# Comments to the Food and Drug Administration Regarding the California Walnut Commission Petition Entitled, "Health Claim Petition: Diets Including Walnuts Can Reduce the Risk of Heart Disease (Docket #02P-0292)

November 13, 2002

These comments reflect the opinion of a broad-based coalition of tree nut organizations who strongly support a health claim petition submitted to FDA by the International Tree Nut Council Nutrition Research and Education Foundation (INCNREF). This petition solicits approval of a health claim on the ability of *all* common nuts to reduce the risk of CHD and applies to almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, peanuts, pecans, pine nuts, pistachio nuts and walnuts.

The totality of scientific evidence supporting the cardioprotective properties of nuts as a group provides compelling evidence that a health claim should be authorized. However, the totality of observational and clinical data provides stronger evidence of the ability of nuts generally to reduce the risk of CHD, than the walnut data in isolation provide for walnuts alone. Furthermore, there are insufficient data to justify authorization of a separate health claim for walnuts in isolation *on the premise that they reduce risk of CHD by a unique mechanism.*

It is strongly recommended that FDA authorize a single health claim for all nuts as requested in the petition submitted by INCNREF.

## Ample evidence demonstrates that nuts, as a group, reduce the risk of CHD.

Epidemiologic evidence

As discussed in the INCNREF petition, a large body of observational data show that nut consumption is inversely associated with the incidence of CHD mortality. Subjects who frequently consume nuts experience a reduced risk of CHD of approximately 30-50% compared to non-nut consumers (Fraser, 1999). These conclusions are supported by analysis of large epidemiological databases including the Physicians' Health Study (Albert *et al.*, 2002), the Nurses' Health Study (Hu *et al.*, 1998), the Adventist Health Study (Fraser *et al.*, 1997, 1995, 1992) and the Iowa Women's Health Study (Kushi *et al.*, 1996).

The epidemiologic evidence is extremely consistent and compelling that nuts, as a group, reduce the risk of CHD. However, because these studies were based on consumption of *all* nuts, they cannot be used to conclude that any single nut, including walnuts, are unique in their ability to reduce CHD risk.

Clinical trials

FDA has accepted serum total cholesterol (T-C) and low density lipoprotein-cholesterol (LDL-C) as valid biomarkers for CHD risk, and has employed this parameter for the authorization of all CHD-related health claims to date: 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); the soy protein and CHD claim §101.82 (63FR 62977 and 64 FR 57700); and the plant sterol/stanol esters and CHD interim final rule (65 FR 54686).

The INCNREF petition provides a detailed review of 19 clinical trials showing that nuts reduce the concentration of serum T-C and/or LDL-C when fed to healthy human subjects in controlled settings. Six of these studies demonstrated that walnuts, like other unsaturated-fat containing nuts, are hypocholesterolemic when fed in reasonable amounts to human volunteers for at least three weeks. Unsaturated fat (both monounsaturated and polyunsaturated) has been shown to reduce serum T-C and LDL-C, and it is likely that this mechanism is utilized by nuts (at least in part) to lower CHD biomarkers. The fatty acid profile of common nuts is presented in Table 1

Table 1
Fatty Acid Class Distribution in Common Nuts

| 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

## Insufficient evidence exists to demonstrate that any individual nut reduces the risk of CHD by a unique mechanism

The intervention studies noted above demonstrate that T-C and/or LDL-C reduction is a plausible mechanism to explain the cardioprotective effect of nuts shown by the epidemiological studies. It is likely that this effect is due largely to the unsaturated fatty

acid content of nuts, but these studies do not provide definitive information on the specific mechanism(s) involved. Therefore, the available intervention trials cannot be used to conclude that any single nut, including walnuts, employs a unique mechanism for the reduction of CHD or its biomarkers.

Other potentially cardioprotective factors in nuts

Tree nuts and peanuts contain a wide range of components that may have cardioprotective properties (see Table 2). These substances include protein, dietary fiber, vitamin E, folate, magnesium, copper, zinc, potassium, phytosterols and n-3 fatty acids.

