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(Article begins on next page)

Are Dietary Bioactives Ready for Recommended Intakes?^{1,2}

P. Courtney Gaine,^{3*} Douglas A. Balentine,⁴ John W. Erdman Jr.,⁵ Johanna T. Dwyer,⁶ Kathleen C. Ellwood,⁷ Frank B. Hu,⁸ and Robert M. Russell⁹

³North American Branch of the International Life Sciences Institute, Washington, DC; ⁴Unilever, Englewood Cliffs, NJ; ⁵University of Illinois, Urbana, IL; ⁶Tufts University Medical School, Boston, MA; ⁷College of Southern Maryland, La Plata, MD; ⁸Harvard School of Public Health, Cambridge, MA; ⁹Tufts University, Boston, MA; and National Institute of Health, Bethesda, MD

ABSTRACT

Research has shown that numerous dietary bioactive components that are not considered essential may still be beneficial to health. The dietary reference intake (DRI) process has been applied to nonessential nutrients, such as fiber, yet the majority of bioactive components await a recommended intake. Despite a plethora of new research over the past several years on the health effects of bioactives, it is possible that the field may never reach a point where the current DRI framework is suitable for these food components. If bioactives are to move toward dietary guidance, they will likely require an alternative path to get there. *Adv. Nutr.* 4: 539–541, 2013.

Introduction

For more than 70 y, U.S. consumers have relied upon the RDAs and the dietary reference intakes (DRIs) for intake recommendations of essential nutrients. These reference values describe the relationships among nutrient intakes and indicators of adequacy, prevention of chronic disease, and avoidance of excessive nutrient intakes in healthy populations. Although a framework exists to establish recommendations for essential nutrients, such a framework does not exist for nonessential bioactive constituents in foods. Bioactives include those food components such as fiber, carotenoids, flavonoids, and n-3 long-chain fatty acids that may be oxidized as fuels, may provide compounds for endogenous synthesis of body constituents, cannot be synthesized by the body, and do not result in biochemical or clinical deficiency. Evidence

is emerging that, although not essential to life, these components confer a range of effects that may support health and quality of life. However, because they have physiological roles not considered essential to humans and because a myriad of factors make measuring their intakes and studying their effects difficult, an alternative framework to determine recommended intakes for bioactives is warranted. The purpose of this symposium was to address the fundamental question: What will it take to develop a framework that can be used for establishing health recommendations for bioactive food components? While the session primarily focused on flavonoids, many of the points raised pertained to bioactives in general.

Dr. Kathy Ellwood provided an overview of the evidence needed to set dietary recommendations, laying out elements for consideration in adapting the current DRI framework for application to bioactives. Dr. Frank Hu provided an overview of the state of the science on flavonoid intake and health benefits and identified challenges and future needs to furthering our understanding of flavonoids and health. Dr. Johanna Dwyer reviewed case studies using flavonoid subclasses, addressing their safety, health benefits, and evaluated whether the current evidence was sufficiently strong to meet the scientific rigor for intake recommendations. Dr. John Erdman provided a historical perspective on the evaluation of bioactives by identifying the progress made during the past 20 y. The symposium concluded with a panel discussion led by Dr. Robert M. Russell, whose experience as chair of the Institute of Medicine's Food and Nutrition Board and

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* To whom correspondence should be addressed. E-mail: cgaine@ilsi.org.

participation in the DRI process was valuable for the discussion on future actions needed if bioactives are to be considered for intake recommendations.

Current Framework for Developing Dietary Recommendations

Several elements are required for a nutrient or food component to be evaluated for a dietary recommendation. First, the data must demonstrate consistent results indicating that the effects of the food component of interest can be attributed to a health impact, including a plausible mechanism of action. Second, accurate intake assessment is needed, with biomarkers of exposure and/or validated food assessment methods required, including the ability to distinguish the effects of the background diet. Large, randomized, controlled intervention studies and studies of humans are typically given the greatest weight in the evaluation. However, because chronic disease develops over a long period of time, making intervention studies sometimes prohibitive, biomarkers of effect or risk biomarkers from observational data are also depended upon. A biomarker is a reliable and accurate indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention. Surrogate endpoints of chronic disease are risk biomarkers that serve as a substitute for clinical endpoints, but few are validated and not all risk biomarkers are surrogate endpoints.

An important public health question is whether intake recommendations should shift focus from disease risk reduction to maintenance of normal physiological function (e.g., enhanced blood flow). Moving beyond classic nutrient-disease biomarkers may be essential in the development of dietary recommendations for bioactives. Although maintaining or improving physiological functions may support optimal health, the challenge is that markers of enhanced physiological function do not always reside in a causal pathway for disease risk reduction, making them ineligible as valid biomarkers. There are many emerging biological indicators of disease risk/health that may be potential intermediary biomarkers and these are likely critical to the ability to attribute flavonoid intake to beneficial health outcomes. For this shift to be possible, more studies validating these markers' ability to predict health outcomes are needed. Additionally, multiple risk biomarkers may be helpful if all show the same beneficial effect on a particular health outcome.

State of the Science and the Complex Reality of Research on Flavonoids

There are 6 subclasses of flavonoids in the diet, defined by structure. Flavonoid intake has been linked to reduced risk for chronic diseases as well as to improved health outcomes, such as appropriate platelet aggregation and flow-mediated dilation. The potential mechanisms for the biological function of flavonoids vary by structure and include activities such as binding at hormone receptor sites, activating endogenous defense systems, modulating cell signaling pathways, having antiinflammatory effects, and inhibiting intestinal glucose transporters.

