Scientific Standards of Evidence for Development of Dietary Guidance and/or Substantiation of Structure/Function Claims for Dietary Bioactives

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Abstract

Dietary bioactive foods and ingredients are becoming increasingly popular due to a growing body of scientific research suggesting potential effects on human health. The food and nutrition scientific communities have struggled to deliver consistent scientifically substantiated messaging regarding health effects of dietary bioactive compounds in part due to their absent role in U.S. nutrition policy. Manufacturers and special-interest groups are in need of a guiding framework that outlines the level(s) of scientific evidence needed to substantiate health messages and product claims, particularly in regard to structure/function claims. Health professionals and consumers ultimately benefit from consistent dietary guidance that is based on rigorous and up-to-date research. This perspectives piece is meant to explore how current and recently proposed frameworks for standards of evidence may be useful in formulating both policy-derived dietary guidance and structure/function claims on products. Consistent and reproducible measurement of a biomarker of effect among two to three small-to-medium intervention and large cohort studies coupled with data demonstrating biological plausibility may be appropriate for validating structure/function claims, whereas more rigorous frameworks indicating dose response may be needed to qualify and establish a dietary reference intake-like value for dietary bioactives.

Glossary of Abbreviations
AI: Adequate Intake
CHD: Coronary Heart Disease
CNS: Chinese Nutrition Society
CVD: Cardiovascular Disease
DRI: Dietary Reference Intake
DSHEA: Dietary Supplement Health and Education Act
FDA: Food and Drug Administration
IOM: Institute of Medicine
SPL: Specific Proposed Level
UL: Tolerable Upper Intake Level

Introduction

The ability to develop effective public policy and consistent messaging to better achieve health promotion and disease prevention goals depends on the availability of valid and reproducible scientific evidence. There is general agreement within the fields of food, nutrition and medical sciences that an individual's diet and lifestyle choices can substantially predispose or protect one against many age- and obesity-related chronic diseases. Over the past two decades, there has been an ongoing international dialogue whether public health recommendations can be expanded to include dietary bioactive foods and ingredients that may pose health effects beyond basic human nutrition. In the United States, manufacturers can communicate health effects of dietary bioactives directly to the consumer via various types of label claims; structure/function claims are arguably the most utilized type of label claim present on foods and dietary supplements. The level of publically available research used to substantiate a structure/function claim is often variable among manufacturers, compared with that used in standard submission of a health claim. Although manufacturer labeling of structure/function claims for essential nutrients may have similar drawbacks in regard to scientific rigor, dietary bioactives pose a unique dilemma of having no current role in nutrition policy and leaving additional room for inconsistent and often misleading messaging among products. It is evident that processes for substantiation of health effects derived from the intake of dietary bioactives needs development and and/or harmonization on a global level. In the absence of public health recommendations, there is no standardized evidence-based process to provide consensus messages for training public health professionals and in turn for manufacturers to convey consistent public health messages via structure/function claims to consumers.[1] Manufacturers and special interest groups need to know what levels of evidence must be collected to support both dietary reference intake (DRI)-like evaluation and structure/function claims on products. Consumers need simple, clear and consistent messaging

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from all sectors of the scientific community that is grounded on up-to-date research. This perspectives piece is meant to better explore how existing frameworks for nutrients and recently proposed frameworks for dietary bioactives may be in part or fully employed to guide both policy-derived dietary guidance and structure/function claims on products.

