Dietary Bioactives: Establishing a Scientific Framework for Recommended Intakes[1,2]

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ABSTRACT

In the United States, dietary reference intakes describe the relations between nutrient intakes and indicators of adequacy, prevention of disease, and avoidance of excessive intakes among healthy populations for essential nutrients but not dietary bioactive components (DBCs), whose absence from the diet is presumably not deleterious to health (i.e., does not cause a deficiency syndrome). An appropriate framework is needed for establishing recommended intakes for which public health messages and food labeling for DBCs can be derived, because their putative health benefits may not be readily defined in the context of nutritional essentiality. In addition, a myriad of factors make determining their intake and status and investigating their discrete contributions to health particularly challenging. Therefore, the ASN Dietary Bioactive Components Research Interest Section felt it worthwhile to convene a special "hot topic" session at the 2014 Experimental Biology meeting to discuss this issue and serve as a call for future scientific dialogue on establishing a framework for recommended intakes of DBCs. This session summary captures the discussions and presentations that transpired during this session. *Adv Nutr* 2015;6:1–4.

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Introduction

The potential role of dietary bioactive components (DBCs) in promoting health maintenance and reducing chronic disease risk is an active and provocative area of nutrition research. The NIH Office of Dietary Supplements defined DBCs 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." Similarly, the North American Branch of the International Life Sciences Institute defines functional foods as "foods that, by virtue of the presence of physiologically active components, provide a health benefit beyond basic nutrition." Recent peer-reviewed articles, conference proceedings, and scientific symposia have addressed the readiness, need, benefits, and challenges for developing recommended intakes and public health messages regarding DBCs. However, there has been less dialogue around what an appropriate framework might entail. The US DRIs describe the relations between nutrient intakes and indicators of adequacy, prevention of disease, and avoidance of excessive intakes among healthy populations for essential nutrients but not DBCs, whose absence from the diet is presumably not deleterious to health (i.e., does not cause a deficiency disease). As an alternative means of seeking public health messaging, food companies may submit a research dossier for any single class of DBC to the US FDA, which has the authority to grant either a health claim or a qualified health claim. This process is typically lengthy and only a short list of successful claims has been approved because disease risk reduction is difficult to demonstrate among healthy populations.

The ASN Dietary Bioactive Components Research Interest Section thus convened a special Experimental Biology 2014 "hot topic" session to discuss this issue and serve as a call for future scientific dialogue on establishing a framework for recommended intakes of DBCs. Andrew Shao opened the session by providing an overview of why recommended intakes of DBCs should be considered from an industry perspective and identified challenges for conducting research on both single DBCs and classes of DBCs. Elizabeth J Johnson then presented a case study for how the totality of

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evidence with regard to lutein, a single DBC known to positively influence visual and cognitive function, supports a recommended intake and public health communications. Jeffrey B Blumberg reviewed how the evidence on flavonoids, a class of DBCs shown to positively influence cardiovascular and other physiologic functions, has been translated from data to public databases and used in observational studies. The session concluded with a panel and audience discussion moderated by Taylor C Wallace on the caveats and future actions needed to move forward to establish recommended intakes for DBCs.

Establishing Recommended Intakes for Phytonutrients and Other Bioactive Food Components: Can/Should We Get There?

The evidence base for single/isolated DBCs (e.g., lutein) and classes of compounds (e.g., flavonoids) has increased substantially over the past 2 decades. Evidence that many DBCs may confer a benefit to maintaining homeostatic balance and/or prevention of chronic disease onset continues to rapidly emerge. Although current public health recommendations to increase the consumption of colorful fruits and vegetables are largely driven by the need to meet essential nutrient intakes from foods, recommendations from policy documents such as the *Dietary Guidelines for Americans* and groups such as the National Fruit and Vegetable Alliance also take into account the contribution of DBCs. The >8000 DBCs characterized today are presumably safe at amounts that occur in habitually consumed foods within the range of recommended intakes of fruit and vegetables and whole grains; however, many unique challenges exist regarding research on health outcomes, because these substances are neither essential nutrients (in the classic sense) nor drugs (1). Many isolated and well-characterized DBCs (e.g., lutein), and less well-characterized classes/mixtures of compounds (e.g., flavonoids), have substantial scientific evidence, including dose-response relations, and statistically significant relations with improved physiologic performance and/or reduction in the risk of chronic disease. Classes of related compounds are commonly found in similar types of foods and are frequently present in mixtures, in which the exact nature and identity are often not known. This caveat alone makes it challenging to define specific recommendations such as those available for the DRIs. On the other hand, it may be more reasonable and practical to base intake recommendations on a mixture of a similar class of substances (e.g., anthocyanins, flavan-3-ols, etc.) that exhibit additive or potentially synergistic actions rather than selecting an individual defined chemical entity, given that most DBCs are normally consumed as mixtures in foods or supplements. Whether the DBCs of interest are in isolate or extract mixtures, their composition in the whole food can vary markedly because of environmental factors such as cultivation, soil, altitude, and weather condition.

