L-arginine per 100 g English walnuts). L-arginine has been shown to attenuate atherosclerotic lesion extent in animals, and to lower blood pressure and improve vascular function in some human studies (for review, see Preli, Klein, & Herrington, 2002). In addition, walnuts are a good source of dietary vitamin E and fiber. Thus, the cardiovascular benefits of walnut consumption may derive from the additive or synergistic effects of the L-arginine, ALA, fiber and vitamin E present in walnuts.

In addition to identifying the active agents in walnuts, it is also important that potential mechanisms for the effects of walnuts on coronary risk be carefully examined. The LSRO report identified 6 peer-reviewed, well-controlled clinical studies of walnut consumption with biomarkers of atherosclerotic risk or atherosclerotic disease extent as endpoints. These studies have shown that walnuts reduce LDL cholesterol, either in the context of a high fat diet, or as part of a lower fat diet (for review, see Feldman, 2002). In a recent study funded by the California Walnut Commission, my colleagues and I found that when saturated fats in the diet are partially replaced by walnuts and walnut oil, small but significant diastolic blood pressure reductions are observed (West, Likos, Schoemer, Zhao, & Kris-Etherton, 2002). Although not all studies show a blood pressure lowering effect, the weight of the evidence suggests that walnut consumption significantly reduces LDL cholesterol, and may also improve other coronary risk factors.

In summary, there is consistent evidence from controlled clinical studies that walnut consumption is associated with improvements in LDL cholesterol, and that plant sources of ALA reduce the risk of cardiac death. The unique nutrient profile of walnuts includes high levels of polyunsaturated fatty acids and high levels of L-arginine. Walnuts provide these nutrients in a form that is safe and convenient for consumers to use (e.g. there is no refrigeration or cooking required). Thus, I provide my support for the scientific basis for a health claim for walnuts.

Sincerely,

Handwritten signature of Sheila G. West, Ph.D. in cursive script.

Sheila G. West, Ph.D.

Assistant Professor of Biobehavioral Health
Pennsylvania State University

Attachments: Reference List

References:

- Clarkson, P., M. R. Adams, et al. (1996). "Oral L-arginine improves endothelium-dependent dilation in hypercholesterolemic young adults." The Journal of Clinical Investigation **97**(8): 1989-1994.
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- Maxwell, A. J., M. P. Zapien, et al. (2002). "Randomized trial of a medical food for the dietary management of chronic, stable angina." J Am Coll Cardiol **39**(1): 37-45.
- Preli, R. B., K. P. Klein, et al. (2002). "Vascular effects of dietary L-arginine supplementation." Atherosclerosis **162**(1): 1-15.
- Rissanen, T., S. Voutilainen, et al. (2000). "Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study." Circulation **102**(22): 2677-9.
- Salonen, J. T., K. Seppanen, et al. (1995). "Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men." Circulation **91**(3): 645-55.
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- Visek, W. J. (1986). "Arginine needs, physiological state and usual diets. A reevaluation." J Nutr **116**(1): 36-46.
- West, S. G., A. Likos, et al. (2002). Effects of omega-3 fatty acids from walnuts on blood pressure (BP) reactivity to stress (abstract). Society for Experimental Biology, New Orleans, LA.