Kris-Etherton *et. al.* (2001) speculated that non-lipid components of nuts may contribute to their hypocholesterolemic effect because the reduction in T-C and LDL-C observed in at least four clinical trials exceeded that predicted by the equations of Mensink and Katan and that of Hegsted *et. al.* It was also found that the reduction in incidence of CHD found in the Nurses' Health Study exceeded that which would be expected from the reduced level of serum lipids due to eating nuts. The authors concluded,

> "This suggests that the fatty acid profile of nuts contributes to only part of the total reduction in CHD risk. The results of our analysis suggest that other bioactive components may be present in nuts that further reduce CHD risk....Additional clinical studies are needed to verify this and to determine whether other bioactive constituents contribute to the reduction in CHD risk with nut consumption."

Therefore, while the myriad of potentially cardioprotective substances in nuts are likely to contribute to their beneficial effects, additional studies are needed before these effects can be attributed to any specific component(s).

n-3 Fatty Acids

Walnuts are the richest source of n-3 fatty acids among the common nuts, and the walnut petition cites this component as primary justification for a separate health claim for this food. However, the following observations suggest that there is little scientific or regulatory rational for such a claim:

- *Significant Scientific Agreement (SSA) for n-3 fatty acids has not been established* FDA has concluded that unqualified SSA has not been established to confirm that n-3 fatty acids reduce the risk of CHD. The agency has explained, "(1) The evidence is suggestive but not conclusive for a relationship between omega-3 fatty acids and reduced risk of CHD in the general population; (2) the studies in the general population have looked at diets containing fish and not at omega-3 fatty acids and have not shown whether diets or omega-3 fatty acids in fish may have a possible effect on a reduced risk of CHD; and (3) it is not known what effect omega-3 fatty acids may or may not have on risk of CHD in the general population." (Lewis, 2000).

- *There are no controlled clinical trials investigating walnuts as a source of n-3 fatty acids on CHD risk*

- *n-3 fatty acids do not lower serum cholesterol*
  Biomarkers for CHD (e.g. T-C, LDL-C and to a lesser extent high density lipoprotein-cholesterol [HDL-C]) are the only biomarkers FDA has accepted for assessing reduced risk of CHD. FDA has concluded, "...omega-3 fatty acids generally have no effect on LDL cholesterol, a validated surrogate marker for CHD, and, therefore, are not useful in establishing, through the mechanism of lowering LDL cholesterol, a direct benefit of omega-3 fatty acids on reduced risk of CHD for the general population." (Lewis, 2000).

- *The DRI for n-3 fatty acids is based on physiological parameters (e.g. membrane structure, precursors to eicosanoids) and not on CHD disease prevention*
  The DRI Macronutrient report (Food and Nutrition Board, 2002) discusses the possibility that n-3 fatty acids (primarily from fish) reduce the incidence of CHD, but the DRI does not take this consideration into account. Therefore, the fact that a DRI has been established for n-3 fatty acids does not lend credence to a CHD-related health claim for walnuts.

## Conclusion and recommendations

There is an abundance of clear and consistent scientific evidence to show that frequent consumption of reasonable quantities of nuts reduces the risk of CHD in healthy adults. Epidemiologic studies reveal that nut consumption is associated with a 30-50% reduction in the incidence of CHD. Controlled clinical trials with individual nuts show that feeding individual nuts causes significant reductions in T-C and/or LDL-C. In addition, a wide range of nutrient and non-nutrient components in nuts may contribute to their cardioprotective effects. This information is sufficient for FDA to conclude that the SSA standard has been met, and to authorize a health claim for all common nuts as a group.

Authorization of a separate health claim for walnuts based on a unique mechanism is *not* justified based on existing science. Substances with potentially cardioprotective properties beyond lipid-lowering unsaturated fat (e.g. fiber, folate, n-3 fatty acids) are present in walnuts, as they are in other nuts, but there are insufficient data to conclude that such components provide a unique cardioprotective mechanism for walnuts. If the walnut petition were to rely exclusively on such factors to demonstrate a health benefit, FDA would have no choice but to deny it.

The health claim proposed by INCNREF has a significant potential to contribute to public health because most consumers like the taste of nuts, and are likely to consider eating more nuts to be a viable option. However, consumers respond best to simple, direct messages. Authorizing a separate health claim for walnuts is likely to lead to confusion, and has the potential to undermine the credibility of the claim among U.S. consumers. It is therefore strongly recommended that FDA move swiftly to authorize a single claim for all nuts based in the petition submitted by INCNREF.

