



THE WISTAR INSTITUTE

Developing the Medicine of Tomorrow™

David Kritchevsky, Ph.D.
Caspar Wistar Scholar

Phone: 215-898-3713
Fax: 215-898-3995

email: kritchevsky@wista.wistar.upenn.edu

November 5, 1999

Office of Food Labeling (HFS-465)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

To the Food and Drug Administration:

Lipton has asked that I provide to you my views on whether the company's petition for a health claim on the association between vegetable oil sterol esters and reduced risk of coronary heart disease is supported by significant scientific agreement. I am familiar with the petition and with the data that support it. I am also familiar with the scientific standard that has formed the basis for approval of other health claims, such as those for soluble fiber from psyllium seed husk and whole oats.

My professional experience is in the field of nutrition, especially as it affects degenerative disease. I am currently Institute Professor and Caspar Wistar Scholar of the Wistar Institute in Philadelphia, PA. From 1975 – 1992 I was Associate Director of the Institute. I have also served on the faculties of the School of Medicine (Biochemistry and Surgery) of the University of Pennsylvania. For 12 years (1972–1984) I was chairman of the Graduate Group on Molecular Biology at the University. I am Professor Emeritus in the School of Veterinary Medicine and lecture in their elective course entitled "The biochemistry of disease". I have been a member of the the Nutrition (1972-1976) and Special Projects (1964-1968) Study Sections of the NIH. I have also been a member of the Subcommittee on Carcinogenesis and Epidemiology of the National Large Bowel Cancer Project (NCI) [1973-1980] and of the AHLMAC (Atherosclerosis, Hypertension and Lipid Advisory Committee) of the NHLBI (1979-1983). I have also been a consultant to the FDA and member of the Food and Nutrition Board, NAS (1976-1980). I was on the Dietary Guidelines Advisory Committee (1983-1985) and on the Population Based Panel of NCEP (1987-1990). I have been North American editor (1977-1989) of *Atherosclerosis*, and am now Honorary Consulting Editor. I am on the editorial advisory boards of *Lipids* and *Nutrition and Cancer* and on the editorial boards of *Artery*, *J. Nutritional Biochemistry*, *Nutrition Research*, *Nutrition Reviews* and *Experimental and Molecular Biology*. In the past I have served on the editorial boards of *American J. Clinical Nutrition*, *Archives of Biochemistry and Biophysics*, *J. Lipid Research*, *J. Nutrition* and *Nutrition Research International*. I have been co-editor of the following series: *Advances in Lipid Research*; *Adv. in Nutritional Research*; *Monographs on Atherosclerosis* and *The Bile Acids*. I have received a Research Career Award (NIH), Borden Award (AIN), Philadelphia Award (ACS), ACN Outstanding achievement award and Special Award from the Council in Arteriosclerosis of the AHA. My primary research activities have included investigation of nutrition effects on experimental atherosclerosis in rabbits; drug effects on lipid metabolism in rats and rabbits; and dietary effects, especially caloric restriction, in experimental carcinogenesis. A copy of my curriculum vitae is attached.

Based on my professional experience, I am familiar with scientific standards for reviewing studies of cholesterol-reducing agents and with the views on this topic held by others in the scientific and medical community.

In my opinion, the association between vegetable oil sterol esters and reduced risk of CHD is supported by a broad range of clinical experience in a wide variety of subjects over many years. The cholesterol-reducing properties of phytosterols, particularly beta-sitosterol, are well established. This conclusion has been thoroughly discussed in the literature (for example, Pollack and Kritchevsky, 1981) and is well accepted by the scientific and medical community.

The chemistry of vegetable oil sterol esters indicates strongly that they will have a cholesterol-reducing effect similar to that of unesterified phytosterols. As Lipton's petition describes, the esterified vegetable oil sterols will be metabolized in the intestine, cleaving the ester bond and releasing the phytosterols, predominantly beta-sitosterol.

Studies of vegetable oil sterol esters confirm that they do in fact reduce cholesterol levels when formulated into everyday foods such as vegetable oil spreads. The lowest tested level, about 1 g per day (in two servings), was associated with an LDL-cholesterol reduction of about 7%, with no significant effect on HDL-cholesterol levels (Hendriks et al., 1999). Other reported reductions were consistent or higher. In my view, these data represent clinically meaningful reductions of cholesterol levels.

Considering all of the studies together, it is my opinion that the data linking cholesterol reduction with consumption of vegetable oil sterol esters are reproducible and sound. These data indicate that the association between vegetable oil sterol esters and reduced risk of CHD is supported by significant scientific agreement. I believe that others in my professional field, reviewing the same data, would reach a similar conclusion.

