Bioactive Food Components: Changing the Scientific Basis for Intake Recommendations
The International Alliance of Dietary/Food Supplement Associations (IADSA) brings together over 50 associations of dietary supplement manufacturers and distributors from across the world. IADSA’s central goal is to ensure a greater exchange of information about the science and regulation of dietary supplements and ingredients among industry, scientists, regulators and consumers.
Bioactive Food Components: Changing the Scientific Basis for Intake Recommendations\textsuperscript{1,2}

\textbf{1 Dr. David Heber}
MD, PhD, FACP, FACN, Centre for Human Nutrition, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

\textbf{2 Dr. Andrew Shao}
PhD, International Alliance of Dietary/Food Supplement Associations Scientific Group, Brussels, Belgium

October 2011
Table of Contents

Abstract .................................................................................................................. 5
Introduction .......................................................................................................... 7
Existing evaluation frameworks ............................................................................ 11
Essential nutrients ................................................................................................. 13
Bioactive or Phytochemicals ............................................................................... 16
Aspects of scientific framework for evaluation of the effects of bioactives .... 17
Informing recommendations ............................................................................... 19
Challenges ........................................................................................................... 21
Tables .................................................................................................................. 23
Figures ............................................................................................................... 27
References ......................................................................................................... 29
Abstract

The recommended dietary allowances, dietary guidelines, and many government licensing and regulatory policies are based on twentieth century science which identified classical nutritional deficiency diseases for vitamins and minerals. In the 1990's, nutrient recommendations for foods were broadened as Dietary Reference Intakes (DRIs) and Dietary Reference Values (DRV) which now incorporate a tolerable upper intake level (UL) below which no adverse effects are noted. Attempting to move beyond a deficiency model, this effort extended to establishing macronutrient ranges for protein, carbohydrate, and fat, and provided information for a very limited number of vitamins and minerals. Since that time, research on bioactive substances, many derived from plant foods with a wide range of traditional intakes such as green tea have pointed to major health benefits for the public. There is clearly a need to develop a scientific framework to communicate the potential benefits of bioactive substances to the public that establishes reasonable certainty of benefits while also providing assurance of safety. Unlike drugs, bioactive substances pose minimal risks when consumed in the nutritional range, and provide evidence for efficacy from a totality of evidence beyond the prospective randomized controlled trials (RCT) used to establish the safety and efficacy of drugs. Nutrients and other bioactive food components do not act like drugs. Often they have less marked acute effects which are not apparent or cannot be tested using the RCT. All scientifically valid evidence of biological effects supporting health benefits based on observations in cell culture, animal models, and in human populations and intervention trials should be considered as a whole in making recommendations for the intake of bioactive substances. A standard based on the totality of evidence is proposed here, and would enable the public to obtain the potential benefits from consuming bioactive substances, while safety could be assured with robust post-marketing surveillance.
Introduction

It is well accepted that diets rich in colorful fruits and vegetables are linked to improved health, longevity and reduced risk for chronic disease. In addition to vitamins, minerals and fiber, bioactive food components and their mixtures are believed to contribute to these health benefits. However, unlike the essential nutrients, there is no accepted scientific framework that can be applied to help inform recommendations for the public on the health benefits of bioactive substances. As a result, regulatory agencies prohibit the introduction of these substances in some countries and restrict what can be communicated about these substances to the public. Compounds such as green tea polyphenols, carotenoids, anthocyanins, and many flavonoids exist in nature and in the diet as mixtures, rendering both the assessment of their health effects and development of exacting intake recommendations more difficult than for simple purified substances such as drugs, vitamins, and minerals. While the complexity of mixtures requires the use of advanced technologies such as high pressure liquid chromatography and mass spectrometry to assess quality and purity, these methods are now available and feasible. There are also post-market surveillance requirements in some markets for dietary/food supplements containing bioactive substances.

