



November 01, 2004

Ms. Leila G. Saldanha
Department of Health and Human Services
c/o Office of Dietary Supplements
6100 Executive Blvd, Room 3B01, MSC 7517
Bethesda, MD 20892-7517

RE: Bioactive Food Components Definition

Dear Ms. Saldanha:

Wine Institute, the association of California wineries, is pleased to submit written comments in response to the "Solicitation of Written Comments on a Proposed Definition of Bioactive Food Components" requested by the Department of Health and Human Services (Federal Register, September 16, 2004, 49 FR 55821). Wine Institute is the public policy trade association of California wineries.

Wine Institute and its 800 California wineries and affiliated businesses are dedicated to initiating and advocating state, federal and international public policy to enhance the environment for the responsible consumption and enjoyment of wine. Since its beginning in 1934, Wine Institute has worked to create a climate in which California's wine industry could thrive and prosper. Today, our membership produces more than 80 percent of the nation's wine and is responsible for 90 percent of U.S. wine exports.

The attachment which accompanies this letter primarily address the first of four questions posed in the notice, i.e, **What categories/classes of compounds should be considered as bioactive food components?**

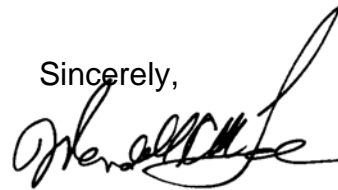
Additionally, we would like to make you aware of our comments in May of 2004 to the Advisory Committee charged with the review of the current scientific literature on the moderate consumption of wine, beer and distilled spirits and development of the 2005 *Dietary Guidelines for Americans*. One of the highest priorities in that submission was **Antioxidants and Wine Compounds**. We state in our comments:

As Wine Institute stated in our submission for the 2000 Dietary Guidelines, we believe that the scientific information on dietary phenolic compounds found in fruits and vegetables, and several beverages, warrants acknowledgement. Since 2000, there has been additional scientific research in the area of dietary antioxidants and their suggested role in health maintenance and disease prevention.

We request that the Advisory Committee expand the current listing of “essential vitamins and minerals, fiber, and other substances that are important for good health” found in the section “Choose a variety of fruits and vegetables daily” to include phenolic compounds. Second, we would like to recommend that the Committee expand the discussion of “other substances” found in fruits and vegetables and their role in disease prevention by addressing the emerging research on phenolic compounds. Third, we suggest that the Committee consider including grapes in addition to other dietary sources for these compounds. An explanation of the current research on the potential health effects of flavonoids and phytochemicals (such as resveratrol) is warranted as these compounds are found in common dietary staples such as apples, nuts, onions, grapes, blueberries, wine and tea.

We appreciate the efforts of the Office of Disease Prevention and Health Promotion and the ad hoc federal working group for bringing forth this issue for public comment. We believe a strong commitment to research both here in the United States and internationally will result in a better understanding of these compounds and their role in disease prevention and health maintenance.

Sincerely,

A handwritten signature in black ink, appearing to read "Wendell C. Lee". The signature is fluid and cursive, with a large initial "W" and "L".

Wendell C. Lee
General Counsel, Wine Institute

Enclosure

Wine Institute Comments – Attachment 1 of 1

Bioactive Food Components Definition

The following pages will review several of the key issues with regard to specific compounds, mechanisms for suggested health effects and examples of current research that demonstrates the growing consensus by the international scientific community.

Review of Specific Compounds

A phytochemical is a natural bioactive compound found in plant foods that works with nutrients and dietary fiber to protect against disease. Research suggests that phytochemicals, working together with nutrients found in fruits, vegetables and nuts, may help to slow the aging process and reduce the risk of many diseases, including cancer, heart disease, stroke, high blood pressure, cataracts, osteoporosis, and urinary tract infections.

Phytochemicals can have complementary and overlapping mechanisms of action in the body, including antioxidant effects, modulation of detoxification enzymes, stimulation of the immune system, modulation of hormone metabolism, and antibacterial and antiviral effect.

The following represent several compounds and groups of compounds we recommend be considered as bioactive food components.

