

MEMORANDUM OF CALL
Between Nancy Schnell (Lipton)
and Dr. Sharon Ross (DSNP, ONPLDS, CFSAN, FDA) 00 MAY 12 P1 52
March 23, 2000 (3:09 pm)
Re: Petition for Health Claim: Vegetable Oil Sterol Esters

A call was placed to Nancy Schnell by Sharon Ross to ask that Lipton verify the status of three studies submitted in the petition as unpublished. It was also requested that Lipton make the agency aware when such studies are published by submitting a copy of the published study to the FDA. Nancy Schnell replied that she would verify the status of such papers.

OOP-1275

MTI

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VINCENT A. KLEINFELD
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March 31, 2000

Via Facsimile: 202-260-8957
and First Class Mail

**CONFIRMATION
COPY**

Sharon A. Ross, Ph.D.
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20004

Re: Petition submitted by Lipton for a Health Claim regarding
Vegetable Oil Sterol Esters and Coronary Heart Disease

Dear Dr. Ross:

I am writing on behalf of Lipton in response to your March 23, 2000 request to Nancy Schnell for additional information on certain publications cited in the above-referenced health claim petition. The information you requested is as follows:

- The article by R. Ayesh et al. was published as:

Ayesh, R., J.A. Weststrate, P.N. Drewitt and P.A. Hepburn. 1999. Safety evaluation of phytosterol esters. Part 5. Faecal short-chain fatty acid and microflora content, faecal bacterial enzyme activity and serum female sex hormones in healthy normolipidaemic volunteers consuming a controlled diet either with or without a phytosterol ester-enriched margarine. Food Chem. Toxicol. 37:1127-1138.
- The paper by P.F. Jones et al. is scheduled for publication in the May issue of the Journal of Lipid Research.
- The paper by K.C. Maki et al. has been submitted to the Archives of Internal Medicine; further information on publication should be available in May. The paper was presented orally at the American College of Nutrition meeting in 1999 and as a poster during the American Heart Association meeting in November 1999. Copies of the abstracts from these meetings are enclosed.

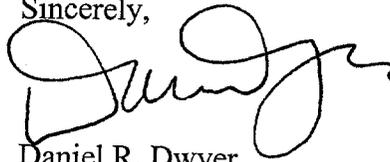
KLEINFELD, KAPLAN AND BECKER

Sharon A. Ross, Ph.D.
March 31, 2000
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These papers will be submitted to the FDA when they are published.

Please contact me or Nancy Schnell if you have any further questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Dwyer", with a stylized flourish at the end.

Daniel R. Dwyer

Counsel to Lipton

enclosures

cc: Nancy L. Schnell, Esq.
Lipton

EFFECTS OF PLANT STEROL-ENRICHED REDUCED-FAT SPREADS ON SERUM CAROTENOID AND FAT-SOLUBLE VITAMIN LEVELS. Maki KC, Davidson MH, Umporowicz D, Dicklin MR, Ingram KA, Gebhart B, Chicago Center for Clinical Research, Chicago, IL; Schaefer E, Tufts University, Boston, MA; Chen S, Franke WC, Lipton, Englewood Cliffs, NJ

