

ISSUE PAPER

NUMBER 24

OCTOBER 2003

NUTRACEUTICALS FOR HEALTH PROMOTION
AND DISEASE PREVENTION**I**NTRODUCTION

The purpose of this paper is to summarize certain scientific and legal issues regarding the chemical compounds known as *nutraceuticals*.¹ The topic is timely because consumer interest in the relationship between diet and health is high, yet media reports about the consequences of certain food compounds may confuse not only consumers but also health professionals. This paper provides background information about nutraceuticals and related products; addresses the regulation of nutraceuticals; discusses scientific issues including safety, efficacy, processing, and plant production; and offers policy and research recommendations.

A rapidly growing focus of research and product development, nutraceuticals are of interest to individuals studying human health and nutrition, agriculture, food science, plant and animal genomics, and molecular biology. In agricultural and biomedical research, *functional foods* and health-protecting materials (i.e., nutraceuticals including *phytochemicals* and *botanicals*) are per-

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ceived as offering some of the greatest opportunities for improving human health. Diet-related chronic diseases such as heart disease, cancer, stroke, diabetes, and arteriosclerosis result in an estimated annual loss to the U.S. economy of more than \$70 billion in medical and productivity costs, not counting premature deaths associated with these illnesses (Frazao 1999). Numerous epidemiological studies suggest that the risks for many chronic diseases are diet related and could be decreased significantly through the change of dietary habits. Consumers' demand for functional foods and interest in self-

medication will fuel markets for these products as U.S. health care costs continue to exceed \$1 trillion annually.

Since ancient times, humankind has relied on foods for the prevention and treatment of disease. With advancements in medical science, synthetic drugs and surgery have been introduced to alleviate, cure, and prevent disease. Recently, however, by recommending a healthy, balanced diet, medical science is returning to an interest in disease prevention. New evidence indicates that foods contain numerous naturally occurring health

¹Italicized terms are defined in Textbox 1.

Textbox 1. Key definitions

Antioxidants	Chemicals that protect against oxidation and free-radical damage to lipids, proteins, carbohydrates, and DNA
Bioactivity	A given agent's effect on a living organism or on living tissue
Biomarker	A test that measures the body's response to a chemical or to a disease condition
Botanicals	Processed plants or their extracts that are believed to affect health. Also known as herbs, herbal medicine, and phytomedicine
Conjugated linoleic acid	A variation of the essential fatty acid—linoleic acid—found in foods from ruminants or prepared synthetically; may have anticarcinogenic effects
Designed foods	Raw, fresh agricultural products that contain supplemental nutraceuticals or phytochemicals to benefit health and decrease chronic disease risk. Example: Designed eggs containing high amounts of omega-3 fatty acids
Dietary supplement	A product (other than tobacco) that is intended to supplement the diet and bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical (or a metabolite or concentrate of any of the listed materials); is intended for ingestion in the form of a capsule, powder, softgel, or gelcap; and is not represented as a conventional food or as a sole item of a meal or diet
Functional foods	Foods containing physiologically active components with a health benefit beyond basic nutrition
Health claim	Nutrition Labeling and Education Act food label statements characterizing the relationship of any food or food component to a disease or health condition
In vitro	In model "test-tube" environments
In vivo	In humans or other living organisms
Metabolite	A compound resulting from the digestion and/or metabolism of nutraceuticals
Natural antioxidant	One broad group of chemical compounds responsible for disease prevention and health promotion in humans
Nutraceutical	Nutrients and nonnutrient compounds in food that have health-promoting, disease-preventive, or medical properties. Nutraceuticals can be purified to make a dietary supplement or added to a food to increase the amount of those substances in the diet
Pharmacokinetics	The process by which a bioactive compound is absorbed, distributed, metabolized, and eliminated by the body
Phytochemicals	Plant compounds imparting a benefit to human health, depending on an individual's dietary practices, lifestyle, and genetic makeup
Structure/function claim	Statement (1) describing the role of a nutrient or dietary ingredient intended to affect the structure or function of the human body or behavior, (2) characterizing the documented mechanism by which a nutrient or dietary ingredient acts to maintain such a structure or function, or (3) describing general well-being resulting from consumption of a nutrient or dietary ingredient

protectants that assist in the prevention of human chronic diseases.

The benefits to humans of future research on nutraceuticals was recognized in the 1988 *Surgeon General's Report on Nutrition and Health*, which stated that five of the ten leading causes of death in the United States are diet-related diseases, in-

cluding certain types of cancer, coronary heart disease, stroke, other atherosclerotic diseases, and diabetes mellitus (U.S. Surgeon General 1988). These five diseases, responsible for approximately two-thirds of the more than two million deaths annually in the United States, also cause diminished productivity, economic hardship, and suffer-

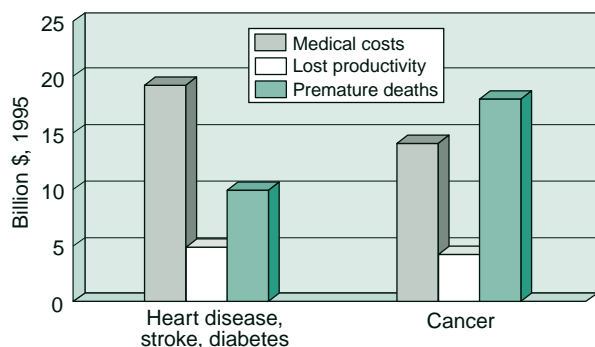


Figure 1. Diet-related costs for four health conditions in 1994. Costs were adjusted to 1995 values based on the consumer price index (Frazao 1999).

ing. Figure 1 illustrates the costs of heart disease, stroke, diabetes, and cancer in 1994. Other illnesses and conditions such as arthritis and obesity have exacted additional tolls from the U.S. economy and from the quality of life of residents. The growing field of nutrigenomics (also referred to as nutrigenomics), which evaluates the effects of nutrients and nutraceuticals on gene expression, may in the future lead to dietary recommendations to prevent or to treat disease (Fogg-Johnson and Kaput 2003).

