Exploring Scientific Evaluation and Intake Recommendations of Bioactive Compounds and the Public/Private Path to Get There
October 23, 2014
MEETING SUMMARY

On October 23, 2014, the Alliance for Aging Research, with support from Mars, Inc., convened key stakeholders from the Institute of Medicine (IOM) and other non-profit organizations, the U.S. and Canadian Governments, academia, and private industry to discuss scientific evaluation of bioactive compounds. Dr. Joanne Lupton, Distinguished Professor of Nutrition at Texas A&M University, co-chaired the meeting with Susan Peschin, President and CEO of the Alliance for Aging Research, and described the goals of the meeting as follows: (1) to identify concrete ideas for creating an evaluation process for bioactives, including intake recommendations, and (2) to address issues with and opportunities for public-private partnerships. She also shared a working definition of bioactive compounds and suggested it be used for the discussion: Bioactives, according to the working definition, are "constituents in foods or dietary supplements, other than those needed to meet basic human needs, which are responsible for changes in health status."

The meeting included four presentations that helped frame the discussion. These presentations were on perspectives from the Subcommittee on Dietary Reference Intakes (DRIs), application of the DRI paradigm to bioactives, lessons learned from research on cocoa flavanols, and development of public-private partnerships.

A. Subcommittee on Dietary Reference Intakes
Composed of 20-plus Federal agencies from the United States and Canada, the US coordinates the DRI Subcommittee and Canada coordinates the DRI Steering Committee. The Subcommittee on Dietary Reference Intake (DRI) of the Interagency Committee on Human Nutrition Research has identified challenges in evaluating nutrients and bioactives, including the lack of funding, the lack of nutrition research suitable to setting DRIs, and the absence of a process for evaluating chronic disease endpoints for bioactives. Additional considerations are how to measure the compounds in foods, how to measure consumption accurately, what length of exposure is enough for putative causal relationships, whether to rely on observational studies, and whether the existing model can be modified to enable examination of a specific effect. Some Bradford Hill criteria for causation are weak for bioactives, including strength, consistency of findings, specificity, biological gradient (e.g. dose-response), and controlled human trials. The existing DRI model most often depends on a single biomarker of exposure and often considers the intake requirement of an enzyme or other functional indicator of nutriture rather than disease. The subcommittee is therefore planning a chronic disease workshop with an expert panel, expected to be held in March 2015, to include discussion of whether chronic disease endpoints can be incorporated into setting DRI values.

B. Application of the DRI Paradigm to Bioactives
The evolution of the Recommended Dietary Allowances since 1941, and especially the DRI framework instituted in 1994, have helped shape the current framework for DRIs. The DRI framework, because it is flexible, is well suited for incorporating bioactives. However, there are several critical points to consider when applying the DRI paradigm to bioactives:

- It will be challenging to decide *when* there is sufficient evidence to undertake review of a bioactive and *what* criteria will be used to evaluate the bioactive.

- There is a tendency to become embroiled in discussions about whether there is sufficient science to move forward and neglect the process. Thus, it would be helpful to designate a group to focus exclusively on process.
- Discussions should incorporate diverse viewpoints. Committees representing a range of disciplines—beyond just the nutrition community—bring new ideas and methods and can create collaboratively what they would not be able to create alone.

C. Lessons Learned from Research on Cocoa Flavanols

Mars, Inc., has spent the past 18 years seeking to define efficacy for bioactive compounds—specifically cocoa flavanols (CFs)—and this presentation featured lessons learned from that process. A collaboration with partners from academia, Government, and industry, their research program endeavored to gain a fundamental, evidence-based understanding of the potential health benefits of CFs.

Early in the program, researchers faced a variety of scientific challenges that likely apply to other bioactive compounds: Studies were often based on poorly characterized materials, had no or insufficient controls, and struggled to identify relevant biomedical endpoints. Continuing challenges include identifying biomarkers of health versus disease, demonstrating that a bioactive reduces risk of chronic disease, determining specificity and equivalence of different components, determining appropriate intake recommendations across the lifespan, and consideration of nutritional source and population variations.

Much of the data presented arose out of FLAVIOLA, an EU research project carried out by a consortium of eight national partners that generated robust datasets on CF safety and efficacy and epidemiologic data on dietary intake across the EU. The workload was organized in six work packages, and each partner took the lead on one or more aspects of the research and shared the results.