Research regarding plant sterols has demonstrated their ability to decrease levels of total and low-density lipoprotein (LDL) cholesterol. Because phytosterols reduce cholesterol absorption, there is concern that they may also decrease absorption of lipophilic nutrients. This double-blind, randomized, controlled clinical trial assessed the impact of two doses of phytosterol-esters (1.1 or 2.2 g/d), delivered in a reduced-fat spread as part of the National Cholesterol Education Program Step I diet, on serum lipids and indicators of lipophilic nutrient status in free-living men and women with hypercholesterolemia. During the 5-week treatment period, mean compliance with study product consumption exceeded 90% in all study groups. In the 1.1 and 2.2 g/d groups, respectively, LDL-cholesterol was reduced from 4.08 (SEM=0.06) to 3.89 (0.06) mmol/L (-5.9% vs. control, $p=0.003$) and from 4.11 (0.09) to 3.91 (0.09) mmol/L (-6.9% vs. control, $p=0.008$). Blood concentrations of all fat-soluble vitamins (subset of 71 subjects) and carotenoids ($n=224$) were within normal reference ranges at baseline and following treatment. There were no significant differences between control and treatment group responses in retinol, 25-hydroxycholecalciferol, alpha- and gamma-tocopherol, or phylloquinone. After total cholesterol correction, trans- β -carotene levels in the 1.1 and 2.2 g/d groups, respectively, were reduced from 0.102 to 0.084 (median, $\mu\text{g}/\text{mg}$) (-13.7% vs. control, $p<0.001$) and from 0.084 to 0.075 (-19.7% vs. control, $p<0.001$). Cholesterol-corrected trans-lycopene levels were significantly reduced in the 2.2 g/d group from 0.099 to 0.079 (-15.8% vs. control, $p=0.027$). There were no significant reductions in cholesterol-corrected α -carotene, lutein, and zeaxanthine levels. Results of this study indicate that a phytosterol-ester containing spread, which is easily incorporated into a low-fat diet, is a useful adjunct in the management of hypercholesterolemia and does not reduce fat-soluble vitamin levels. Carotenoid concentrations were significantly decreased, however, they remained within normal ranges.

ACN abstract and citation:

- > Journal of the American College of Nutrition. Volume 18, Number 5, October
- > 1999. Abstract Number 59, page 536.
- > Effects of Plant Sterol-Enriched Reduced-Fat Spreads on Serum Carotenoid
- > and Fat-Soluble Vitamin Levels. KC Maki, MH Davidson, D Umporowicz, MR
- > Dicklin, KA Ingram, B Gebhart.

<<ACN0520c.doc>>

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T J LIPTON

MAR-31-2000 14:58

the Young, Epidemiology & High Blood Pressure Research, Cardiovascular Disease:

Insulin Resistance, and Fatty Acids

Press Center Exhibit Hall

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Why Fatty Acid Block of the α Subunit of the Human

Harvard Med Sch, Boston, MA; Shu-Ya Wang, SUNY Albany, Albany, NY; Qing Kuo Wang, James P Morgan, Alexander Leaf, Boston, MA

... diets containing long chain n-3 polyunsaturated fatty acids ... sudden cardiac death in patients with coronary ... critical for membrane excitation and the effects of ... play an important in their antiarrhythmic action *in vivo*. In this ... on the I_{Na}^+ current (I_{Na}^+) in human embryonic kidney ... of the human cardiac Na^+ channel ($\alpha 1$). We also ... point mutations of hH1, at D1-S6 (M406K) and D4-S6 (Y1767K) ... mutations of hH1, did not alter the activation of I_{Na}^+ . The ... Y1767K was shifted to the depolarizing direction by 7 mV ... 20 nM significantly inhibited I_{Na}^+ in a concentration-dependent ... the wildtype or two mutated isoforms of hH1. EPA at 5 ... 10, 50 \pm 5% (n = 7), and 40 \pm 6% (n = 1) for the ... respectively. The Y1767K isoform of hH1, is less sensitive to ... In addition, 5 μ M EPA significantly shifted the steady-state ... to the hyperpolarizing direction by 27 \pm 1 mV (n = 6, p < ... 5 μ M EPA was less for Y1767K (14 \pm 1 mV, n = 6, p < 0.05). ... effects on I_{Na}^+ similar to EPA. It is interesting that 5 μ M ... inhibited I_{Na}^+ of the wildtype, but not the Y1767K isoform. Our ... interact with the protein and that D4-S6 is the possible ... which also critical for the local anesthetic effects.

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Added Cholesterol on Plasma Lp(a), ApoB and

Edward M Rubin, Ronald M Krauss, Lawrence Berkeley

... genetically determined, recent studies have shown that ... levels Lp(a) in humans, and also lowers apoB levels in ... yeast artificial chromosome containing the apo(a) gene.