Definitions

The White House's 1969 Conference on Food, Nutrition and Health often is acknowledged as the first official recognition by the U.S. government that diet, and specifically food components, can affect health. By the mid-1980s, food processors (most notably Kellogg, with its bran cereal campaign) and the National Cancer Institute, which had begun promoting a diet of high-fiber foods for the prevention of colorectal cancer, began marketing jointly certain foods on the basis of health benefits.

This focus on health-protectant food components generated a variety of vocabulary terms (see Textbox 1). *Functional foods*, *designed foods*, and *nutraceuticals* are some of the terms that have been developed to identify the existence of foods and food components with health-enhancing or disease-preventive properties. Scientific focus on the identification of health-protectant components within food and their mechanism(s) of action, such as beta-glucan in oat bran, directs attention to the term *nutraceuticals* rather than to the whole-food concepts implicit in a term such as *functional foods*. *Nutraceuticals* are nutrients and nonnutrient com-

pounds in food that have health-promoting, disease-preventive, or medicinal properties. The role of nutrients in health is evolving beyond the classic nutritional role of preventing deficiencies that was the focus of research in the twentieth century. Nutraceuticals can be purified to make a *dietary supplement* or added to a processed food to increase the amount of nutrients and nonnutrient compounds in the diet. Foods containing physiologically active components that have a health benefit beyond basic nutrition are also called *functional foods* (Hasler 2002).

In the United States, the terms “functional foods,” “nutraceuticals,” and other related terms have no legal or regulatory identity in food and drug law (Hutt 2000). The U.S. Dietary Supplement Health and Education Act of 1994 (DSHEA) regulates dietary supplements as foods, not as food additives, and does define dietary supplements as “vitamins, minerals, herbs or other botanicals, amino acids, or other dietary substances for use by man to supplement the diet by increasing the total dietary intake, including concentrates, metabolites, constituents, extracts, or any combination of the above” (U.S. Congress 1994, p. 7). Discerning dietary supplements from nutraceuticals is not always simple.

Scope of the Market

Nutraceuticals are part of a \$53 billion U.S. nutrition industry composed of several relevant segments. The value of the U.S. nutraceutical and functional foods segment was estimated at \$20.6 billion in 2002, or a 9.1% increase since 2001. This increase compares with growth rates of 3% and 3.5% for conventional foods and dietary supplements, respectively (NBJ 2003). Dietary supplement sales grew at a rate of approximately 1.3% from 2001 to 2002, but certain product categories experienced a significant decline in sales (Marra 2002). The nutraceutical industry, which is perceived as consumer driven, must meet several conditions to continue expansion. These conditions include

- a continued consumer emphasis on preventive health care and health maintenance;
- the U.S. demographics of an aging population with both information access and disposable income to pursue nutraceutical products;

- an increased acceptance and recommendation of nutraceutical-based products by the medical establishment;
- products and marketing characterized by higher quality, more extensive scientific documentation, and broader retail distribution; and
- affordability.

The primary consumers of nutraceuticals come from a range of backgrounds but often are female, well educated, reasonably affluent, and middle aged (35 to 55 years [yr]) (Childs and Poryzees 1997). Product development tends to follow the scientific discoveries and health states that preoccupy consumers. Scientific consensus recognized by a formal U.S. Food and Drug Administration (FDA)-accepted *health claim*, such as the soy protein health claim for cardiovascular health and the calcium osteoporosis claim, is believed to be a marketing advantage; therefore, companies have targeted product development and reformulation to use health claims and nutrient content claims on their food labels. This phenomenon emphasizes the intimate and interconnected relationships among nutraceutical discovery and documentation, product development, regulatory policy, and consumer behavior.

REGULATION

Three significant changes in the regulation of food occurred between 1990 and 1997, changes that enabled, by means of food labels, the enhanced dissemination of information to consumers regarding the relation between diet and health. These changes were (1) passage of the Nutrition Labeling and Education Act (NLEA) of 1990, (2) pas-

sage of the Dietary Supplement Health and Education Act (DSHEA) of 1994, and (3) enactment by Congress of the Food and Drug Administration Modernization Act (FDAMA) of 1997.

The Nutrition Labeling and Education Act of 1990

The legislative acknowledgment of foods for health occurred with the passage in 1990 of the NLEA, which formally permitted health claims on food labels, for qualified products (U.S. Congress 1990). The NLEA allowed food label statements that characterized the relationship of any food or food component to a disease or health condition—a relationship called a *health claim* (USFDA 1993). For a product to qualify for health claim approval, the manufacturer or petitioner must demonstrate to the FDA that there exists significant scientific agreement on the documentation indicating the food or food component’s effect on health. Under the NLEA, the FDA was mandated by Congress to review ten diet-disease relationships, eight of which eventually were approved as health claims. Although many of these health claims addressed specific nutrition-related relationships, only three involved the nonnutrient components of foods, such as dietary fiber (see Table 1).