Several robust frameworks in the United States and around the world exist for establishing recommended intakes of "classic" essential nutrients, defined as chemical substances found in foods that are essential for human life and tissue growth and repair; however, no evaluative process currently exists for DBCs. A recent advancement in this field 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. This scientific opinion laid the groundwork for better-defined standards of evidence needed for product development, food labeling, and public health communications about DBCs.

To act in the absence of ultimate certainty on this matter requires a broad consideration of all research approaches (including randomized controlled trials, observational studies, animal models, and in vitro experiments) along with revised estimates of the necessary certainty level and confidence (e.g., as with RDAs) needed to act in support of public health. A recent warning letter from the FDA to Unilever United States, Inc., regarding their product Lipton Green Tea illustrates the rationale for the food industry seeking establishment of reference intakes for DBCs. 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 put a system for industry compliance in place as well as institute a "guardrail," particularly for companies manufacturing dietary supplements and functional foods. Establishing DRI-like guidelines for DBCs may also help to stimulate increased consumption of fruits and vegetables by providing much-needed awareness about the benefits of phytochemicals and rationally formulated dietary supplements. Such recommendations could also help foster research on key questions and issues, such as the health consequences of failing to achieve recommended amounts of DBCs in the diet. For example, daily intake recommendations (or ranges) might be based on amounts delivered by adherence to the *Dietary Guidelines for Americans* or other patterns associated with healthy endpoints. A modified evidence-based systematic review approach from what is used for drugs and, in some cases, essential nutrients may be necessary to achieve this goal. Defining an AI–like reference value within the current DRI framework may be a reasonable first step when sufficient evidence is available. In the absence of sufficient evidence to define a tolerable upper intake level for DBCs, an evidence-based risk assessment or highest observed intake (2) approach may be beneficial.

Case Study: Establishing Dietary Guidance for Lutein

Lutein, a dietary carotenoid, is an important DBC found in green leafy vegetables and other foods such as eggs that can be readily isolated and has been well characterized. Like all DBCs, lutein is not synthesized in the body. Among the carotenoids, lutein is preferentially distributed in the macula of the retina by steroidogenic acute regulatory protein

related lipid transfer domain-3 (StARD3), a protein that binds specifically to this xanthophyll (3). In the macula, lutein and its isomer zeaxanthin are referred to as macular pigment. Rhesus monkeys fed a lifelong diet devoid of lutein or zeaxanthin have distinct morphologic changes in the retina compared with monkeys raised on diets containing lutein or zeaxanthin [reviewed in Johnson (4)]. The structural changes involved the retinal pigment epithelium (RPE), cells that are crucial for nourishment of the retina. Lutein/zeaxanthin-free monkeys had a decrease in the RPE cell density profile at the foveal center (center of the macula containing the largest concentration of cone cells and responsible for high-resolution vision), rather than the normal peak. After supplementation with lutein or zeaxanthin, the RPE profile of monkeys low in n–3 FA intake no longer had a decrease at the foveal center. Therefore, RPE cells are sensitive to the absence of macular pigment. Carotenoid-free monkeys also exhibited damage to the fovea when exposed to visible light; however, the severity of damage decreased when lutein was added back to the diet.

The evidence to date suggests that lutein has protective effects on age-related eye diseases (4); furthermore, the presence of the StARD3 binding protein gives biological plausibility for the outcomes observed in humans. The Age-Related Eye Disease Study 2 provided evidence that supplementation with dietary levels of lutein and zeaxanthin (10 and 2 mg/d, respectively) and other antioxidants significantly decreased the progression of age-related macular degeneration when intakes of these carotenoids were low (5).

Lutein may also be beneficial toward maintaining cognition. Similar to the retina, there is preferential uptake of lutein into the human brain. Infants consume ~12% of their dietary carotenoids as lutein; however, lutein accounts for ~58% of an infant's brain carotenoids. Preferential uptake of lutein into the brain has been noted later in life and may be linked to the presence of the same binding protein found in the macular region of the eye (4).

Lutein has a 5- to 6-d half-life (6), binds to a specific protein (3), protects neural tissue (4), and shows a dose-response in both the serum and the macula (higher intakes result in greater uptake in tissues). Lutein consumption of ~6 mg/d has been postulated to be optimal for eye health (4); no signs of toxicity were reported among clinical trials at intakes 3 times this dose. Defining criteria for a DRI-like process for DBCs would help fill in gaps toward advancing public health messaging about this important phytonutrient and stimulate new products that deliver beneficial amounts.