Flavonoids

Flavonoids are a large family of protective phytochemicals found in fruits and vegetables. Flavonoids, also called bioflavonoids, act as antioxidants. Antioxidants neutralize or inactivate highly unstable and extremely reactive molecules, called free radicals that attack the cells of our body every day. Free radical damage is believed to contribute to a variety of health problems, including cancer, heart disease and aging. There are many different types of flavonoids and each appears to have protective health effects. Some of the better known flavonoids include resveratrol, anthocyanins, quercetin, hesperidin, tangeritin, kaempferol, myricetin, and apigenin. Flavonoids are found in a variety of foods such as oranges, kiwifruit, grapefruit, tangerines, berries, apples, red grapes, red wine, broccoli, onions, and green tea.

Resveratrol

Resveratrol may reduce the risk of heart disease, cancer, blood clots and stroke. Red grapes, red grape juice, and red wine contain resveratrol.

Anthocyanins

Anthocyanins, which are particularly high in blueberries, have been shown to protect against the signs of aging. In one study, elderly rats ate the equivalent of a half-cup of blueberries daily for eight weeks and improved balance, coordination, and short term memory. Scientists think these results may apply to humans as well.

Quercetins

Quercetins may reduce inflammation associated with allergies, inhibit the growth of head and neck cancers, and protect the lungs from the harmful effects of pollutants and cigarette smoke. Apples, pears, cherries, grapes, onions, kale, broccoli, leaf lettuce, garlic, green tea, and red wine contain quercetins.

Phenolic Compounds

Phenolic compounds may reduce the risk of heart diseases and certain types of cancer. Phenolic compounds may be found in berries, prunes, red grapes and red grape juice, kiwifruit, currants, apples and apple juice, red wine, and tomatoes.

Ellagic Acid

Ellagic acid is a phenolic compound that may reduce the risk of certain types of cancer and decrease cholesterol levels. Ellagic acid is found in red grapes, kiwifruit, blueberries, raspberries, strawberries, blackberries and currants.

General Overview

Phenolic compounds, commonly referred to as polyphenols, are present in all plants and, thus, are in the diet. Flavonoids are the most common and they can be categorized into 13 classes comprising more than 5,000 compounds. Although polyphenols are present in virtually all plant foods, their levels vary enormously among diets depending on the type and quantity of plant foods in the diet. There also can be marked variability in the polyphenolic compounds within a food based on genetic factors and environmental and processing conditions. Red wine is a rich and concentrated source of polyphenolic substances and over 200 individual phenolic compounds had been

identified as of the year 2000. Studies have shown that red wine inhibits oxidation of LDL in vitro and increases antioxidant capacity of plasma. Catechin is one of the most abundant phenolic compounds in red wine and the flavonol quercetin has also been identified. All of these phenolic compounds have antithrombotic effects that appear to be the result of reduced susceptibility of platelet aggregation, reduced synthesis of prothrombotic and proinflammatory mediators, decreased expression of adhesion molecules, and tissue factor activity. In addition, there is some evidence that wine polyphenols can modulate the production of nitric oxide by the vascular endothelium, resulting in vasorelaxation. Several population studies have reported an inverse association between flavonoid intake and risk of coronary heart disease. (Kris-Etherton et al, 2002)

Review of Mechanisms for Health Effects

An independent review of recent scientific literature by Parks and Booyse supported by the Wine Institute as part of our Dietary Guidelines submission concludes, ..."the majority of the prospective cohort studies demonstrate an inverse association between alcohol and/or polyphenol consumption and cardiovascular risk. In spite of the considerable persuasive epidemiological data demonstrating a strong relationship between moderate alcohol or wine consumption and protection from cardiovascular disease, the precise cellular and molecular mechanisms underlying the cardiovascular protection remain incompletely defined. Moderate consumption of alcohol or wine components can exert diverse biological effects on heart muscle, vessels and blood components that may act in combination or perhaps synergistically to reduce the risk for CHD mortality. The complexity and varied nature of the alcohol and wine component-induced biological effects will require continued research effort to identify and define these cardioprotective effects at the cellular, molecular and gene levels". (Parks and Booyse, 2004)

Examples of Scientific Research Findings

Recent published scientific reports continue to provide a growing body of knowledge in this area both in terms of mechanisms and the relationship to health effects. The following examples demonstrate the scope of this work.