While there is a widespread recognition that methods exist both to assess the cellular effects of bioactive substances and to assure their purity, these methods are not being recognized as valid by authoritative bodies such as the US Food and Drug Administration (US FDA) and the European Food Safety Authority (EFSA). Evidence-based medicine (EBM), the accepted scientific framework for the assessment of the science base for recommending drugs and medical devices, has been misapplied to the evaluation of research on bioactive substances. By its nature, EBM and its heavy emphasis on randomized controlled trials (RCT) research favors acute and easily detected marked effects characteristic of drugs. It is not surprising that such an approach often fails to detect any benefit of bioactive substances even when there has been considerable evidence published in the peer-reviewed scientific literature in cell culture, animal models and humans. There are frequently cited examples in the literature of studies using a drug-based RCT approach to investigate the effects of selected micronutrients such as vitamins C and E, vitamin B₁₂ and folic acid and beta-carotene e.g. (1-3). Such studies are often interpreted as proving that bioactives are not effective despite the fact that the EBM approach may be an inappropriate method for assessing bioactives. In fact, it can be argued that the EBM approach should be abandoned as a way of evaluating the potential health benefits of bioactive substances (4-6).

In this regard, the absence of evidence from EBM on bioactives is not equivalent to evidence of absence. That is, a failure to show a benefit in a RCT should not be characterized as a negative trial but rather as an inability of a particular study to show a benefit based on size and characteristics of the population studied or the magnitude of the potential benefit expected. In RCTs involving drugs, the clear and significant effect size is known a priori and the size of the response is predictable based on considerable prior evidence. Such large trials are communicated to regulators and the expectation of a significant and marked outcome in these expensive trials is a requirement for their conduct. On the other hand, the resources available to study bioactive substances in clinical applications, where there is no patent protection, is severely limited making it impossible to use the same approach practiced for the licensing and regulation of potent drugs. In addition, drugs are known to have
potentially significant side effects often missed in RCTs but detected in post-marketing surveillance (7, 8). Thus, it can be argued that even for drugs, overreliance on the RCT model for licensing and regulation has significant drawbacks. Therefore, post-market surveillance may be a more appropriate standard to use for safety assessment of bioactives once a potential health benefit is defined based on the totality of scientific evidence available.

A corollary problem is the overinterpretation of adverse events as causal when only an association has been demonstrated. Reports describing the effects of bioactives on metabolic processes in the liver which are expected as part of the metabolism of a bioactive are an example of this type of overinterpretation. Consumption of cranberry juice as a sole nutrient by one individual in the UK (9) was the basis of warnings being placed on anticoagulants that cranberry juice should not be consumed. There are numerous examples of side effects attributed to bioactives that are poorly documented and irrational on biological grounds (10). Nonetheless, there is an ongoing publication of these types of reports which impact the consideration of a scientific framework for bioactives by giving the public and government agencies the impression that these substances are highly toxic when in fact they are safe in the nutritional range (e.g.,(11)).

The Dietary Reference Intakes (DRI) (12) in North America and Dietary Reference Values (DRV) (13) in Europe are examples of well accepted scientific and policy frameworks that have been developed for recommendations for essential macro and micronutrients. These recommendations are largely aimed at avoidance of diseases of overt nutrient deficiency or adverse effects from excessive intakes, but do not address health promotion. Furthermore, these recommendations, by and large, are developed for specific essential nutrients – well defined and characterized chemical entities. Bioactives tend to be chemically complex and in fact may exert their beneficial effects as part of naturally occurring synergistic groups of related molecules (14, 15). Therefore, approaches such as that employed through the traditional DRI process, may be too reductionist for establishing recommendations for bioactives (16, 17).