The NLEA also permitted authorization of new health claims after submission and approval of a petition to the FDA. Thus, health claims were to be approved by the FDA before manufacturers could publish them on food labels. Petitioning the FDA for a health claim can be a lengthy and expensive process. In addition, because a primary goal of the NLEA is to protect consumers from unfounded health claims, the standards for approval

Table 1. Diet/Disease relationships mandated for FDA review under the NLEA and currently approved as health claims

Diet/Disease Relationship	Model Claim
Fiber-containing grain products, fruits, and vegetables/ Cancer	Low-fat diets rich in fiber-containing grain products, fruit, and vegetables may decrease the risk of some types of cancer, a disease associated with many factors.
Fruits, vegetables, and grain products that contain fiber, particularly soluble fiber/ Coronary heart disease	Diets low in saturated fat and cholesterol and rich in fruits, vegetables, and grain products that contain some types of dietary fiber, especially soluble fiber, may decrease the risk of heart disease, a disease associated with many factors.
Fruits and vegetables/ Cancer	Low-fat diets rich in fruits and vegetables may decrease the risk of some types of cancer, a disease associated with many factors.

of such claims are quite rigorous: There must be “significant scientific agreement” about a diet-disease relationship after a review of the publicly available evidence. Indeed, under the NLEA, only five additional health claims have been approved, of which four have been related to nutraceuticals (see Table 2). The U.S. Department of Agriculture (USDA), which regulates most animal-based foods, currently does not permit health claims for those foods that fall under its jurisdiction.

What constitutes significant scientific agreement has been a matter of considerable debate since the passage of the NLEA. In December 1999, the FDA released a guidance document outlining what constitutes significant scientific agreement (USFDA 1999). This schematic (Figure 2) clearly distinguishes emerging evidence composed of in vitro or animal studies from consensus (i.e., a body of consistent evidence from well-designed clinical studies and expert opinions from independent experts). As shown, the strength of the evidence for a diet/disease relationship grows with movement from left to right on the schematic.

In a departure from the significant scientific agreement standard of evidence required for health claim approval under the NLEA, the FDA announced in July 2003 that it will allow “qualified health claims” on conventional foods, and it outlined the criteria necessary for approval of quali-

fied health claims in an industry guidance document (USFDA–DHHS 2003). Health claim petitioners need to demonstrate, based on a fair review by scientific experts of the totality of information available, that the “weight of the scientific evidence” in support of the claim outweighs the scientific evidence against the claim. If such a demonstration is made, the FDA will consider approving the claim with appropriate qualifying language. Under the new scheme, the highest level of scientific evidence, equivalent to significant scientific agreement, will be designated as “A.” Three other rankings of health claims will be allowed, with standardized qualifying statements (Table 3).

The guidance document is part of the new Consumer Health Information for Better Nutrition Initiative. The goals of this initiative are to make available more and better information about foods and dietary supplements and to help American consumers prevent diseases and improve their health by making sound dietary decisions. Concern has been expressed, however, by certain public health organizations, including the American Medical Association, about the consequences of relaxing the significant scientific agreement standard for health claims. The FDA plans to study consumer understanding of the new ranking system and qualifying statements after, not before, implementation of the new health claim process in September 2003.

Table 2. Nutraceutical-related health claims and label statements approved by the FDA after petitions submitted by the food industry, as permitted by NLEA

Diet/Disease Relationship	Model Claims and Label Statements
Soluble fiber from certain foods (whole oats, psyllium)/ Coronary heart disease	Diets low in saturated fat and cholesterol that include soluble fiber from whole oats, Betatrim, or psyllium seed husk may decrease the risk of heart disease. A serving of [name of food product] supplies ___ grams (g) of the [necessary daily dietary intake for the benefit] soluble fiber from [name of soluble fiber source] necessary per day (d) to have this effect.
Soy protein/ Coronary heart disease	Diets low in saturated fat and cholesterol that include 25 g of soy protein/d may decrease the risk of heart disease. A serving of [name of food product] provides ___ g of soy protein.
Plant sterols/ Coronary heart disease	Plant sterols: Foods containing at least 0.65 g/serving of plant sterols, eaten twice/d with meals for a daily total intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, may decrease the risk of heart disease. A serving of [name of food product] supplies ___ g of vegetable oil sterol esters.
Plant stanol esters/ Coronary heart disease	Plant stanol esters: Foods containing at least 1.7 g/serving of plant stanol esters, eaten twice/d with meals, for a total daily intake of at least 3.5 g, as part of a diet low in saturated fat and cholesterol, may decrease the risk of heart disease. A serving of [name of food product] supplies ___ g of plant stanol esters.