A review of close to 70 research studies from around the world found that the major biological activities of the wine compound, resveratrol, include inhibition of lipid peroxidation, chelation of copper, free-radical scavenging, alteration of eicosand synthesis, inhibition of platelet aggregation, anti-inflammatory activity, vasorelaxing activity, modulation of lipid metabolism, anti-cancer activity and estrogenic activity (Fremont, 2000)

Dutch researchers reviewed the biological mechanisms and clinical applications of flavonoids, which occur naturally in fruit, vegetable and beverages such as tea and wine. Mechanisms covered include antioxidative eddects, radical scavenging, nitric oxide and interaction with other enzyme systems. Clinically, flavonoids have been shown to have anti-atherosclerotic, anti-inflammatory, anti-tumor, anti-thrombotic, anti-osteoporotic and anti-viral effects. They conclude, "Currently, the intake of fruit, vegetables, and beverages (e.g. tea and moderate amounts of red wine) containing flavonoids is recommended, although it is too early to make recommendations on daily flavonoid intakes" (Nijveldt et al, 2001).

Researchers investigated whether individual red wine phenols affect the fibrinolytic system, given that the promotion of fibrinolysis is likely to be a cardioprotective mechanism. They conclude, "Wine phenolics increase fibrinolytic activity, independent of ethanol, and it is likely that the overall cardioprotective benefits associated with moderate red wine consumption are attributable to the combined, additive, or perhaps synergistic effects of alcohol and other wine components" (Abou-Agag et al, 2001).

Researchers in New York and China provided an overview of the broad spectrum of biological effects of resveratrol. The numerous studies summarized include findings on resveratrol's defense against oxidative stress and inflammation, inhibition of cell proliferation and modulation of cell signaling events. They also discuss the issue of absorption, noting that biological response appears to require more than just acute ingestion of resveratrol, and that future results require further in vivo studies with human models. They conclude, "The beneficial effects of red wine or resveratrol may be attributed to its antioxidative, antiplatelet aggregation, anti-inflammation, vasorelaxing activities as well as abilities to inhibit SMC [smooth muscle cell] and EC [endothelial cell] proliferation" (Wu et al, 2001).

Some antioxidant phenols present in extra virgin olive oil, such as tyrosol and caffeic acid, have also been found in white wine. Their antioxidant properties are known but their biological effects have not yet been elucidated. Study results show that, "Low concentrations of these phenols, which can be found in the bloodstream after intake of moderate quantities of white wine, exert significant inhibitory activity on the release of several inflammatory cytokines" (Bertelli et al, 2002).

"The mechanisms through which the consumption of alcoholic beverages, in particular wine, protects against cardiac and vascular diseases remain largely unexplored. Several groups are now beginning to use animal models of myocardial ischemia and reperfusion to explore whether certain nutrients, including ethanol and non-ethanolic components of wine, may have a specific protective effect on the myocardium, independently from the classical risk factors involved in vascular atherosclerosis and thrombosis" (De Lorgeril et al, 2003).

A recent report investigated the relationship of alcohol consumption to risk of prostate cancer in men. While no clear association in risk was seen for total alcohol consumption, each additional glass of red wine consumed per week showed a

statistically significant 6 percent decrease in relative risk and there was evidence for a decline in risk estimates across increasing categories of red wine intake. (Schoonen et al, 2004).

In September 2004, researchers funded by the National Science Foundation (NSF) and affiliated with the Salk Institute in San Diego, CA have succeeded in converting chalcone synthase, a biosynthetic protein enzyme found in higher plants, into an efficient resveratrol synthase. Resveratrol, a beneficial component of red wine, is thought to contribute to the improved cardiovascular effects associated with a moderate consumption of red wine. (Austin MB et al, 2004)

Laboratory studies with resveratrol have demonstrated an impressive list of health benefits, including roles as antioxidants, cancer preventing agents, blood thinners and blood pressure-lowering compounds. Resveratrol was recently shown to increase life span in fruit flies and yeast, suggesting an additional role in our diets as a promising anti-aging natural chemical. (Royner S, 2004)

Please find attached the review by Parks and Booyse commissioned by Wine Institute for inclusion with our submission to the Dietary Guidelines Advisory Committee as well as a table of scientific research studies published between the years 2000 and 2004.



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