An alternate scientific and policy approach is proposed on which recommendations for bioactives could be based, and which could form a scientific framework for communication of potential health benefits to the public (18, 19). Such an approach should incorporate aspects of basic, pre-clinical and clinical research, including the RCT, but should allow for decision-making based on the totality of the evidence. Potential elements of such a framework include 1) Evidence on the chemical composition of the bioactive substance or the complex mixture in which it is found in nature; 2) Studies demonstrating the biological underpinning of proposed health benefits in appropriate cell culture, and animal models; 3) Information on the bioavailability, site of action, absorption and metabolism of the bioactive substance or mixture; 4) Well-designed human intervention studies of a much smaller scale than those used to evaluate drug efficacy and safety which clearly demonstrate potential benefits and 5) Post-marketing surveillance for potential adverse events with a system in place to evaluate the probable association with intake of the bioactive substance (20). Risk-benefit analysis can then be used to interpret the evidence and inform recommendations on potential health benefits. The recommendations will necessarily be qualitative and not quantitative suggesting a range of intakes based on inherent limitations in the science base and the low risk/benefit ratio.

¹ Recommendations based on the proceedings from the scientific session “Assessing the effects of bioactives in humans: Establishing the framework for an evidence-based approach”, presented by Erdman et al as part of the 2011 annual meeting of the American Society of Nutrition at the Federation for Advancement of the Societies of Experimental Biology in Washington, DC.
While outside the scope of this review, other public health recommendations such as the Dietary Guidelines for Americans in the US (21), and the Food-Based Dietary Guidelines for Europe (22), as well as Health Claim evaluations, undertaken by the US FDA (23) and EFSA (24) would be able to incorporate elements of the above approach or its spirit in recommendations to the public.
Existing evaluation frameworks

The selection and approval of prescription drugs and medical devices is generally based on the well-accepted scientific framework of evidence-based medicine (EBM). The primary form of evidence currently relied on for EBM is the randomized, controlled trial (RCT). Often other types of evidence such as observational data and preclinical evidence tend to be ignored, the latter despite its significant impact on understanding of the mechanisms of action and biologic plausibility. While the RCT is essential for establishing causality between an intervention and outcome of interest, in its current form, it is ill-suited to properly test the health benefits of bioactives in the context of diet and lifestyle. Aspects of RCT design and data interpretation, appropriate for assessing the effects of drugs, cannot be directly applied to questions regarding the health effects of nutrients and bioactive food components. Many experts have commented in recent years on the inherent limitations of the RCT (Table 1) to address nutrition-related questions. Drugs differ in many key aspects from nutrients, which in turn differ from bioactives (Table 2). Drugs tend generally to have single, targeted therapeutic effects; drugs are not homeostatically controlled by the body and can easily be contrasted with a true “placebo” group; drugs can act within a relatively short therapeutic window of time, often with large effect sizes. In contrast, nutrients tend to work in complex systems in concert with other nutrients and affect multiple cells and organs; nutrients are homeostatically controlled, and thus the body’s baseline nutrient “status” affects the response to a nutrient intervention; a nutrient intervention group cannot be contrasted with a true placebo group (i.e., “zero” exposure group); with respect to chronic disease prevention, nutrient effect sizes tend to be small and may take decades to manifest. The very absence (or inadequacy) of a given nutrient produces disease, which is a fundamental difference compared to drugs (summarized in Table 2). In contrast to drugs, the intent of nutrient and bioactives is for health promotion and maintenance, not disease treatment. These types of studies would impossibly raise the cost and logistical difficulty of evaluating nutrients and bioactives by orders of magnitude, rendering any evaluation prohibitively costly and unfeasible (Table 3).