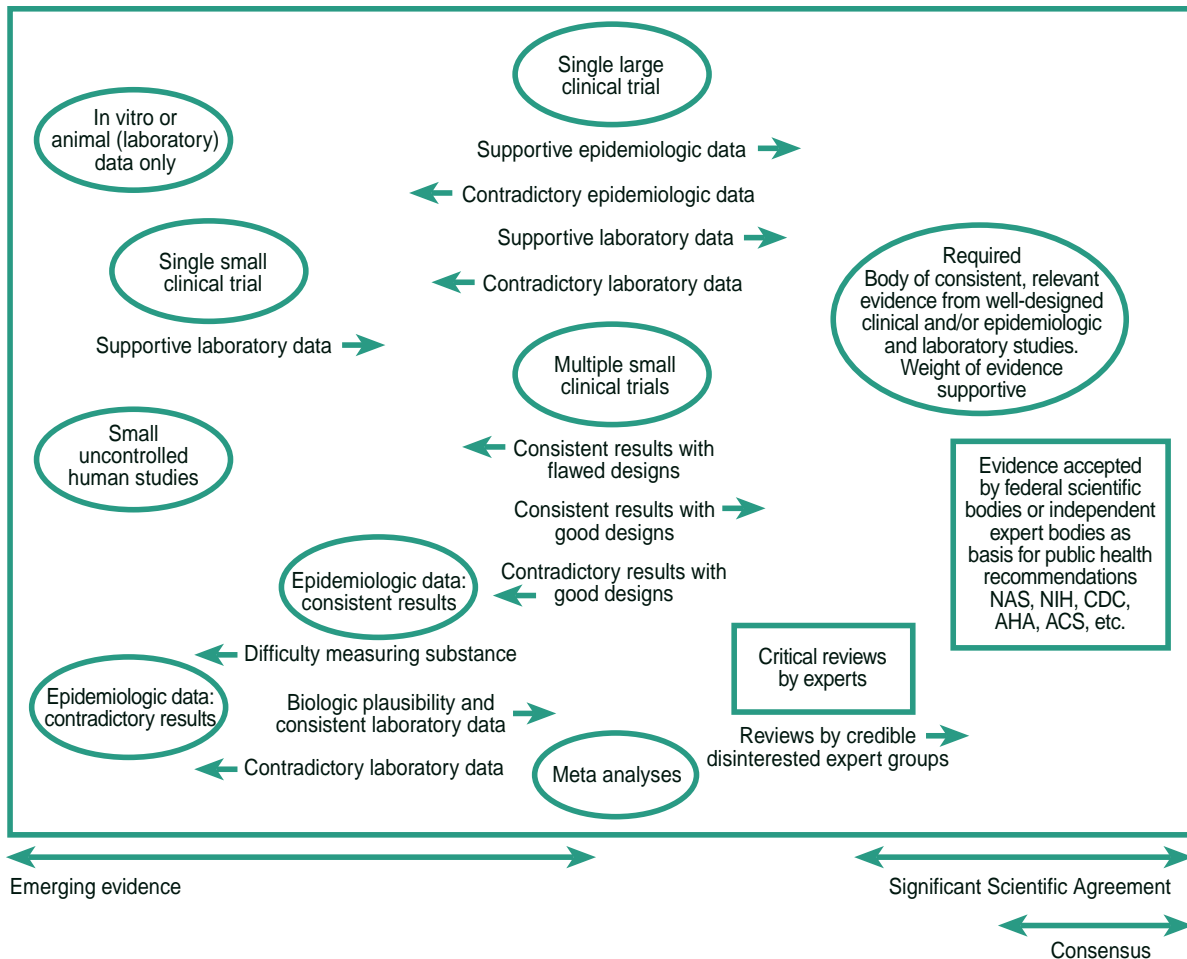


Figure 2. Scheme for assessing strength and consistency of evidence leading to significant scientific agreement (USFDA 1999).

Dietary Supplement Health and Education Act of 1994

The second and undeniably most controversial change in recent food regulations was the passage of the DSHEA in 1994 (U.S. Congress 1994). Under this Act, dietary supplements are allowed to

bear so-called *structure/function claims*—i.e., statements (1) describing the role of a nutrient or dietary ingredient intended to affect the structure or function of the human body or behavior, (2) characterizing the documented mechanism by which a nutrient or dietary ingredient acts to maintain such a structure or function, or (3) describing

Table 3. Standardized qualifying language for qualified health claims that do not require significant scientific agreement (USFDA–HHS 2003)

Scientific Ranking	FDA Category	Appropriate Qualifying Language
Second level	B	“... although there is scientific evidence supporting this claim, the evidence is not conclusive.”
Third level	C	“Some scientific evidence suggests ... however, FDA has determined that this evidence is limited and not conclusive.”
Fourth level	D	“Very limited and preliminary scientific research suggests ... FDA concludes that there is little scientific evidence supporting this claim.”

general well-being resulting from consumption of a nutrient or dietary ingredient. Foods also are permitted to bear structure/ function claims, but such claims must be limited to nutrients for which a daily requirement has been established. The current regulatory situation does not permit food or dietary supplement manufacturers to provide consumers with product label claims that address consumer health concerns, such as relieving arthritis pain or preventing cancer, inasmuch as these claims would be construed as drug claims.

Structure/function statements for dietary supplements are not subject to FDA preapproval; manufacturers using structure/function claims in product labeling simply must notify the FDA within 30 days (d) of marketing a product that displays the claim. The product must be accompanied by the disclaimer, “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.” Thus, the DSHEA puts the burden of proof regarding the safety and efficacy of dietary supplements on the FDA. Unlike the NLEA, which has resulted in the approval of only five additional health claims since the legislation was passed in 1990, the DSHEA has resulted in a large, yet undetermined number of dietary supplement structure/function claims.

More important, however, to circumvent the complex, costly, and lengthy process associated with health claim approval under the NLEA, certain companies have attempted to market functional foods as dietary supplements, the most notable example being Benecol margarine. The manufacturer initially attempted to offer this product as a dietary supplement, which therefore would be permitted to have on its label structure/function claims related to heart health without undergoing the health claims authorization process required by the NLEA. The FDA blocked this effort (Brewster 1998), however, and the manufacturer took the necessary steps to obtain a health claim approved for plant stanol esters, for which an interim final rule was issued on September 8, 2000 (USFDA-DHHS 2000b).

The Food and Drug Administration Modernization Act of 1997

The third significant change in food regulations took place when Congress enacted the

FDAMA in 1997 to facilitate the health claims approval process and thus to expedite for consumers the availability of health information on package labels. This legislation enables the use of so-called “authoritative statements” on food labels as health claims, without FDA preapproval (USFDA 1997). Such statements must be published by specific U.S. government bodies responsible for the protection of public health, such as the National Institutes of Health (NIH), the Centers for Disease Control and Prevention, or the National Academy of Sciences. Food manufacturers intending to use authoritative statements as health claims must notify the FDA at least 120 d before marketing a product bearing the claim, and the FDA must prohibit or modify the claim within that time frame. To date under the FDAMA, two nutraceutical-related health claims—(1) for whole grains in the reduction of risks for heart disease and cancer, and (2) for potassium in the reduction of risks for high blood pressure and stroke—have been authorized based on authoritative statements from the National Research Council’s 1989 publication *Diet and Health Implications for Reducing Risk of Chronic Disease* (NRC-FNB 1989).

Consumer advocacy groups have recommended that the FDA prohibit companies from marketing functional foods containing nutraceuticals as dietary supplements and that the agency issue regulations controlling structure/function claims for foods (International Association 1999). Although the FDA issued final regulations governing structure/function claims for dietary supplements on January 6, 2000 (USFDA-DHHS 2000a), the line between dietary supplements and foods remains blurred. The regulation of functional foods in the United States, as well as in other countries where such products are being developed, will continue to be a source of debate for years to come.