Based on this experience with CFs, a DRI-like framework for evaluating bioactives might include the following key components:

- A clear and commonly accepted definition of the bioactive compound;
- Well-established, accredited methods of analysis;
- Epidemiologic data that link habitual intake and disease outcomes;
- Efficacy data from adequate clinical and dietary intervention studies;
- Comprehensive understanding of the absorption, distribution, metabolism, and excretion of the bioactive in humans;
- Comprehensive safety data;
- Plausible explanation for the mechanisms of action that underlie the observed effects; and
- Meta-analyses—systematic and evidence-based reviews.

The framework should also consider the impact of food processing and isomerization and should involve consumers as key stakeholders. Moving forward, if this framework can be used intentionally and strategically, it will help deliver evidence-based results.

The presentation concluded with a list of questions and challenges:

- Should we include high-risk populations in study groups?
- How do we recruit study populations that are representative?
- How do we address the challenges around contract research organizations, which use methods that are not necessarily appropriate for studying healthy individuals?
- How do we evaluate multi-biomarker assessments?
- How do we understand compounds like CFs that have many different forms with variable potency and effects?

- How do we identify research appropriate for inclusion in systematic reviews?
- What is the role of food and food components in the management of disease?

D. Creating an Evaluation Process for Bioactives

Dr. Lupton facilitated a discussion to identify concrete ideas for a bioactives evaluation process, including intake recommendations. First, the group discussed how the definition of "bioactive" is unclear but chose not to become involved in a debate about the definition in this meeting. Instead, they elected to move ahead with the understanding that bioactives are food components for which there is no clear deficiency but that may have health benefits and/or risks. Next, the group considered the five questions below.

1. **Would it be helpful to have an evaluation process for bioactives?**
   The group agreed that it would be helpful to have an evaluation process for bioactives. There is an abundance of research related to food components, and there should be some basic standards and structure to help organize this research. An evaluation process would help guide thinking with regard to the research and would help industry and researchers to know what is necessary, from both a scientific and a regulatory standpoint, to approve a claim.

2. **In what ways might the process for evaluating bioactives differ from or be similar to the current evaluation process for nutrients?**
   The group identified the following differences between nutrients and bioactives that are important to consider in the context of the evaluation process:
   - Nutrients are fairly well defined; bioactives are not. Bioactives are not necessarily single compounds but are often groups of compounds with similar activity.
   - Bioactives exist in a complex food matrix. They may facilitate the health outcomes associated with nutrients, and their value may be observed only in the presence of other variables.

   It was also observed that, traditionally, research on nutrients uses a threshold model, which does not work well with chronic disease endpoints. Further, because the impact of a bioactive may be synergistic and may depend on other variables, it is critical to articulate the causal pathway.

   The group defined the following key steps in the bioactive evaluation process: Identifying the need for a bioactive, conducting a pre-review, and conducting a formal review, each of which are discussed below.
   - ***Who* identifies the need for a bioactive to be evaluated?** The group considered whether the Government should initiate this process, the Institute of Medicine Food and Nutrition Board (FNB), industry, or another entity. The current process is that anyone can initiate a response to an RFP on a particular nutrient, and then the government will prioritize which ones to fund. It was discussed that this current process could be modified to include bioactives.
   - ***When* is there sufficient evidence to undertake review of a bioactive?** There is a need to articulate an agreed-upon set of criteria for entrance into the evaluation process. This could help determine when there are adequate data to submit a bioactive for evaluation and/or could provide regulators with a framework for initial review prior to formal evaluation. There were differences of opinion regarding whether this should take the form of a simple checklist or a more involved evaluation like what the Federal DRI Steering Committee currently does to determine if there is adequate evidence for consideration of a nutrient.
   - ***What* criteria should be used in formal evaluation of the bioactive?** The group agreed that there also need to be criteria for use in determining what is important in evaluating bioactives. Among these criteria should be (1) an indication of the value of the bioactive to public health and (2) articulation of the causal pathway that links the biomarker to the outcome.

In regard to the last point, one participant proposed a more loosely structured approach to evaluating bioactives, based on the EU model that examines (1) safety, (2) efficacy, and (3) the final, branded product. The approach would not specify how to demonstrate safety or efficacy but would permit multiple pathways toward the same goal. While current frameworks exist, such as the FDA Generally Recognized as Safe (GRAS) program, they may not be sufficient for advancing the field.

3. **What would be the endpoints for determining intake values for bioactives?**
   The group agreed that the clinical endpoint does not necessarily have to be decreased risk for disease; instead, it can be a health endpoint such as a beneficial physiologic effect that is validated as a biomarker. Since biomarker qualification is handled through the FDA Center for Drug Evaluation and Research (CDER), it would be worthwhile to meet with the agency to discuss potential opportunities for bioactives.