These inherent, yet critical aspects have largely been overlooked, both unintentionally and for practical reasons, in the design, interpretation and communication of RCTs involving supplemental nutrients, particularly those high profile studies relied on to inform policy recommendations (e.g., PHSII (26, 27); SELECT (28), WAFACS (29); WHI (30)). In each of these major expensive studies the effects of nutrition on health were evaluated using a drug-like RCT design and the duration of the studies were arguably too short to demonstrate the health benefits of the nutrients and bioactives studied. As interpreted, they failed to demonstrate benefits due to their design, but the interpretation has invariably been that the bioactive provided no benefit. However, there now appears to be some agreement within the nutrition science community that an alternate scientific framework is needed to inform recommendations for nutrition, health promotion and disease prevention, that may include appropriately designed RCTs but would consider the totality of scientific evidence in developing recommendations and communication to the public on the health benefits of bioactives (31, 32).

---

EBM is also heavily dependent on the process of meta-analysis, the collection of often disparate studies which fail to demonstrate the effectiveness of a drug or its superiority over existing approaches. Meta-analysis attempts to combine studies with different populations and designs, and this approach is often flawed due to an inability to account for the differences in study design, population size, and the dose and preparation of the bioactive substances being studied (32, 33).
Essential nutrients

Recommendations for essential nutrients are developed using well accepted frameworks – the Dietary Reference Intakes (DRI), in the US and Canada (12) and the Dietary Reference Values (DRV) (13) in Europe – which establish recommended nutrient intakes and tolerable upper intake levels for the various age-gender groups. These recommendations are intended for the generally healthy population and are focused primarily on prevention of overt nutrient deficiency and excessive intakes (see Figure 1). Attempts are made to develop consistency between these nutrient intake recommendations and food-based dietary guidance in the US (21) and Europe (22).

Despite their widespread acceptance for establishing recommended nutrient intakes the DRI and PRI processes still hold the RCT as the “gold standard” of evidence, and thus are at the mercy of its limitations. This approach was evident with the IOM’s revised recommendations for calcium and vitamin D (34, 35). Recommendations are slow to develop and evolve due to a lack of compelling RCT data from appropriately designed trials. Furthermore, these represent reductionist approaches, narrowing recommendations only to specific essential nutrients. Due to their lack of established essentiality, tendency to be less well chemically defined and appearance in the diet as mixtures, bioactives likely cannot be evaluated using the current DRI and PRI approaches (36, 37). Clearly, if they are to be used to develop recommendations for bioactives, the DRI and PRI processes must evolve to recognize that foods and food components may have benefits beyond their essentiality in prevention of nutrient deficiency diseases, including health maintenance and promotion (16, 17).
Bioactives or Phytochemicals

Bioactives include classes of compounds, such as carotenoids, phenolics and organosulfur compounds (15) (Figure 2). These classes are comprised of thousands of compounds which are distinguished from both drugs and essential nutrients (as defined by the DRI and PRI), both chemically and functionally (Table 2). Thus they are considered nonessential but “nutritive” in the sense that intake is associated with a variety of health benefits. These compounds are food components, many having been present in the diet for millennia. Often, but not always biologic activity and function are defined through various “classes” of compounds, e.g. isoflavones, anthocyanins, carotenoids, etc…These classes are often found in similar food types (i.e. colorful fruits and vegetables) and are present as mixtures. With some exceptions, e.g. lutein (38), observed effects cannot be attributed to a single bioactive entity in a dose-response manner. In contrast, optimal effects may be achieved through these naturally occurring mixtures, the composition of which is often not well defined (15, 39).

While bioactives have been the subject of a number of health claim petitions – most of them rejected or denied - both in the US and Europe, an appropriate scientific framework has yet to be developed for assessing effects of bioactives and interpreting data to inform recommendations. The US FDA (23) and EFSA (24) have established EBM criteria as the sole acceptable method to assess the evidence for health claims. For evaluation of disease risk reduction claims, the US FDA states “when several randomized, controlled intervention studies are consistent in showing or not showing a substance/disease relationship, they trump the findings of any number of observational studies” (23, 40). EFSA’s negative opinions for health/functional benefit claims frequently cite the failure of the evidence “to support a cause and effect relationship” between the substance that is the subject of the health claim and the claimed effect and has been widely criticized by the industry and academic community, e.g. (41). These regulatory and advisory bodies do not recognize the inherent limitations in RCTs or the substantial logistical and feasibility issues inherent in conducting RCTs with nutrients and bioactives. Requiring RCTs as the primary or sole evidence base when such studies are not feasible may not be in the interest of public health (31). Furthermore the US Institute of Medicine of the National Academy of Sciences (IOM) has yet to formally include bioactives within the DRI process.