Regulation of Nutraceuticals

Many countries are struggling with how to regulate nutraceuticals, or at least how to regulate what can be said about nutraceuticals on product labels or in advertising. Japan is the only country with a formal regulatory system allowing approved health benefit claims to be made for functional foods. Known as Foods for Specified Health Use (FOSHU), such products are eligible to bear a special logo, accompanied by a statement that they

have the endorsement of the Ministry of Health and Welfare (Arai 1996). Currently, more than 300 FOSHU products are on the market in Japan.

In Canada, the term *nutraceuticals* has been included in a new legislative category called natural health products. Writing in 1998, Stephen proposed that *functional foods* be defined as foods that resemble traditional foods but provide benefits beyond what is expected of them nutritionally. In late 2001, Health Canada announced that under the current Canadian Food and Drugs Act permitting health claims for foods, a new regulatory definition of functional foods would not be required. In Canada, the term functional foods is used extensively to describe foods that have demonstrated physiological benefits, and/or that decrease the risk of chronic disease while fulfilling basic nutritional functions. Harmonization of definitions and labeling practices among U.S. trading partners may become an important trade issue within the next few years. The European Union currently is seeking harmonization of health claim regulations.

SAFETY ISSUES

Although significant evidence exists that functional foods and nutraceuticals can play key roles in disease prevention and health promotion, as in decreasing the risk of certain chronic diseases, safety considerations must not be ignored. Specifically, safety concerns have been raised recently with regard to the addition of botanicals to foods. Many “functional” bars, beverages, cereals, and even soups are being enhanced with botanicals. The safety issues related to herbs are complex, and herb-drug interactions are receiving increasing attention. St. John’s wort, for example, has been shown to interact with or to diminish the efficacy of certain widely used prescription medicines such as cyclosporin, digoxin, and anticonvulsants (Barnes, Anderson, and Phillipson 2001). As a result, the FDA issued a Public Health Advisory about St. John’s wort in February 2000.

Consumer groups also have questioned the process for ensuring safety of dietary supplements and functional foods containing nutraceuticals. In July 2000, the Center for Science in the Public Interest held a press conference urging the FDA to halt the sale of 75 functional foods enhanced with popular botanicals (Center for Science in the Public Interest 2000). That press conference followed soon

after the release of a General Accounting Office (GAO) report that also raised concerns about the safety of functional foods (USGAO 2000). The GAO report stated that the FDA “has not developed regulations or provided guidance to companies on the type of safety-related information that should be included on their labels for functional foods and dietary supplements. The absence of such safety information poses a significant safety risk to some consumers” (USGAO 2000, p. 17). The GAO recommended that the Commissioner of the FDA take these steps to ensure the safety of dietary supplements and functional foods:

- develop and promulgate, for use by the industry, regulations or other guidelines regarding the evidence needed to document the safety of new dietary ingredients in dietary supplements;
- develop and promulgate, for use by the industry, regulations or other guidelines regarding the safety-related information required on labels for dietary supplements and functional foods; and
- develop an enhanced system of recording and analyzing reports of health problems associated with functional foods and dietary supplements (USGAO 2000, p. 29)

In 2001, the FDA issued warning letters to the food industry regarding the marketing of conventional foods containing novel ingredients, including botanicals. The FDA expressed concern that these ingredients were neither approved food additives nor generally recognized as safe (GRAS) for the uses to which they were being put (USFDA 2001). Safety and efficacy as well as the determination of dose-response relationships for nutraceuticals and functional food ingredients must be considered carefully if such products are to become effective tools for maximizing health and decreasing disease risks in consumers.

SCIENTIFIC BASIS FOR EFFICACY

Types of Research

Technological advances in testing methods, such as immunoassays and gene arrays, permit rapid and relatively inexpensive screening of chemicals and food/botanical extracts for *bioactivity* within the narrow scope of each assay. The relevance of these new methods to *in vivo* issues

(those in living animals or humans) such as absorption and *pharmacokinetics* cannot be determined for many such assays. Nevertheless, press releases regularly extol the virtues of products for health benefits based on *in vitro* research (i.e., model “test-tube” environments). Animal studies provide information about safety and efficacy, but species differences can limit applicability to humans.

Studies involving humans are not without their own challenges. Inadequate controls, insufficient populations, and a host of other limitations exist. Additionally, most human research fails to evaluate multiple health benefits—for example, consumption of a certain food may prevent both cardiovascular disease and cancer. Nutraceuticals may offer a benefit to one group of individuals, but in other populations any benefit or risk will depend on lifestyle and genetic risk for disease. For example, soy nutraceuticals may protect adult women from certain cancers and undesirable effects of menopause and may protect older men from prostate disorders. Both genders may have decreased risks for cardiovascular disease when adequate amounts of soy are consumed.

The European Community has developed guidelines for research on functional foods (Diplock et al. 2000), and the U.S. Federal Trade Commission has provided manufacturers with information about the types of research needed to support advertising claims. The FDA (2003) plans to classify research studies submitted for food and

dietary supplement health claims based on minimizing bias and achieving a “level of comfort.” Claims also will be evaluated for the numbers of studies reported, the consistency of findings among studies with similar experimental designs, and the relevance to disease risk reduction in either the general population or in a target subgroup of the U.S. population.

Source of Biological Activity

Humans consume few pure chemical compounds, because foods can contain hundreds of chemicals. Table 4 provides examples of nutraceutical compounds in foods. Nutrition research in the twentieth century uncovered the role of vitamins and minerals in the prevention of basic nutrient deficiencies; yet, how nutrients work together in the body for optimal health is understood only partly, as is how nonnutrient food chemicals affect health. Experiments that focus on doses of single compounds may underestimate or overestimate the health benefits of those compounds when combined with others.