Dietary Bioactive Compounds

The National Institutes of Health Office of Dietary Supplements has defined dietary bioactives as "compounds that are constituents in foods and dietary supplements, other than those needed to meet basic human nutritional needs, which are responsible for changes in health status."[2] Dietary bioactives are widely distributed in nature and may be considered part of a healthy diet; however, unlike essential nutrients, their absence does not result in a deficiency disorder. These compounds are generally thought to be safe in food at normal consumption levels (e.g., anthocyanins in berries). Their biological activities may be defined as a single compound (e.g., lutein in spinach) or class of compounds (e.g., avenanthramides in oats) for which optimal effects may be achieved through consumption of mixtures in which the exact identity and composition is often unknown. Classes of similar compounds are commonly found in similar types of foods; however, their composition in the whole food can vary significantly because of environmental influences such as cultivation, soil, altitude, and weather conditions. Many isolated characterized compounds as well as less characterized classes/mixtures of compounds have a substantial amount of published scientific evidence regarding their putative improvements in physiological performance and/or reduction in the risk of chronic disease. The inability to fully isolate mixtures of similar compounds creates a challenging setting for defining specific recommendations such as those available for essential nutrients. On the other hand, it may be more reasonable and practical to base intake recommendations on a mixture of a similar class of compounds that exhibit additive or potentially synergistic actions rather than select an individual defined chemical entity, given that most dietary bioactives are normally consumed as mixtures in foods and dietary supplements.[3] Table 1 describes parameters that influence the study of dietary bioactives, as adapted from Heber and Shao.[4]

Structure/Function Claims

The Food and Drug Administration (FDA) has issued a guidance document on labeling of structure/function claims[5]; however, the agency is severely limited by the current statute because these claims, unlike health claims, are not subject to premarket review by the FDA. The Dietary Supplement Health and Education Act (DSHEA) of 1994 amended the Nutrition Labeling and Education Act of 1990 to include structure/function claims for dietary supplements. The Federal Food, Drug, and Cosmetic Act defines a drug prior to DHSEA under 21 USC 321(g)(1)(c) as "articles (other than food) intended to affect the structure or any function of the body of man or other animals." The explicit exclusion of food from this piece of the statute permits structure/function claims to be made on conventional food products; thus, a conventional food only becomes a drug if it makes a disease claim.

The Role of DRIs in U.S. Nutrition Policy and Relevance to Dietary Bioactives

The DRIs are a set of common nutrient standards set by the Institute of Medicine (IOM) for use in the United States and Canada based on scientifically grounded relationships between nutrient intakes and indicators of adequacy, as well as the prevention of chronic diseases, among generally healthy populations. The DRIs are essential for assessing the nutritional adequacy of dietary intakes and may also be used to plan nutritious diets. The IOM has set nutrient standards for the United States since 1943. The framework for establishing DRIs is recognized as akin to a risk analysis, which analyzes the "risks" that may be experienced by a population of interest. In DRI development for essential nutrients, the risk is that nutrient intakes are either too high or too low. Availability of data and current research, which is often limited, informs the DRI committee deliberations. Dose-response data are key to establishment of DRIs; however, many of the existing DRIs for children have been extrapolated from adult requirements or from other age groups of children. Although this approach is necessary when requirement data are unavailable, it has led to unrealistic values for both requirements and tolerable upper intake levels (ULs) in several instances. For example, our group recently showed that over 20% of children aged 4 to 8 years have intakes above the UL for zinc (12 mg/d) as assessed by the National Health and Nutrition Examination Survey. This value increases to 30% when multivitamin-mineral supplements are also considered in this age group,[6] yet there is no evidence of zinc toxicity, seen as compromised copper metabolism, in this age group.

DRIs support many program, policy and regulatory initiatives. For example, federal guidance based on the Dietary Guidelines for Americans available to consumers through *MyPlate.gov* are related to food modeling to achieve recommended intakes of essential nutrients as defined by the DRIs. Government programs that support food assistance, such as the Supplemental Nutrition Assistance Program, the National School Breakfast and Lunch Programs, and the Special Supplementation Program for Women, Infants, and Children, require that the daily portion for that assistance meet the recommendations of the Dietary Guidelines for Americans and, therefore, the DRIs. The food label reports amounts of essential nutrients provided by a serving of that food relative to the DRIs.