Many bioactives are ubiquitous in the diet, and when consumed within the nutritional range the available literature suggests these are generally safe (16). In the US and across Europe, daily consumption of bioactives varies across a broad range of intakes (15, 17, 42-46), and bioactive content of food also varies greatly (47). Systematic risk assessment reviews have revealed that, with some exceptions, defined adverse effects have not been established for these compounds at and well above amounts typically consumed (48-52). However, the effects of isolated bioactives are difficult to quantify in a dose-response manner, particularly in RCT due to their complex nature and subtle effects.
Aspects of scientific framework for evaluation of the effects of bioactives

A key to an appropriate scientific framework is to understand the distinction between bioactives and pharmaceuticals. As articulated elsewhere (4, 31), the effect size, risk of adverse effects and targeted nature of drugs tend to be far different from those of nutrients and bioactives (See also Table 2). Drugs generally have significant side effects and raise safety concerns which are anticipated based on pre-approval clinical trials. However, the vast majority of problems are discovered during post-marketing surveillance of large populations, leading to market withdrawal (7). Bioactives, in contrast, are ubiquitous in the food supply and don’t present the same risks. It is feasible to assess risk-benefit for bioactives only when the anticipated benefit is recognized as being greater than zero. If there is no benefit, then no risk is permissible. In fact, a system for recognizing potential benefits which incorporates the totality of scientific evidence will promote public health and stimulate more research on bioactives in health promotion (32). Since the effects of bioactives tend to be subtle, manifest for example, on chronic disease risk, over an extended period of time, evaluation of their effects is often unattainable via the traditional RCT (25).

An appropriate scientific framework to support recommendations for bioactives should be proportionate to the risk posed by the substance. While the standards of evidence for what constitutes “proof” of a benefit should not necessarily change whether one is considering drugs, essential nutrients or other bioactive food components, it is the amount of evidence necessary to inform a policy recommendation that should be tailored more appropriately to risk and benefit (31).

The type, scope and level of evidence needed to help inform recommendations will depend on a number of factors, including, but not necessarily limited to, the health benefit under consideration, the target population and the chemical characterization of the substance under consideration. The widely held assumption is that bioactives pose inherently low risk (relative to drugs), in turn allowing for recommendations in the face of less than optimal data. Such assumptions, where possible, must be validated through risk-benefit analysis. Methods for nutrient and bioactive risk assessment have been well established (51, 53). Benefit assessment, (e.g. health claims) has proven to be more elusive. While quantitative methods for risk-benefit analysis for foods, micronutrients and other food components are still yet to be defined, the concept has been discussed extensively in the literature (54-59). At some level, qualitative risk-benefit analysis should be incorporated to identify, for example, unreasonable risks to a sensitive population in the face of limited data on benefit. To be effective, risk-benefit analysis of bioactive food components should be informed by robust post-market surveillance. This is especially critical for bioactives, since globally, these tend to enter the marketplace via notification or registration rather than pre-market approval. Some regions and individual countries have implemented post-market surveillance and reporting requirements for foods, e.g. US (60), Canada (61, 62) and France (63). The food supplements industry is developing global self-regulatory guidelines for post-market surveillance (64). Data collected from post-market surveillance can be used to inform risk assessment of
products and food components present in the food supply (65), which in turn can inform risk-benefit analysis. In the case of bioactives where the risk posed is not nearly as high as that posed by drugs³, it may be possible to have a more proportionate approach to generating and evaluating the scientific evidence needed to inform recommendations (20).