One barrier to improved understanding of how nutraceuticals aid health is the lack of suitable *biomarkers* for certain health conditions. Although most consumers and medical personnel are familiar with biomarkers such as serum cholesterol as a predictor of risk for cardiovascular disease, simple tests are not yet available commercially to identify predictors of risk for many other diseases.

Table 4. Examples of popular foods and their nutraceuticals

Food	Nutraceutical(s)
Broccoli	Sulfurophane and other glucosinolates
Carrots	Carotenes, anthocyanins, lycopene
Cranberries	Anthocyanins, flavonoids, tannins
Dairy foods	Conjugated linoleic acid (CLA), lactoferrin
Fatty fish (salmon, mackerel) and fish oil	Long-chain omega-3 (n-3) fatty acids
Flaxseed	Lignan, omega-3 (n-3) fatty acids
Garlic	Allicin and related sulfur-containing compounds
Onions	Organosulfur compounds, quercetin, anthocyanins
Peppers	Carotenes, quercetin, luteolin
Soybeans	Isoflavones and soy protein
Teas (green and black)	Catechins, theaflavins, thearubigins
Tomatoes	Lycopene

Academic and Industry Partnerships

Today's market for nutraceuticals contains primarily fresh or processed fruits, vegetables, and other food plants, as well as specialized animal products. Research and development is increasing rapidly at both universities and private companies, as is the development of public and private partnerships. Several universities have created centers that partner with farmers and food processors to undertake research and outreach activities. As a result, the commercialization of new nutraceutical products is increasing. Extracts from foods and herbs promising potential health benefits are being evaluated in capsules or in other forms as dietary supplements.

ANALYTICAL AND PROCESSING ISSUES

The synergistic and antagonistic effects of nutraceuticals and nutrients should be considered. The chemical nature, bioactivity, and bioavailability of many nutraceutical compounds are affected by processing. For example, isoflavones are released from their sugars during soy sauce production or may be lost during preparation of tempeh and tofu (Hendrich and Murphy 2001). Similarly, during fermentation of green tea leaves in the production of black tea, catechins are converted to thearubigins and theaflavins; the resulting chemicals have very different bioactivities from those of their parent compounds. Although the bioavailability of lycopene is improved by the processing of tomatoes into paste and ketchup (Bruno and Wildman 2001), many other processing operations lead to loss of active components, such as that of vitamin C from fruits and vegetables. Vegetable oil processing leads to the loss of vitamin E (Albanes and Hartman 1999) and sterols, as well as to the loss of carotenoids and phospholipids, many of which are recovered in distillates and sold as dietary supplements. But many processing effects remain unknown.

To complicate things further, lack of standards and uniform validated methodologies can make the comparison of results from one laboratory to another very difficult, if not impossible. Although a nutraceutical may be consumed, it may not be absorbed fully. Moreover, benefits derived from the nutraceutical may be ascribed not to the dietary source but to a *metabolite* of it. All these unknowns challenge scientists engaged in this field

of research and development.

The interactions of nutraceuticals with one another, as well as with drugs and nutrients, constitute another important topic of research. Dietary supplement research is evolving to emphasize proprietary blends of nutraceuticals so that manufacturers can obtain the greatest benefits from their investments, yet research models for demonstrating the improved efficacy of mixtures are rare.

Analytical Procedures for Antioxidants

One broad group of chemical compounds responsible for disease prevention and health promotion in humans may be referred to collectively as *natural antioxidants*, which include phenolic and polyphenolic compounds in plants, as well as tocopherols, tocotrienols, carotenoids, and vitamin C (Croft 1999; Shahidi 1997). Establishing uniform and standardized analytical procedures to allow quantification of *antioxidants* is still needed, and comprehensive assessment of complementary biochemical activities of antioxidants has been difficult. When consumed, phenolics act in the body by several mechanisms to prevent the adverse effects associated with the action of free radicals. Free radicals and reactive oxygen species are known to play a role in the onset and progression of several diseases, including atherosclerosis, ischemia of the heart and brain, arthritis, cancer, and diabetes, as well as in radiation damage, infection, and aging (Kehrer and Smith 1994; Shahidi 1997). Not all known antioxidants are phenolic in nature, however. For example, beta-carotene and related compounds as well as aromatic amino acids also are antioxidants (Halliwell and Gutteridge 1999). In healthy individuals, antioxidant enzymes neutralize free radicals, but in the elderly and the disease-stricken, the need for consumption of dietary antioxidants may be greater.

PLANT PRODUCTION ISSUES

Plant scientists working on improving fruits and vegetables for high uniform concentrations of phytochemicals have observed that quantities differ significantly between varieties and between plants within varieties. For instance, white onions contain almost no quercetin, whereas red or yellow onions may contain low to very high amounts (Figure 3) (Patil, Pike, and Yoo 1995). Plant maturity, location, and other environmental conditions also

affect quercetin concentration (Patil, Pike, and Hamilton 1995).

Similar findings have been reported for different phytochemicals in other crops. Peppers may contain ascorbic acid ranging from very low concentrations to amounts higher than those in oranges. Grapefruit may be rich in lycopene or contain almost none. Certain carrots have little carotene and no anthocyanins, and other cultivars contain high concentrations of both types of phytochemicals. Scientists in the field of plant development have an excellent opportunity to improve food crops genetically, through traditional breeding or by genetic engineering, to contain higher, more uniform concentrations of known nutritional and health-promoting nutraceuticals.