Phytosterol and phytosterol esters have been shown to possess similar cholesterol (C)-lowering properties, however, whether C metabolism is influenced identically by these plant sterol types has not been addressed. To compare the mechanism of action of unsaturated versus saturated plant sterols, C absorption, biosynthesis and turnover were measured in 15 hypercholesterolemic subjects each consuming prepared diets over three phases of 21 d containing either (i) margarine (M), (ii) margarine with phytosterol esters (MPE)(1.8 g/d) or (iii) margarine with phytosterol esters (MPA)(1.8 g/d). All diets were fed to maintain body weight, providing 15, 40 and 35% energy as protein, CHO and fat, respectively. Over d 19-21, C absorption was measured using the ratio of ^{14}C -cholesterol_{inc}:D₃-cholesterol_{inc}; C biosynthesis using D incorporation from D₃; and C turnover by O₃-cholesterol_{inc}:decay rates. Plasma total C level at d 21 was lower (p<0.05) for MPE (-13.4% versus d) and MPA (-10.2%) versus M (-6%) diets, but did not differ between MPE and MPA. Similarly, for LDL-C level mean reductions (-12.9 and -7.9% for MPE and MPA, respectively) were larger (p<0.01) than that after diet M (4%). Plasma TG and HDL-C levels did not differ across diets. At d 21, C absorption was decreased (p<0.05) (-36 and -26% for MPE and MPA, respectively) versus the M diet, while C biosynthesis increased (p<0.05) reciprocally (53 and 38% for MPE and MPA, respectively). Turnover rate for C was not influenced by diet. These results indicate that, contrary to previous data suggesting better lipid-lowering efficacy of free sterols, plant sterol and sterol esters reduce total and LDL-C similarly by suppression of C absorption and enhancement of C synthesis in hypercholesterolemic subjects.

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Lipid Responses to Plant Sterol-Enriched Reduced-Fat Spreads Incorporated into a Step 1 Diet

Kevin C Maki, Michael H Davidson, Denise Vmporowicz, Chicago Clin Res, Chicago, IL; Ernst J Schaefer, Tufts Univ, Boston, MA; Mary R Dicklin, Kate A Ingram, Chicago Clin Res, Chicago, IL; Shirley Chen, Lipton, Englewood Clm, NJ; Brian Gebhart, Chicago Clin Res, Chicago, IL; William C Franke, Lipton, Englewood Clm, NJ

This double-blind, randomized, three-arm parallel, controlled clinical trial was designed to evaluate the efficacy of two doses of esterified phytosterols (1.1 or 2.2 g/d) administered in a reduced-fat (40%) spread, for lowering serum cholesterol in 224 free-living men and women with mild to moderate primary hypercholesterolemia while consuming a National Cholesterol Education Program Step 1 diet. Clinically significant changes in the serum lipid profile were evident at 2 weeks and were maintained throughout the 5-week treatment period. Relative to control, LDL-cholesterol was decreased (p<0.01 for all) by 5.9% and 6.9%, and apolipoprotein B concentrations by 5.1% and 6.4% in the 1.1 and 2.2 g/d groups, respectively. Subjects who consumed \geq 80% of scheduled servings had corresponding decreases in LDL-cholesterol of 7.6% and 8.1% and in apolipoprotein B of 6.2% and 8.4%. Triglyceride concentration in the high-dose group was reduced by 15.9% vs. control (p=0.01). HDL-cholesterol concentrations were unchanged from baseline. Blood concentrations of fat-soluble vitamins and beta-carotene were within normal reference ranges at baseline and following treatment. There were no significant differences in response between the control and treatment groups for retinol, 25-hydroxycholecalciferol, alpha- and gamma-tocopherol, or phytylquinone. Cholesterol-corrected trans- β -carotene levels were reduced by 13 to 20% (p<0.001) vs. control. Plant sterol concentrations increased from 0.46% to 0.64% (1.1 g/d group) and 0.71% (2.2 g/d group) of total circulating sterols. These results indicate that a phytosterol-ester containing spread, which is easily incorporated into a low-fat diet, is a useful adjunct in the management of hypercholesterolemia.

American Heart Assoc Poster Session Nov. 1999

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