The scientific framework for information and recommendations on bioactives should be based on an evaluation of the totality and strength of the evidence, and not limited to only one form of evidence (i.e. RCT), a point that has been frequently reinforced but it seems rarely practiced (18, 19, 32, 66-68). The three basic types of evidence needed for bioactives includes analytical, pre-clinical and clinical (Table 4).

Analytical methods, which are now widely available, are necessary to chemically characterize the substance(s) of interest, detect and quantify in human serum and tissues, to assess dietary exposure, to obtain bioavailability and pharmacokinetic data and for quality control purposes. Pre-clinical data are needed to establish the biologic plausibility and provide initial estimates of risk (i.e. establishment of a no observed adverse effect level or lowest observed adverse effect level). Clinical data are needed to determine population intake patterns and their relation to health outcomes, and intervention data are needed to reinforce the relation between bioactive intake and health and to better inform risk. When and where feasible, RCT data should be generated to provide further confidence, but should not be the sole form of evidence considered. Biomarkers of bioactive exposure (i.e. status) and efficacy are a critical component of the evidence base, as it is these markers that are used to relate intake and status to relevant health outcomes. A comparison of case studies appears in Table 5, comparing an essential nutrient (vitamin D), a chemically well-defined bioactive (lutein) and a bioactive mixture (isoflavones) with respect to the state of the evidence in some of the aforementioned key areas. Information obtained from the IOM (35) and literature reviews on lutein (32, 69-71) and isoflavones (72-77) indicates that the three are somewhat comparable with respect to the amount of evidence accrued in key areas, suggesting that at least qualitative recommendations for some bioactives is entirely possible (20).

³ In the US in the years spanning 1969 – 2002, 75 FDA-approved drugs were withdrawn from the market due to safety issues (40). During the same time period, no dietary supplements or dietary ingredients were removed from the market. To date, only ephedra and ephedrine alkaloids have been removed from the market by FDA.
Informing recommendations

Establishing recommendations for bioactives through the IOM DRI process has been previously proposed (16, 17). However, DRIs and PRIs may be too focused and specific for application to bioactives; “proving” essentiality through traditional approaches (e.g. depletion-repletion studies) is no longer feasible or ethical. Bioactives may not be as clearly defined and benefit may not be reflected in achieving a specific intake level, making qualitative recommendations more appropriate. One approach would be analogous to the adequate intake (AI), defined as a recommended average daily nutrient intake level, based on experimentally derived intake levels or approximations of observed mean nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate (12) (Figure 1). The AI may be more appropriate as it encompasses a range rather than a single firm value, and thus may be better suited for mixtures of compounds, which is how bioactives are typically obtained in the diet (20). Combining recommendations for bioactives with dietary guidance has been proposed as an effective means to reinforce fruit and vegetable intake (16). As described by Williamson, following basic fruit and vegetable intake recommendations can result in a daily intake of polyphenols in excess of 500 mg (16). Promoting the health benefits of fruits and vegetables by communicating the amounts of specific bioactives provided could assist in improving compliance with these recommendations. The AI could be used as such a tool to reinforce the US and European Dietary Guidelines and other government programs that emphasize fruit and vegetable intake (78). Increased education on bioactives may also help increase the intake of fruits and vegetables and other healthy foods which has so far been a difficult goal for governments to achieve (79). Furthermore, if the AI designation were to be expanded to broader applications to bioactives such as lutein, this should provide a basis for establishing a daily value (DV, US) or dietary reference value (DRV, Europe), both of which serve as reference values for food labeling. Having a DV or DRV would provide a sanctioned target amount for food and food supplement manufacturers and for consumers to better inform their dietary habits.