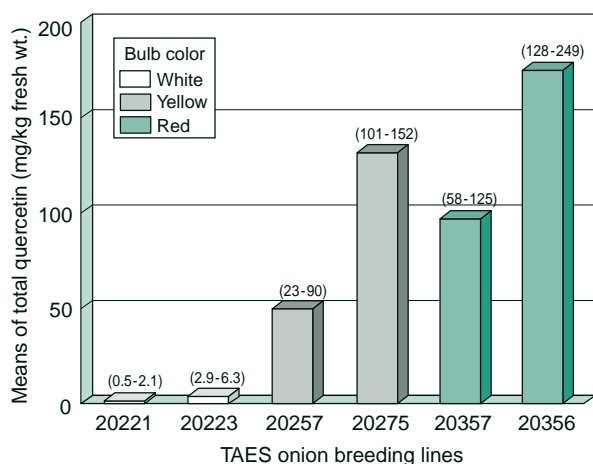


Figure 3. Average concentration of quercetin in different lines (cultivars) of onions. Shown in parentheses are the minimum and maximum levels of quercetin concentrations found in an analysis of 8 white, 22 yellow, and 6 red onion breeding lines developed at the Texas Agricultural Experiment Station (TAES).

ANIMAL PRODUCT ISSUES AND OPPORTUNITIES

Although attention has been focused on the development of functional foods from phytochemicals derived from plant products, numerous opportunities exist to develop similar food products from meat, dairy, poultry, and marine food ingredients.

Foods can be designed from animals to create nutritionally modified food products that improve human health or decrease human risk of disease;

this technology is receiving increasing attention in the animal production industry. The industry is positioned to take the lead in making designed animal products because of the perceived enhanced role that food and food ingredients play in disease prevention and because of the increased consumer demand and need for foods that benefit health. Interests in improving the quality of life for the expanding older population and in decreasing the costs of health care and disease treatment have contributed to the development of designed animal foods.

Benefits of Animal-Based Nutraceuticals

Two examples of nutraceuticals under study for their possible health benefits are provided here. *Conjugated linoleic acid* (CLA), which is found predominantly in dairy products and red meat, has generated recent interest among obesity and cancer researchers. An NIH conference titled “Perspectives on Conjugated Linoleic Acid Research: Current Status and Future Directions” was held in May 2002 to address the benefits of this fatty acid (NIH 2002). Conjugated linoleic acid seems to be important in the modulation of many biochemical and physiological processes that may decrease the risk of cancer, heart disease, and other types of inflammatory responses (Watkins and Li 2001); yet, questions have been raised regarding its potential to increase insulin resistance and inflammation in obese men (Riserus et al. 2002).

Fish oils are another source of lipids with health-promoting activity. Although omega-3 (n-3) fatty acids can be found in certain plant foods, fatty fish such as salmon, herring, and sardines are especially rich sources of the longer-chain eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. Researchers who conducted an American Heart Association (AHA) review concluded that supplementing the diet with 0.5 to 1.8 g of these fatty acids per day, either from fish or from fish oil dietary supplements, decreased the risk for subsequent cardiac events in persons who had suffered a previous heart attack (Kris-Etherton, Harris, and Appel 2002).

Dosages for other health benefits are less clear and must be balanced with the risk of heavy metal and other environmental pollutants. Although the AHA review considered dietary sources of n-3 fatty acids as most desirable, the authors

acknowledged that daily doses of over 1 g could not be met easily through food alone. Opportunities exist, however, to increase the amounts of these fatty acids in more common foods that have not been traditional sources of these fats.

Improvement and Impact of Modified, Processed Animal Foods

Because of its implications in cardiovascular disease, stroke, and, more recently, cancer, one of the first animal food constituents altered by the food industry was fat. Food scientists and human nutritionists introduced low-fat foods, which led to a decline in consumption of foods rich in saturated fatty acids. The quality of beef, pork, and poultry products was improved through genetic selection, specifically through the selection of animals that were less fat and more efficient at converting nutrients to lean mass. Fluid milk was improved from a health point of view with the introduction of low-fat products and by fortification with vitamin D, which increased the bioavailability of calcium.

Regrettably, these low-fat foods have not deterred the rising incidence of obesity in the United States. In addition, eating less animal fat and more plant oil has increased the ratio of omega-6 (n-6) to n-3 polyunsaturated fatty acids (PUFAs) in the human diet, which, according to biochemical data, favors inflammatory responses contributing to cardiovascular disease, certain cancers, and bone disease (Calder and Grimble 2002). Processed foods and hydrogenated vegetable oils also contain fewer n-3 fatty acids and may contribute to the aforementioned inflammatory processes. The relationship between dietary fat and chronic disease suggests that both total fat and fat type influence disease risk. A movement to introduce more foods with greater amounts of n-3 PUFAs, or with a lower ratio of n-6:n-3 fatty acids, is supported by nutritionists, the medical community, and the food industry. In addition to the opportunities provided by designed foods from animal products, postprocessing methods provide the means of making a variety of functional foods from meat, dairy, and poultry ingredients.

For reasons of simplicity and cost efficiency, modern animal rations contain a limited number of different types of ingredients. In contrast, 50 yr ago, poultry was fed fishmeal, and other food animals were fed fish by-products. As farmers

switched to feeds that did not contain fish, the n-3 content of poultry, pork, and beef declined. Omega-3 concentrations now can be restored in meat, eggs, and fish by feeding animals small amounts of flaxseed- and algae-derived n-3 fatty acids.

Animal products enriched with different types of fatty acids and vitamin E resulting from feeding these nutrient sources to animals have been marketed successfully in the United States, Canada, Europe, and Australia. These designed foods are beginning to change the way people eat. Designed table eggs containing a significant amount of n-3 fatty acids are marketed widely in the United States, Canada, Australia, and Europe. Dairy products with active microbial cultures, such as probiotics in yogurt and acidophilus milk and drinks, have been quite successful in Europe and Japan, as well as in the United States.