Two DRI values, the adequate intake (AI) and the UL are relevant to the discussion of scientific substantiation for

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Table 1. Parameters that influence the study of dietary bioactives versus drugs and essential nutrients

Parameter	Drugs	Essential Nutrients	Dietary Bioactives
Chemically defined and well characterized	Yes, single entities	Yes, single entities	No, often complex mixtures
Essentiality	None	Essential	Unclear
Inadequacy results in disease	No	Yes	No
True placebo group	Yes	No	No
Targets	Single organ or tissue	All cells and tissues	Multiple cells and tissues
Systematic function	Isolated	Complex	Complex
Baseline status affects response to intervention	No	Yes	Unclear
Effect size	Large	Small	Small to moderate
Side effects	Large	Small	Small
Nature of effect	Therapeutic	Preventive	Preventive and therapeutic

Adapted from Heber and Shao (2011).[5]

dietary bioactives. The estimated average requirement and recommended dietary allowance, though preferred in DRI development for essential nutrients are not applicable for dietary bioactives because their absence from the diet does not result in a deficiency disorder. The AI is a recommended average daily intake level based on observed or experimentally determined approximation or estimate of intake by a group (or groups) of apparently healthy people that are assumed to be adequate. Dietary fiber is an example of a bioactive with a DRI value. In the case of total fiber, the IOM was able to set an AI based on intake levels observed to prevent coronary heart disease (CHD) as the primary endpoint and reduction in risk for diabetes as a secondary endpoint to support recommended intake levels. Epidemiological studies played a significant role in development of the AI for total fiber, providing consistent evidence that high intake of dietary fiber and fiber-rich foods reduced CHD risk. This evidence coupled with that from clinical and mechanistic studies enabled the DRI committee to determine an AI for total fiber. The AI serves as a more appropriate standard, especially for mixtures of bioactive compounds because it provides a range rather than a single definite value. The UL or highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population should continue to be utilized when defined adverse effects have been established. In the absence of sufficient evidence to define a UL, an evidence-based risk assessment or highest observed intake[7] approach may be beneficial for bioactives with a well-known safety profile where no known hazards exist.

Applying Frameworks for Communicating Benefits of Dietary Bioactives

A similar but less expensive and rigorous framework than the one used by IOM to set the AI for total dietary fiber may serve as the basis for evaluation of dietary bioactives. Anthocyanins have a similar research profile as dietary fiber. Evidence from epidemiological studies consistently supports potential preventive and therapeutic effects of dietary bioactives toward the onset of cardiovascular disease (CVD) or CVD mortality.[8-11] An inverse dose-response relationship between anthocyanin intake and CVD mortality has been shown in both men and women enrolled in the Cancer Prevention II Nutrition Cohort.[9] Clinical studies of purified anthocyanins and anthocyanin-rich extracts illustrate consistent decreases in low-density lipoprotein cholesterol among diseased individuals and/or those with hyperlipidemia,[12-15] prehypertension[16] and metabolic syndrome,[17] as well as those individuals with postmyocardial infarction.[18] A systematic review was recently conducted on clinical trials assessing the effects of purified anthocyanins and anthocyanin-rich extracts on biomarkers of CVD in both healthy and unhealthy individuals.[19] A plethora of animal and *in vitro* mechanistic data supports the biological plausibility of these compounds to improve markers and incidence of CVD.[20] The Chinese Nutrition Society (CNS) recently defined a specific proposed level (SPL) (which is similar to an AI) of 50 mg/d for anthocyanins based on the inverse relationship to development of CVD. The CNS also defined SPLs (which is similar to an AI) and ULs for eight other dietary bioactives in China as of 2013, as shown in Table 2, based on disease outcomes or endpoints.[21]

Table 2. SPLs and ULs as defined by the Chinese Nutrition Society

Non-Nutrient Substances	SPL	UL
Dietary fiber (g/d)	25a	ND
Phytosterols (g/d)	0.9	2.4
Lycopene (mg/d)	18	70
Lutein (mg/d)	10	40
Proanthocyanidins (mg/d)	ND	800
Isoflavones (mg/d)	55b	120b
Anthocyanins (mg/d)	50	ND
Glucosamine (mg/d)	1000	ND
Curcumin (mg/d)	ND	720

ND=Not defined; SPL= Specific proposed level; UL= tolerable upper intake level. Translation credit: the laboratory of Dr. M. Monica Giusti.
[a] Adequate intake.
[b] Defined for postmenopausal women.