An important issue to ponder is how the framework described above and establishing an AI for certain bioactives might impact other nutrition policy recommendations. If intake recommendations for bioactives can be developed and applied through dietary guidance and/or an AI, then it should follow that other recommendations, such as health claims, might also be subject to a different approach. Currently, the US FDA’s evidence-based review of health claims and EFSA’s opinions of submitted health claim petitions apply drug-like criteria in the review and approval or opinion process for health claims. A scientific framework that tailors the amount of evidence needed to inform dietary guidance or an AI may also help inform the health claim review process.
Challenges

The challenges to establishing a scientific framework that would support recommendations for bioactives are many and far reaching. The main challenge, as it is for nutrition and health in general, is lack of or inadequate data in key areas, such as biomarkers of exposure and efficacy (20, 80). The tendency for bioactives to be present in the diet as complex mixtures that are not specifically and chemically well-defined can cause confusion making recommendations difficult. With the current economic environment prompting fiscal conservatism, there also continues to be inadequate resources made available to address research gaps in our knowledge of bioactive substances.

Governments clearly have an interest in protecting the public from potential harm. However, the risks of bioactives are minimal when they are consumed in the nutritional range. The impression that bioactives are both ineffective and toxic distorts the scientific facts and is drawn from a misinterpretation of both RCTs in EBM and overinterpretation of adverse events where the connection to the bioactive substance is tenuous. Robust post-marketing surveillance will clearly provide more protection to the public than pre-market RCTs conducted in small numbers of individuals. Consideration of the totality of the evidence on bioactives will promote more basic and applied research on bioactives. Increased education on bioactives may also help increase the intake of fruits and vegetables and other healthy foods which has so far been a difficult goal for governments to achieve (79).
### Tables

**Table 1. Strengths and limitations of RCTs**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>Narrow application</td>
</tr>
<tr>
<td>Minimizes bias, confounding</td>
<td>Cost</td>
</tr>
<tr>
<td>Establishes causality</td>
<td>Feasibility</td>
</tr>
</tbody>
</table>

**Table 2. Contrast between drugs, essential nutrients and bioactives**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drugs</th>
<th>Nutrients</th>
<th>Bioactives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemically defined and well characterized</td>
<td>Yes, single entities</td>
<td>Yes, single entities</td>
<td>No, complex mixtures</td>
</tr>
<tr>
<td>Essentaility</td>
<td>None</td>
<td>Essential</td>
<td>Unclear</td>
</tr>
<tr>
<td>Inadequacy results in disease</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Homeostatically controlled by the body</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>True placebo group</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Targets</td>
<td>Single organ/tissue</td>
<td>All cells/tissues</td>
<td>Multiple cells/tissues</td>
</tr>
<tr>
<td>Systematic function</td>
<td>Isolated</td>
<td>Complex networks</td>
<td>Complex networks</td>
</tr>
<tr>
<td>Baseline “status” affects response to intervention</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Effect size</td>
<td>Large</td>
<td>Small</td>
<td>Small to moderate</td>
</tr>
<tr>
<td>Side effects</td>
<td>Large</td>
<td>Small</td>
<td>Small</td>
</tr>
<tr>
<td>Nature of effect</td>
<td>Therapeutic</td>
<td>Preventive</td>
<td>Preventative and therapeutic</td>
</tr>
</tbody>
</table>
Table 3. Cost comparison between therapeutic and risk reduction RCTs*

<table>
<thead>
<tr>
<th></th>
<th>Therapeutic (drug) trial</th>
<th>Risk reduction (nutrient, bioactive) trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those with disease at baseline</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Placebo administration</td>
<td>20% cured (80% still have disease)</td>
<td>20% acquire disease (80% do not acquire disease)</td>
</tr>
<tr>
<td>Intervention administration – if 25% effective</td>
<td>¼ of 80% (20%) cured; 60% still have disease</td>
<td>¼ of 20% (5%) do not acquire disease; 15% acquire disease</td>
</tr>
<tr>
<td>Desired statistical power</td>
<td>$\alpha = 0.05$, power = 0.8</td>
<td>$\alpha = 0.05$, power = 0.8</td>
</tr>
<tr>
<td>Subjects required per group</td>
<td>64</td>
<td>714</td>
</tr>
<tr>
<td>Cost ($)</td>
<td>1.3 million</td>
<td>&gt;15 million</td>
</tr>
</tbody>
</table>