Table 2

Potentially Cardioprotective Substances in Common Nuts

| Nut (per 1 oz. serving) | Protein (g) | n-3 Fatty Acids (g) | Dietary Fiber (g) | Vitamin E (mg, ATE) | Folate (µg DFE) | Vitamin $B_6$ (mg) | Magnesium (mg) | Copper (mg) | Zinc (mg) | Potassium (mg) | Phytosterols (mg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Almonds | 6.0 | 0 | 3.3 | 7.4 | 8.2 | 0.04 | 78 | 0.3 | 1.0 | 206 | 34 |
| Brazil nuts | 4.1 | 0.02 | 1.5 | 2.1 | 1.1 | 0.07 | 64 | 0.5 | 1.3 | 170 | N/A |
| Cashew nuts | 5.1 | 0.02 | 0.94 | 0.41 | 7.1 | 0.12 | 83 | 0.6 | 1.6 | 187 | N/A |
| Hazelnuts | 4.2 | 0 | 2.8 | 4.3 | 32 | 0.16 | 46 | 0.5 | 0.7 | 193 | 27 |
| Macadamia nuts | 2.2 | 0.06 | 2.4 | 0.15 | 3.1 | 0.08 | 37 | 0.2 | 0.4 | 105 | 33 |
| Peanuts | 7.3 | 0 | 2.4 | 2.6 | 68 | 0.10 | 48 | 0.3 | 0.9 | 200 | 62 |
| Pecans | 2.6 | 0.28 | 2.7 | 1.2 | 6.2 | 0.06 | 34 | 0.3 | 1.3 | 116 | 29 |
| Pine nuts | 6.8 | 0.19 | 1.3 | 0.99 | 16 | 0.03 | 66 | 0.3 | 1.2 | 170 | 40 |
| Pistachios | 5.8 | 0 | 2.9 | 1.3 | 15 | 0.48 | 34 | 0.4 | 0.6 | 291 | 61 |
| Walnuts | 4.3 | 2.57 | 1.9 | 0.83 | 28 | 0.15 | 45 | 0.5 | 0.9 | 125 | 20 |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

Source: USDA Nutrient Database for Standard Reference, Release 15

## References

Albert, C.M., Gaziano, M., Willett, W.C. and Manson, J.E. 2002. "Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study." *Arch. Intern, Med.* 162:1382.

Fraser, G.E., Sabaté, J., Beeson, W.L. and Strahan, M. 1992. "A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study." *Arch. Intern. Med.* 152:1416.

Food and Nutrition Board, Institute of Medicine, 2002. Dietary Reference Intakes for Carbohydrates, Fiber, Fat , Protein and Amino Acids (Macronutrients). National Academy Press, Washington, DC. http://www.nap.edu/books/0309085373/html/

Fraser, G.E., Lindsted, K.D, and Beeson, W. 1995. "Effect of risk factor values on lifetime risk of and age at first coronary event, The Adventist Health Study." *Am. J. Epi.* 142:746.

Fraser, G.E., and Shavlik, D.J. 1997. "Risk factors for all-cause coronary heart disease mortality in the oldest-old." *Arch. Intern. Med.* 157:2249.

Fraser, G.E. 1999. "Nut consumption, lipids, and risk of a coronary event." *Clin. Cardiol.* 22(supp III): III -11 - III-15.

Hu, F.B., Stampfer, M.J., Manson, J.E., Rimm, E.B., Colditz, G.A., Rosner, B.A., Speizer, R.E., Hennekens, C.H. and Willett, W.C. 1998. "Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study." *Br. Med. J.* 317:1341.

Kris-Etherton, P.M., Zhao, G., Binkoski, A.E., Coval, S.M. and Etherton, T.D. 2001. "The effects of nuts on coronary heart disease risk." *Nutr. Rev.* 59:103.

Kushi, L.H., Folsom, A.R., Prineas, R.J., Mink, P.J., Wu, Y. and Bostick, R.M. 1996. "Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women." *New Eng. J. Med.* 334:1156.

Lewis, C.J. 2000. "Letter regarding dietary supplement health claim for omega-3 fatty acids and coronary heart disease." U.S. Food and Drug Administration. http://vm.cfsan.fda.gov/~dms/ds-ltr11.html