Cocoa flavanols, another class of dietary bioactives, have also accumulated substantial research to merit DRI evaluation. A major advancement was made in 2012 when the European Food Safety Authority published a scientific opinion on the substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation.[22] This scientific opinion laid the groundwork for better-defined standards of evidence needed for product development, food labeling and public health communications about dietary bioactives.

Similar to structure/function claims, the European Commission has reviewed and approved several "general function" claims that do not include disease risk reduction but are instead based on reliably measured biomarkers (e.g., maintenance of normal platelet aggregation) as indicators of optimal health.[23] This process takes into account risk biomarkers that may be in the causal pathway versus those that serve as validated surrogate marker end points. Biomarkers are becoming increasingly important in that they can help improve understanding of healthy dietary choices and patterns; however, they cannot be assumed to be a surrogate endpoint.[24]

Consistent and reproducible measurement of a biomarker of effect among two to three small-to-medium intervention and large cohort studies coupled with data demonstrating biological plausibility has been suggested to serve as adequate evidence to validate manufacturer use of a current structure/function claim.[25] In my opinion, "consistent and reproducible" evidence may be defined as 80% of acceptable quality studies (i.e., four or five cohort studies designed to measure the outcome/endpoint of interest) showing similar effects among heterogeneous populations when numerous studies are available. Qualification of DRI-like evaluation should merit additional criterion. Lupton, et al.[26] described the following reasonable criteria that if met may qualify a bioactive for DRI-like evaluation: (1) a commonly accepted definition of a substance or class of compounds; (2) an approved method of measurement so that intake can be assessed across the population; (3) a database referencing the amount of the dietary bioactive in foods; (4) prospective cohort data with dose response or at a minimum highest versus lowest quintile; (5) clinical trials on digestion, absorption, activation, transport, and excretion of the substance; (6) clinical trials showing efficacy and dose response; (7) safety data at the level of intake that might be anticipated; (8) systematic reviews or meta-analyses showing efficacy; and (9) biological plausibility for efficacy. I would like to challenge that these criteria be utilized for both qualification and establishment of a DRI-like value for dietary bioactives. A decision tree approach must be utilized in the development of messaging and in policy development.

The IOM reviewed carotenoids in 2000; however, no DRI values were assigned.[27] In 1998, phenols, polyphenols and flavonoids were excluded from the DRI panel's consideration due to lack of food composition data and knowledge of actual intake amounts and limited information on their absorption and metabolism.[28] Since then, our knowledge of the absorption, distribution, metabolism, and excretion of various dietary bioactives has increased considerably. Great strides have been made in the development of intake databases, such as the U.S. Department of Agriculture Flavonoid Database, which have become publically available and useful for assessing population intakes of dietary bioactives.

Benefit to the Industry

DRIs and/or a framework for substantiation of structure/function claims specific to dietary bioactives would provide guidance for manufacturer claims and messaging. A recent warning letter from the FDA to Unilever United States Inc. regarding its product Lipton Green Tea illustrates the rationale for the food industry seeking establishment of reference intakes for dietary bioactives. The warning letter stated the following: "The claim 'packed with flavonoid antioxidants' does not comply with 21 CFR 101.54(g)1 because no DRI has been established for flavonoids thus making it an unauthorized nutrient content claim causing the product to be misbranded under section 403(r)(2)(A)(i) of the Act." Establishment of a DRI-like process for bioactives would result in the following: (1) A system for industry compliance would be put in place and would institute a "guardrail," particularly for companies manufacturing dietary supplements and functional foods; (2) Dietary bioactives would be recognized as important for human health and evaluated accordingly; (3) Investigators, regulatory agencies and consumers would know how strong the science was behind the messaging; (4) Consumers and their health professionals would have a target to aim for in terms of intake; and (5) Such a process

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would provide an incentive for research to close critical gaps. The ultimate beneficiary of public health messaging is the consumer.

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