In recent years, there has been a surge in research on the bioactivity and health benefits of bioactive food components, including flavonoids. Substantial observational evidence exists for beneficial effects of the intake of flavonoids and flavonoid-rich food and beverages such as chocolate, fruits, tea, and vegetables on decreasing risk of chronic diseases. Small, short-term trials have found potential benefits of flavan-3-ols, in particular, on blood pressure, endothelial function, and insulin resistance and of green tea on blood lipids. However, larger and longer term trials are needed to validate the findings. Future research is needed to clarify whether the observed beneficial outcomes result from flavonoids or from other dietary constituents. Specifically, large, prospective cohort studies in combination with shorter term trials of intermediary endpoints are critical in establishing causality in the absence of trials with disease endpoints.

Is the Current Science Enough for Dietary Recommendations?

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. The DRI committee report concluded that although these components "may be important dietary constituents, insufficient data are available... at this time." The report also stated that with regard to "food components grouped as 'other food components,'.... other data may emerge in the future that could allow a consideration of setting DRIs for these compounds as well." The amount of evidence needed is at hand for discussion, including consideration of the risk: benefit ratio of consuming the constituent. For example, a high-risk, low-benefit constituent should require more evidence (e.g., selenium and cancer prevention given selenium excess may be toxic) and one with low risk and high benefit may require less (e.g., potentially lutein and age-related macular degeneration, for which there is little evidence of harm). One of the larger obstacles in such an evaluation is the lack of randomized clinical trials of intakes and health outcomes. However, it is difficult to run trials with bioactives due to the costs of a large study population of long duration to detect small effects. In addition, even if studies are successful, they may not provide sufficient data for convincing systematic, evidence-based reviews. Another issue is the complexity that results from grouping data from all subclasses of flavonoids, constituting total flavonoids, and assuming that one body of evidence should and will have a single effect. In reality, flavonoids differ in the quantities found in foods, bioavailability, metabolites they produce, and the health effects they may have.

Does the Science, the Framework, or Both Need Fixing?

Developing a path forward for dietary recommendations for bioactive components will require evidence-based scientific data. There is consensus within the scientific community that

it must strive to generate literature that is valid and reliable so that consistent results are demonstrated. During the past several decades, in addition to the increased number of studies, there have been improvements in the design, intake assessment, substance characterization, biomarker discovery, and reporting of research on flavonoids and other bioactives. Although these enhancements to the science must and will continue, the possibility exists that the field of bioactives can never provide the same type of evidence that essential nutrients do, and thus the question is whether they should be considered under the same framework as the DRI. If they should not, a concerted effort requiring expert resources and funding will be required to develop an alternative path to recommended intakes for bioactives. One logical next step is for the Institute of Medicine's Food and Nutrition Board to develop and test a blueprint that can be used to evaluate each of these constituents in a formal review of the type that is required for establishing a DRI.

Consequences of Inaction

From a public health perspective, without dietary recommendations for flavonoids and other bioactives, there is a perpetuation of the status quo of current dietary patterns containing lower intakes of bioactive-containing foods than may support optimal health. Consumer confusion is also of concern and yet, at the same time, leaves an "open range" of intake amounts suggested for dietary supplement claims. Conveying accurate and reliable information about the health benefits of many of these bioactive food components would enhance the public's understanding of the importance of safe use of these compounds for promoting optimal health. For the scientific community, dietary recommendations stimulate research, and without momentum forward, there may be a dearth of the type of critical research needed to close the gaps in knowledge.

In Summary

Some of the challenges and obstacles that bioactives face with regard to making intake recommendations are given below. These are followed by future actions likely needed for clearing the path forward to dietary intake recommendations for flavonoids and other bioactive compounds.

Challenges/Obstacles to Intake Recommendations

- The bioavailability and bioactivity of flavonoid subclasses differ widely according to chemical structure.
- Flavonoid intake from dietary supplements and foods differs in content, matrices, and dose consumed.
- The polyphenol content of plant foods is influenced by numerous factors (i.e., sun, ripeness, storage, preparation, processing, etc.), making accurate assessment of flavonoid intake difficult.
- There are errors in intake measurement (i.e., accuracy of food composition databases, reliability of FFQs, and intake amounts do not always equate to bioavailable doses).
- The health benefits of flavonoids in the current literature are often based on surrogate biomarkers of effect rather than actual health outcomes (endpoints), such as disease incidence or mortality.
- Given that bioactives are nonessential, the funding required in undertaking a formal federal review of their intake has not been viewed as a priority.

Future Actions Needed

- Continue to increase the focus on hypothesis-driven research rather than "fishing expeditions."
- Strengthen the science and craft messages that reflect that the benefits of flavonoids justify intake recommendations.
- Shift the focus of conducting and evaluating research toward biomarkers of function and health and wellness compared with disease risk reduction.
- Continue to explore and validate biomarkers of intake and metabolites and incorporate these in dietary assessment of large prospective studies.
- Replicate studies on various subpopulations of interest.
- Continue efforts to harmonize the characterization of bioactive components in research.
- Fund and conduct larger and longer term trials, using accepted and new biomarkers of effect.
- Use advanced statistical techniques (e.g., mixed evidence synthesis, cross design synthesis, including the confidence profile method) to better summarize existing data.
- Demonstrate the safety of bioactives for intended uses for supplements and conventional foods.
- Further explore the independent and synergistic effects of multiple compounds to delineate the bioactivities and health effects of specific flavonoids.
- Solidify funding to make the evaluation of bioactives possible.

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