* Based on presentation at CRN’s Day of Science, May 8, 2008. NCCAM research initiatives focused on prevention by Josh Berman, MD, PhD, National Center for Complementary and Alternative Medicine, NIH. Council for Responsible Nutrition, Washington, DC.
Table 4. Basic types of data needed to inform bioactive intake recommendations

<table>
<thead>
<tr>
<th>Type of data</th>
<th>Specific application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical</td>
<td>Methods to characterize bioactive(s)</td>
</tr>
<tr>
<td></td>
<td>Detect and quantify bioactive(s) in human sera and tissues</td>
</tr>
<tr>
<td></td>
<td>Quantify bioactive(s) in the food supply</td>
</tr>
<tr>
<td></td>
<td>Quality control</td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>In vivo data suggesting health benefit, bioavailability, pharmacokinetics, risk assessment</td>
</tr>
<tr>
<td></td>
<td>In vitro data to establish mode of action, biologic plausibility</td>
</tr>
<tr>
<td>Clinical</td>
<td>Population intake patterns</td>
</tr>
<tr>
<td></td>
<td>Epidemiologic observations</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td>Biomarkers of exposure and efficacy</td>
</tr>
<tr>
<td></td>
<td>Risk assessment</td>
</tr>
<tr>
<td></td>
<td>Post-market surveillance</td>
</tr>
</tbody>
</table>
### Table 5. Case studies

<table>
<thead>
<tr>
<th></th>
<th>Vitamin D</th>
<th>Lutein/zeaxanthin</th>
<th>Isoflavones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional category</strong></td>
<td>Essential nutrient</td>
<td>Defined bioactive</td>
<td>Bioactive mixture</td>
</tr>
<tr>
<td><strong>Analytical methods</strong></td>
<td>(+++)</td>
<td>(+++)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Pharmacokinetic/ bioavailability &amp; metabolism</strong></td>
<td>(+++)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Functional role/ biologic plausibility</strong></td>
<td>(+++)</td>
<td>(+++)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Good status marker</strong></td>
<td>Serum 25(OH)D3 (+++)</td>
<td>Macular pigment density (+)</td>
<td>Serum isoflavones (+)</td>
</tr>
<tr>
<td><strong>Observational studies link to relevant health outcome</strong></td>
<td>Bone (+++) Cancer (+) Cardiovascular disease (+)</td>
<td>Macular degeneration (+) Cataracts (+)</td>
<td>Bone (+++)</td>
</tr>
<tr>
<td><strong>Prospective RCTs</strong></td>
<td>Bone density (+++) Fracture risk (+++)</td>
<td>Macular pigment (+) Visual function (+) Cognitive function (+)</td>
<td>Bone density (+/-) Hot flashes (+)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Established UL (+++)</td>
<td>Recommended OSL (+)</td>
<td>Mixed, no consensus (+/-)</td>
</tr>
</tbody>
</table>
Figure 1. US Institute of Medicine’s Dietary Reference Intakes
Figure 2: Examples of bioactive food components
Adapted from Liu et al. 2004 (15)


References

33. Tucker K. The use of epidemiologic approaches and meta-analysis to determine mineral element requirements. The Journal of nutrition 1996;126(9 Suppl):2365S-72S.


41. Starling S. EU researchers revolted as EFSA clears health claims vault. Nutraingredientscom 2011.


64. AADSA Guidelines on the handling of adverse event complaints for supplement manufacturers and distributors (working title). In process publication, Brussels, Belgium: International Alliance of Dietary/Food Supplement Associations, 2011.