I also support Lipton's request that vegetable oil sterol esters be exempt from certain regulatory requirements that would otherwise not permit a health claim on the labeling of foods containing this substance. In my experience, the most difficult problem in reducing CHD risk is achieving meaningful long-term dietary modification. If vegetable oil sterol esters can be formulated in convenient and palatable foods such as spreads and salad dressings, this will increase the likelihood that dietary modification will be successful. Therefore, I believe it is appropriate that Lipton's request for exemption be granted and that a health claim be permitted on the labeling of these foods.

As the above discussion reflects, I am confident that a health claim about the association between vegetable oil sterol esters and reduced risk of CHD would assist consumers in maintaining healthy dietary practices. I am grateful for the FDA's consideration of my views.

Sincerely,



David Kritchevsky
Professor

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enclosure

CURRICULUM VITAE

DAVID KRITCHEVSKY, PhD

PERSONAL DATA

Date of Birth: January 25, 1920
Place of Birth: Kharkov, Russia
Citizenship: U.S.A.
Marital Status: Married, three children
Office Address: The Wistar Institute
3601 Spruce Street
Philadelphia, PA 19104
(215) 898-3713

EDUCATIONAL BACKGROUND

1939 University of Chicago, Chicago, IL
B.S., Chemistry
1942 University of Chicago, Chicago, IL
M.S., Organic Chemistry
1948 Northwestern University, Evanston, IL
Ph.D., Organic Chemistry

RESEARCH EXPERIENCE

1940-1946 Chemist, Ninol Laboratories, Chicago, IL
1942 (Summer) Analyst, U.S. Food and Drug Administration, Chicago, IL
1948-1949 Postdoctoral Fellow, National Research Council Committee on Growth, Federal Institute of Technology, Zurich, Switzerland
1950-1952 Staff Member, Bio-Organic Group, Radiation Laboratory, University of California, Berkeley, CA
1952-1957 Staff Member, Virus and Rickettsial Research Section, Lederle Laboratories, Pearl River, NY
1957-1962 Associate Member, The Wistar Institute, Philadelphia, PA
1962-1975 Member, The Wistar Institute, Philadelphia, PA
1985-present Institute Professor, The Wistar Institute, Philadelphia, PA
1975-1991 Associate Director, The Wistar Institute, Philadelphia, PA
1965-1993 Member, Graduate Group in Biochemistry, Graduate School of Arts and Sciences, University of Pennsylvania, Philadelphia, PA

Research Experience (continued)

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| 1965-1992 | Member, Graduate Group on Molecular Biology, Graduate School of Arts and Sciences, University of Pennsylvania, Philadelphia, PA (Chairman, 1972-84) |
| 1966-present | Wistar Professor of Biochemistry, Division of Animal Biology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA |
| 1971-present | Member, Graduate Group in Pathology, University of Pennsylvania, Philadelphia, PA |
| 1972-1984 | Chairman, Graduate Group on Molecular Biology, Graduate School of Arts and Sciences, University of Pennsylvania, Philadelphia, PA |
| 1972-1992 | Professor of Biochemistry in Surgery, School of Medicine, University of Pennsylvania, Philadelphia, PA |
| 1988-present | Adjunct Professor of Biochemistry, Medical College of Pennsylvania, Philadelphia, PA |

RESEARCH INTERESTS

Lipid Biochemistry, Atherosclerosis, Nutrition, Aging, Nutrition in Cancer

HONORS AND AWARDS

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| 1962 | Research Career Award from the National Heart Institute, National Institutes of Health |
| 1968 | St. Ambrose Medal of the City of Milan for Contribution to the Cultural and Scientific Progress of the City |
| 1974 | Borden Award in Nutrition, American Institute of Nutrition |
| 1977 | Philadelphia Award, American Chemical Society |
| 1978 | American College of Nutrition Outstanding Achievement Award |
| 1979 | Professional Achievement Award, University of Chicago |
| 1987 | Visiting Professor, Royal Society of Medicine (London) |
| 1987 | Fellow, American Institute of Nutrition |
| 1992 | Burroughs-Wellcome Visiting Professor, Univ. of Alabama School of Medicine |
| 1992 | Robert H. Herman Memorial Award, American Society for Clinical Nutrition |
| 1993 | Special Recognition Award - American Heart Association - Council on Arteriosclerosis |
| 1993 | Distinguished Service Award, Institute of Nutrition, University of North Carolina |
| 1994 | Auenbrugger Medal, University of Graz, Austria |
| 1996 | Supelco-AOCS Research Award |

