



Dietary n-3 and n-6 fatty acids compete for accumulation in tissues as 20- and 22-carbon highly unsaturated fatty acids (HUFA)

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The following article is based on the address given by Bill Lands, the 2010 Ralph Holman Lifetime Achievement Award winner. His address was given at the 101st AOCS Annual Meeting & Expo, held in Phoenix, Arizona, USA, May 16–19.

The vitamin-like essential fatty acids were conceived in 1929 (as I also was). Over the years, knowledge of 18-carbon omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFA) grew to include details of their metabolism to 20- and 22-carbon highly unsaturated fatty acids (HUFA) and selective accumulation of HUFA at the 2-position of membrane phospholipids. HUFA are released when various stimuli activate cellular phospholipases, and the released HUFA form potent eicosanoid hormones that have receptors on nearly every cell in the human body. Thus, these vitamin-like nutrients and their derived hormones affect a wide range of physiological and pathological events.

Excessive n-6 hormone actions cause more severe atherosclerosis, arthritis, asthma, bone loss, cancer growth, heart attacks, immune-inflammatory events, length of hospital stays, plus major depression, suicide, classroom disruptions, and unproductive workplace behaviors. An important difference between the n-3 and n-6 types of hormone is that n-6 actions tend to be more vigorous and intense than those of n-3. Primary prevention of excessive activation of many hormone receptors will likely prevent many severe chronic immune-inflammatory diseases that every year cause more than a trillion dollars of loss in the United States. Clearly, the longer we keep people healthy, the less health care treatments need to be paid and the less personal and corporate financial loss occurs.

The proportion of n-6 hormone precursors in tissue HUFA strongly correlates with cardiovascular mortality rates in several



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populations (Lands, 2003). People with more than 50% n-6 in HUFA have an n-3 deficit and a greater risk of death from heart attacks. The HUFA-associated risk for heart attacks per 100,000 people was estimated to be near $[3 \times (\% \text{ n-6 in HUFA}) - 75]$. Overall evidence supports a hypothesis that lowering the proportion of n-6 in HUFA from the 78% now common to 50% will likely lower the CHD (coronary heart disease) mortality rate by more than half, preventing over 800,000 clinical CHD events and 200,000 deaths annually in the United States. For large, self-insured corporations paying a substantial part of employee health care costs, a shift from 78% to 50% may prevent annual losses of \$100 million per 100,000 employees. Health-related absenteeism and presenteeism may cause corporate

losses severalfold greater than medical and pharmacy costs. Thus, employees who eat more n-3 and less n-6 to shift from 78% to 50% n-6 in their HUFA may lower corporate health-related annual losses by \$500 million per 100,000 employees. Any corporation combining HUFA assay status with records of overall health costs will obtain useful internal evidence of corporate benefits in motivating food choices that lower the current n-3 HUFA deficit.

Food choices that prevent a dietary imbalance of n-3 and n-6 nutrients prevent accumulating n-3 HUFA deficits with their excessive proportions of n-6 hormone precursors in tissue HUFA. The enzymes that convert dietary PUFA into tissue HUFA seem fairly diffident about details of the n-3 and n-6 chemical structure, indiscriminately treating them mostly in accord with their relative abundance. As a result, the relative dietary abundance determines the proportions accumulated in tissue HUFA. Neglect in acknowledging quantitative competitive interactions of linoleic acid (18:2n-6) and linolenic acid (18:3n-3) maintains the imprecise belief that the 18-carbon n-3 acid is inherently less able to form HUFA. Investigators reluctant to study dietary conditions beyond those that maintain n-3 deficits continue to misinterpret the nearly equal competitive elongation and desaturation of n-3 and n-6 acids.

Quantitative comparisons of accumulated tissue HUFA derived from the 18-carbon dietary essential fatty acids were first detailed in 1963 by Mohrhauser and Holman and confirmed later in my lab in 1990 and 1992. The observations led to describing an empirical quantitative relationship (<http://efaeducation.nih.gov/sig/hufacalc.html>) that estimates the competitive hyperbolic influence of dietary essential fatty acids on the proportion of n-6 in accumulated

FOR FURTHER READING:

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- Wada, M., C.J. DeLong, Y.H. Hong, C.J. Rieke, I. Song, R.S. Sidhu, C. Yuan, M. Warnock, A.H. Schmaier, C. Yokoyama, E.M. Smyth, S.J. Wilson, G.A. FitzGerald, R.M. Garavito, D.X. Sui, J.W. Regan, and W.L. Smith, Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products, *J. Biol. Chem.* 282:22254–22266 (2007).

HUFA of tissues. A simple calculator using the equation estimates likely outcomes from various dietary combinations (<http://efaeducation.nih.gov/sig/dietbalance.html>). The empirical equation was also combined with the US Department of Agriculture's Nutrient

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Database to form the interactive personalized menu-planning software, KIM-2, that is freely available at <http://efaeducation.nih.gov/sig/kim.html>. The software assembles nutrient data for desired food servings selected from nearly 12,000 options, sums the milligrams of PUFA and HUFA, and estimates the likely outcome in terms of the percentage of n-6 in a person's HUFA. The outcome can be confirmed by a simple finger-tip blood assay. Such quantitative feedback about the consequence of food choices gives explicit guidance on foods that will meet each individual's personal tastes and sense of risk.

In contrast to the relatively indiscriminate process of accumulating HUFA in tissues, the processes making active hormones and their receptor-mediated actions do discriminate and give stronger actions for n-6 than n-3 derivatives (detailed by Wada *et al.*, 2007). That difference makes the choice of dietary supplies (which determine tissue precursor proportions) an important aspect of human health. Ignoring the preventable overabundance of n-6 in tissue HUFA maintains an imprecise belief that current

health-related financial losses are inherently "normal" human conditions. Employers and employees reluctant to observe quantitative assay results of each individual's HUFA status (and likely n-3 deficit) will probably neglect or misinterpret the simple dietary steps already available for choosing foods that balance competing n-3 and n-6 acids and preventing massive annual financial losses by American employers and employees.

Many social, ethical, and financial concerns caused by health-related events might be prevented by providing explicit information to the public about food choices that balance the competing metabolic steps that maintain tissue proportions of HUFA at levels that prevent an n-3 deficit and decrease unintended health risk. Personalized, quantitative, interactive menu planning software aids in designing explicit advice for successful primary prevention of what the Centers for Disease Control and Prevention regard as a preventable condition that is still predicted to cause \$503 billion of losses in 2010. The past 80 years have provided us tools to prevent future health-related losses

by individuals and corporations. Will we use them?

Bill (William E.M.) Lands was professor of biochemistry at the University of Michigan (1955–1980) and the University of Illinois (1980–1991) Medical Schools. He wrote more than 260 papers, plus the text Fish, Omega-3 and Human Health, 2nd Edition. One of the world's 1000 most cited scientists in 1965–1978, his awards include: 1985 Pfizer Biomedical Research, 1997 Supelco/Nicholas Pelick-AOCS Research, 2006 ISSFAL Alexander Leaf Distinguished Scientist Award for Lifetime Achievement, and the 2010 AOCS Ralph Holman Lifetime Achievement. He is also a Fellow of American Association for the Advancement of Science, American Society for Nutrition, and the Society for Free Radical Biology and Medicine. He served at the National Institute on Alcohol Abuse and Alcoholism/National Institutes of Health (1990–2002). Now retired, he serves on the board of directors of Omega Protein, Inc. Reach him via email at wemlands@att.net.