4. **What would be considered essential/not essential for evaluating bioactive efficacy?**
   To evaluate bioactive efficacy, the group agreed that it is essential to first clearly define what the compound is, whether single- or multi-component, though there are rare exceptions such as the case of dietary fiber. They also agreed that it is not essential to have a specified number of randomized controlled trials (RCTs) to evaluate bioactive efficacy. While an RCT approach is appropriate with some compounds, it is not appropriate with others. In short, there are potentially multiple approaches to demonstrating bioactive efficacy, so it is not necessary to dictate the type and amount of data needed. To this point, two participants suggested that FDA guidelines for the evaluation of health claims could be used more generally to guide examination of the science. Also important are biomarkers of both deficiency levels and toxicity levels of bioactives.

5. **What types of gaps in research exist, and how might they be filled?**
   The group identified the need for further research in the following areas:
   - **Biomarker validation.** There is a need to validate biomarkers for use in research on nutrient and non-nutrient compounds. In particular, biomarkers to measure optimal health are needed versus simply lack of disease.
   - **Dose response.** There needs to be research on the safe and effective upper and lower intake levels of nutrients and non-nutrient compounds. Validated rapid methods and standards to measure nutritional status are also needed.
   - **Diet context.** There needs to be a better understanding of how the efficacy of bioactives varies according to the dietary context in which they are consumed.
   - **Chemistry.** There needs to be a better understanding of and appreciation for the chemistry underlying research on food compounds.

   It was suggested that there be further discussion, in another forum, on research gaps in the context of the proposed DRI-like framework presented earlier in the day.

E. Public-Private Partnerships

There are opportunities for public-private partnerships throughout the continuum of biomedical research and development. Examples of organizations that have substantial experience in public-private partnerships include the International Life Sciences Institute Research Foundation, the Foundation for the NIH, the newly established Foundation for Food and Agriculture Research, and the Agricultural Technology Innovation Partnership Foundation. Successful public-private partnerships must be transparent and have well-developed requirements for managing conflicts of interest to ensure public trust.

The group made the following observations about public-private partnership models for funding research on bioactives:

- A simple model of public-private partnership, in which a partner donates a drug or product and does not see the data until after the study is completed, is limiting. The field needs a partnership model that allows scientists to interact more freely to move the research forward.
- If partnerships are not structured to enable commercialization, the information gleaned will not be applied. In the case of the EU consortium FLAVIOLA, partners considered multiple agreement templates and ultimately chose to keep the intellectual property (IP) they brought into the consortium and to share the IP that was mutually generated. The approach worked well for Mars, which shared its analytical and chemistry platforms and in return got access to data, scientists, and regulators. Notably, this model melds the scientific and regulatory elements, which is rare in nutrition research.
- The pharmaceutical model does not serve the nutrition community well. Public-private partnerships are much better suited to addressing the complex chemical matrix of food products.
- There are few economic models of value capture for primary prevention. For this reason, there are no biomarkers for health. Thus, a forum on the economics of prevention was suggested to discuss this further.

F. Summary and Next Steps

Co-chairs Dr. Lupton and Ms. Peschin identified major areas of consensus that arose from the presentations and discussions as follows:

- A process for evaluating bioactive compounds can be developed.
- The greatest challenge is funding. This includes the amount, source, and distribution of funding.
- It is important to explore the role of food and food components in the management of chronic disease. This is particularly the case as the population ages and as chronic disease increases.
- A salient question is how to measure health beyond the absence of disease.
- There are significant research gaps, including problems with use of terms and definitions and with dose response. Other questions that need to be addressed are whether to investigate one specific biomarker or to look at the effect on the system more broadly, who will qualify the biomarkers, what are the criteria for evaluation, what types of studies should be undertaken (RCTs, observational studies), how intake and safety are captured across the lifespan, and who is responsible for determining criteria for the science (e.g., FDA, USDA, NIH, FNB).

To these summary points, meeting participants added that science does not happen in a vacuum and therefore regulatory issues need to be considered simultaneously, the field of nutrition science needs to demand the same rigor as the pharmaceutical industry, and the consumer is a key stakeholder in this process. In addition, there was a reminder that bioactives can serve as markers for broader dietary patterns.

Among next steps identified by meeting participants were the following:

- **Discuss issues and challenges around chronic disease endpoints.** There was excitement about the March 2015 workshop on chronic disease endpoints, tempered by the understanding that the meeting is a first step in gathering experts on the topic and is not intended to be a consensus conference.
- **Involve CDER in the conversation.** Since FDA CDER has extensive experience in biomarker qualification, and the process can be lengthy, it may be useful to solicit feedback.
- **Examine the FDA guidance document for structure/function claims.** The document, which describes what is necessary to substantiate a claim for dietary substances, may inform the discussion.