HONOR SOCIETIES

Sigma Xi, Phi Zeta, Phi Lamda Upsilon

SOCIETY MEMBERSHIPS

American Association for the Advancement of Science, Fellow
American Chemical Society
American Heart Association, Council on Arteriosclerosis
1963 Executive Committee; 1966-67 - Program Committee
1971-73 Credentials Committee; 1975-76 - Publications Committee
American Institute of Nutrition
1976- Nominating Committee; 1978 - President Elect
1979- President; 1980 - Council Member
American Oil Chemists Society
1963-64 Chairman, Biochemical Methods Committee
1964-65 Chairman, Biochemical Program Committee
1974- National Program Committee; Chairman, Biology and Nutrition Subcommittee

Society Memberships (continued)

American Society for Biochemistry and Molecular Biology
American Society for Clinical Nutrition
College of Physicians of Philadelphia
European Atherosclerosis Group, Corresponding Member
Federated American Societies of Experimental Biology (FASEB)
1979-80 Member, Board of Directors
International Union of Angiology
1962-64 Member, Dietary Council
International Society of Biochemical Pharmacology
John Morgan Society (University of Pennsylvania honorary medical research society)
1968- Recorder; 1969 - Secretary-Treasurer; 1970 - President
New York Academy of Sciences, Fellow
Philadelphia Biochemists Club
1975- President
Society of Experimental Biology and Medicine
1984-86 President

SPECIAL ACTIVITIES

1964-1968 Member, Special Projects Study Section, National Institutes of Health
1972-1976 Member, Nutrition Study Section, National Institutes of Health
1973-present Member, Subcommittee on Carcinogenesis and Epidemiology, National Large Bowel Cancer Project
1979-1983 Member, Atherosclerosis, Hypertension, and Lipid Metabolism Advisory Committee, National Heart, Lung and Blood Institute
1976-1980 Member, Food and Nutrition Board, National Academy of Sciences
1979-present Consultant, Food and Drug Administration
1983-1985 Dietary Guidelines Advisory Committee, USDA
1986-1990 Committee on Animal Models in Human Nutrition Research of the International Union of Nutritional Sciences
1987-1990 Population Based Panel, National Cholesterol Education Program

EDITORIAL ACTIVITIES

Atherosclerosis, Western Hemisphere Editor (1977-1989); Consulting Editor (1990-present)
(See attached list of books authored and edited by David Kritchevsky.)

EDITORIAL BOARD MEMBER of

ARTERY
EXPERIMENTAL AND MOLECULAR PATHOLOGY
JOURNAL OF MEDICINE
JOURNAL OF NUTRITIONAL BIOCHEMISTRY
NUTRITION AND THE M.D.
NUTRITION RESEARCH
PROGRESS IN FOOD & NUTRITION SCIENCE
PUBLIC HEALTH REVIEW
INTERNATIONAL JOURNAL OF TISSUE REACTIONS

PAST EDITORIAL BOARD MEMBER of

ACCOUNTABILITY IN RESEARCH
AMERICAN JOURNAL OF CLINICAL NUTRITION
ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS
ATHEROMA
CORONARY CLUB BULLETIN
DRUG-NUTRIENT INTERACTIONS
FEDERATION PROCEEDINGS
INTERNATIONAL JOURNAL OF CARDIOLOGY
JOURNAL OF LIPID RESEARCH
JOURNAL OF MEDICINE
JOURNAL OF NUTRITION
NUTRITION REPORTS INTERNATIONAL
NUTRITION AND THE M.D.
NUTRITION RESEARCH NEWSLETTER
STERIODS AND LIPIDS RESEARCH
THE PROFESSIONAL NUTRITIONIST
HEART CORPS

EDITORIAL ADVISORY BOARD

CURRENT CARDIOVASCULAR PATENTS
LIPIDS

SERIES EDITOR

Advances in Experimental Medicine and Biology (Plenum Press, NY)
Advances in Lipid Research (Academic Press, NY; R. Paoletti, co-editor)
Advances in Nutritional Research (Plenum Press, NY)
Contemporary Issues in Clinical Nutrition (Wiley-Liss)
Current Topics in Nutrition and Disease (Alan R. Liss, NY)
Monographs in Lipid Research (Plenum Press, NY)
Monographs on Atherosclerosis (S. Karger Basel; A.C. Beynen and O.J. Pollak, co-editors)
The Bile Acids (Plenum Press, NY; P.P. Nair, co-editor)

OTHER ACTIVITIES

International Program Committee of the International Symposia on Atherosclerosis
Organizing Committee on the International Meetings on Drugs Affecting Lipid Metabolism
Nutrition Research Committee of the California Avocado Advisory Board
Advisory Committee to the Biochemistry Technology Dept., Spring Garden College, Philadelphia, PA
Advisory Board Member of the Dairy Council of Philadelphia
Scientific Advisory Board, American Longevity Association
Scientific Advisory Board, American Institute for Cancer Research
Advisory Committee, American Council for Science and Health
Board of Managers, Philadelphia Cancer Society