Future Designed Foods

Dietary fats, phytochemicals, and antioxidants have been identified as having the potential to decrease the risks of cancer and heart disease. The real issue now is to identify how these ingredients act at the cellular level. Cyclooxygenase 2 is an enzyme responsible for the inflammatory process associated with various cancers and joint disease. Opportunities exist to design foods to modulate the activity of this enzyme. Modifying the fatty acid composition of animal products can be accomplished easily by dietary means, but this type of modification occurs more readily in nonruminant animals. Designed foods include animal products that contain a modified nutrient or health protectant directly beneficial to human health. Because it is unclear how these health protectants affect cell activity and influence disease risk, additional research is needed so that beneficial labeling claims can be made and supported for the health-protectant and nutraceutical ingredients in these new foods.

Some of the first designed foods should increase n-3 fatty acids to the human diet, to balance the ratio of n-6 to n-3 fatty acids. Perhaps in the near future the health benefits of CLA will be better understood, and the amounts of CLA in dairy products and red meat will be increased so as to decrease human risk for cancer, heart disease, osteoporosis, and inflammatory diseases. The cre-

ation of new designed foods also will involve examining raw materials and modifying nutritionally fortified, processed animal products containing nutraceuticals and other health protectants.

CONSUMER EDUCATION

A quick scan of newspaper headlines and popular magazine covers invariably reveals stories describing new findings regarding certain foods or food components and health. Certain stories may highlight the benefits of that food, whereas others may focus on the harmful effects or the lack of benefits shown in research studies. Health benefits of nutraceuticals must be communicated clearly to consumers and health professionals. Perceived “quick fixes” such as special diets and supplements may be more appealing to certain consumers than would be conventional dietary advice such as “eat a variety of foods in moderation.” Certain nutraceuticals may offer benefits only in combination with exercise or other lifestyle changes. For other products, effective and safe doses are not yet known. For example, with regard to n-3 fatty acids, an occasional egg enriched with n-3 fatty acids might not offer much protection against heart disease for an overweight person who smokes and makes no other dietary and lifestyle changes.

Are nutraceuticals necessary for maintaining good health? A federal report concluded that improved efforts to educate Americans about the value of fruits and vegetables in the diet could improve health significantly (USGAO 2002). Persons with lower incomes, who may be at greater risk for chronic diseases, may consider conventional foods more affordable and accept them more easily than specially formulated foods or supplements. A recent study reviewed diet records from nearly 106,000 health professionals, and the Healthy Eating Index developed by the USDA was not found to be an accurate predictor of chronic disease risk (McCullough et al. 2002). The researchers concluded that consumers could achieve improved risk rates for chronic diseases, especially for cardiovascular disease, if they received more specific and comprehensive dietary advice.

A 1989–1990 USDA analysis of diet records revealed that 40% of household meal planners or preparers perceived their diet to be of higher quality than the calculated nutritional value indicated (Variyam, Shim, and Blaylock 2001). Additional

research is needed to establish whether consumers today realistically evaluate their own diets; false optimism about nutraceuticals could diminish significantly the impact of any nutrition education program.

Over the past few years, certain major food companies have introduced nutraceutical product lines that have, in general, been economic failures. Although the extent of financial losses for these products is unknown, the U.S. food industry could be spared further losses if consumer markets for nutraceuticals were better understood. For example, how do consumers balance taste, cost, and nutritional benefits when selecting foods and dietary supplements? Once they were provided with information about the health benefits of cranberry juice and the amount of cranberry juice present in blends with white grape juice, women liked the more acidic-tasting blend containing 41% cranberry juice as much as the blend with 27% cranberry, which is typical in the market (Ghazanfar and Camire 2002). Successful examples of nutraceutical product launches do exist. Tropicana invested in consumer research and targeted marketing before launching calcium- and vitamin C-fortified orange juice (Green 1999). Calcium-fortified foods have generally fared well, as have many new soy products.

RESEARCH NEEDS

Clearly, the topic of nutraceuticals is multidisciplinary, and additional information is needed in the pursuit of both basic science and applied technology. How this information void is to be filled is unclear. Industry-funded research may be focused so narrowly on proprietary information that extrapolation to whole foods or extracts is impossible, as in the instance of European testing for botanical preparations. The USDA focuses research funding toward disease prevention, rather than treatment. The NIH traditionally has not funded studies involving whole foods and dietary approaches to therapy because the experimental designs for such studies may not follow conventional randomized, double-blind, placebo-controlled designs such as those used for drug therapies. It is indeed difficult to create a placebo that mimics a food without the health benefits of that food. For 2 yr, the USDA did fund functional food research through its Initiative for Future Agricul-

ture and Food Systems program; however, funding for that program was cut in 2001. Cooperation among federal agencies may be necessary to ensure that nutraceutical research needs from farm to table or medicine cabinet are met.

RECOMMENDATIONS

Policy

- Legally define the term *nutraceuticals* to provide guidance to the industry and to decrease consumer confusion.
- Clarify the process for documenting the health benefits of nutraceuticals.
- Increase research funding for both basic and applied studies related to nutraceuticals.
- Establish new funding categories and expand existing ones for nutraceuticals within USDA and NIH competitive grant programs.
- Improve communication of nutraceutical benefits and risks to consumers.

Research

- Examine interactions, both beneficial and adverse, with other nutraceuticals, nutrients, and drugs.
- Identify benefits of nutraceuticals for specific human populations.
- Devise appropriate standardization protocols for evaluating nutraceuticals and health-protectant chemicals.
- Identify appropriate human biomarkers to evaluate the effectiveness of dietary nutraceuticals.
- Gain more understanding of factors affecting the bioavailability of nutraceuticals.
- Develop guidelines for producers to enhance nutraceutical benefits of their crops or animals without compromising sensory quality and cost effectiveness.
- Devise technologies to inhibit nutraceutical degradation in foods during processing and storage.
- Gain an improved understanding of educational and psychological barriers to consumer adoption of nutraceuticals.

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