Case Study: Considering Flavonoids—From Data to Databases to AIs

The development of reference values for DBCs could provide consumers with guidance about healthy food choices via education and food product labeling, as well as provide the nutrition industry with definitions to guide innovative product development and truthful, nonmisleading communications about existing and new products. Although defining a new framework and achieving a broad consensus for it would prove difficult, the use of the current DRI model provides a well-understood basis for dietary recommendations, even though some criteria would need to be modified to deal with the differences between essential nutrients and DBCs. Flavonoids offer a contrasting illustration to lutein because they represent a broad and large class of phytochemicals, albeit with subclasses of closely related compounds that have been substantially characterized and for which a suitable nomenclature has been established. Even though several caveats exist in the measurement of these DBCs in foods and in humans, the scientific community may still push forward toward establishing reference values in the midst of several complexities. For instance, nutrient composition databases do not necessarily need to be precise (it is likely they will always be incomplete) as long as they have the ability to differentiate between intakes within a population and establish ranges of intakes that confer a benefit. Bioavailability of a compound present in the food matrix at an adequate level to deliver the beneficial bioactivity must also be considered so that an intake range (similar to an AI) can be established by examination of the current scientific literature. For instance, in the dietary assessment of tea intake, marked variability is introduced in the amount of constituent flavonoids consumed on the basis of the pre- and postharvest environments as well as the preparation of the final infusion. An average amount of flavonoids (or other DBCs) in any particular product may not obtainable if the composition is assessed at only one time point. Similarly, many databases only assess the aglycone (e.g., USDA flavonoid database); however, many conjugate groups (e.g., anthocyanin sugar and acid moieties) alter the bioavailability and bioactivity of DBCs. In nutrition, small to modest effects can have large public health implications. Thus, it is critical to assess the range and duration of intake when considering health outcomes. An evaluation of lutein and flavonoids by using the proposed criteria by Lupton et al. (7) warrants further discussions on establishing recommended intakes for these DBCs.

Recommendations

In conclusion, we offer the following recommendations. First, the nutrition science and public health communities should move forward to establish a framework for recommended intakes of DBCs. Intake recommendations could be used by consumers for dietary guidance and by nutrition companies to innovate new products and fairly communicate their ingredients and benefits. Second, defining an AI-like reference value for carefully considered single and/or classes of DBCs within the current DRI framework is a reasonable first step and is appropriate to the totality of the available evidence for DBCs such as lutein and flavan-3-ols. There may or may not be sufficient evidence to define a Tolerable Upper Intake Level–like reference, so an evidence-based risk assessment or Highest Observed Intake (2) approach may be beneficial for DBCs with a well-known safety profile in which no known hazards exist. Third, understanding the challenges and successes of the recent

process used for defining DRIs for fiber (for which a deficiency disease is uncertain) may help to begin mapping out a framework for DBCs because no deficiency disease has yet been defined for this dietary constituent.

Finally, additional government funding is needed, because the Institute of Medicine can only accept <50% of funding for a particular project from the private sector. Government agencies such as the US Department of Health and Human Services and the USDA are not adequately funded to currently undergo a large project such as this with the Institute of Medicine. However, the ASN may be well positioned to rally this political movement on Capitol Hill.

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References

1. Heber D, Shao A. Bioactive food components: changing the scientific basis for intake recommendations. International Alliance of Dietary Supplement Associations (IADSA) [cited 2014 Jul 31]. Available from: http://www.iadsa.org/publications/1320152635_Bioactive_Food_Components__Ch.pdf.
2. Hathcock J, Kriengsinyos W. Highest observed intake: definition, regulatory uses and provisional values. Regul Toxicol Pharmacol 2011;61:115–8.
3. Li B, Vachali P, Frederick JM, Bernstein PS. Identification of StARD3 as a lutein-binding protein in the macula of the primate retina. Biochemistry 2011;50:2541–9.
4. Johnson EJ. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. Nutr Rev 2014 Aug 7 (Epub ahead of print; DOI: 10.1111/nure.12133.
5. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309:2005–15.
6. Thürmann PA, Schalch W, Aebischer JC, Tenter U, Cohn W. Plasma kinetics of lutein, zeaxanthin, and 3-dehydro-lutein after multiple oral doses of a lutein supplement. Am J Clin Nutr 2005;82:88–97.
7. Lupton JR, Atkinson SA, Chang N, Fraga CG, Levy J, Messina M, Richardson DP, van Ommen B, Yang Y, Griffiths JC, et al. Exploring the benefits and challenges of establishing a DRI-like process for bioactives. Eur J Nutr 2014;53(Suppl 1):1–9.