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Bioactive nutrients - Time for tolerable upper intake levels to address safety

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ABSTRACT

There is increasing interest by consumers, researchers, and regulators into the roles that certain bioactive compounds, derived from plants and other natural sources, can play in health maintenance and promotion, and even prolonging a productive quality of life. Research has rapidly emerged suggesting that a wide range of compounds and mixtures in and from plants (such as fruits and vegetables, tea and cocoa) and animals (such as fish and probiotics) may exert substantial health benefits. There is interest in exploring the possibility of establishing recommended intakes or dietary guidance for certain bioactive substances to help educate consumers. A key aspect of establishing dietary guidance is the assessment of safety/toxicity of these substances. Toxicologists need to be involved in both the development of the safety framework and in the evaluation of the science to establish maximum intake/upper limits.

1. Introduction

There is increasing interest by consumers, researchers, and regulators into the roles that certain bioactive compounds, derived from plants and other natural sources, can play in health maintenance and promotion, and even prolonging a productive quality of life. Research has rapidly emerged suggesting that a wide range of compounds and mixtures in and from plants (such as fruits and vegetables, tea and cocoa) and animals (such as fish and probiotics) may exert substantial health benefits. There is interest in exploring the possibility of establishing recommended intakes or dietary guidance for certain bioactive substances to help educate consumers. A key aspect of establishing dietary guidance is the assessment of safety/toxicity of these substances. Toxicologists need to be involved in both the development of the safety framework and in the evaluation of the science to establish maximum intake/upper limits.

2. Models for establishing upper levels

Possible approaches to determining safety of dietary bioactive components are those used to establish upper intake levels for nutrients (IOM, 1998a). Initiated by the Food and Nutrition Board (FNB) in 1994 for the United States and Canada, the development of Dietary Reference Intakes (DRIs) for nutrients though 2004 included not only recommended dietary intakes (RDAs) as had been issued since 1941, but also introduced Tolerable Upper Intake Levels (ULs) for nutrients, applying risk assessment methodology. This approach followed reports from the United Kingdom in 1991 (COMA, 1991) and from ILSI in 1994 (Mertz et al., 1994) which identified the need for upper reference values due to the increased use of fortified foods and availability of dietary supplements, permitting nutrient intakes to exceed that typically obtained from

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natural foods alone.

The DRI process as envisioned by the Food and Nutrition Board in 1994 (IOM, 1994) not only included reviews of known nutrients, but also reviews of the literature to establish reference values for other food components, now termed *bioactives*, wherever possible. While past FNB RDA reports focused on amelioration of deficiency conditions, the DRI process was to also include endpoints related to decreasing risk of chronic disease. While this had been the plan, over the 10 years of the DRI process, reference values were only developed for one bioactive compound class evaluated, fiber (IOM, 2002).

The DRI Upper Level model as developed draws heavily on toxicology tenets that must be tweaked since a nutrient, unlike most additives and contaminants, has a minimum level of intake that is required to maintain health. The definition of the UL focuses on adverse health effects in the general population. A rotating subcommittee composed of toxicologists and nutritionists developed and reviewed all the published data over the 10-year period to develop ULs for 24 of the 37 vitamin and mineral nutrients reviewed. The UL is based on either a *No Observed Adverse Effect Level (NOAEL)* or a *Lowest Observed Adverse Effect Level (LOAEL)*, and then decreased by dividing by a factor based on the uncertainty of how applicable to the entire population the available data are, and the seriousness of the known adverse effects. The process for developing ULs based on nutrient risk assessment is now globally accepted as the approach for establishing upper level reference values and regulatory maximums and is used in US/Canada, Europe, China, Southeast Asia and some Latin American markets.

Aspects to consider when applying the DRI UL method to bioactive components are the extent of data regarding intakes of bioactive components and documented adverse effects, and available estimates of typical dietary intakes of the substances in the population. While detailed food composition databases are available for nutrients (e.g., USDA Nutrient Database, www.ndb.nal.usda.gov), such databases for content of bioactive components in foods are in their infancy. In addition, many bioactive components with possible health benefits are groups of chemical compounds within foods (such as flavonoids), rather than easily identifiable single substance such as a vitamin or mineral.

While there is an idealized benefit/risk curve for nutrients, there may be overlapping distributions in a population where the amount needed to obtain maximum benefit for one individual may be greater than the amount that may result in an adverse effect due to excess for another, or the adverse effect in the same individual overlaps with the amount needed for benefit; for example, the effect of increasing fluoride intake to decrease dental caries overlaps with the increasing incidence of dental fluorosis or mottling (IOM, 1997, 2007).

While there can be a number of adverse effects associated with high intakes of a nutrient, the UL is based on a specifically defined adverse effect that would be most detrimental to the population. For example, for folate, the adverse effects reported in the literature prior to 1998 when the DRI review was done included a) neurological damage in vitamin B12-deficient individuals, b) general toxicity as found in mental changes, sleep disturbances, and GI effects at 15 mg/day, c) increased cancer of oropharynx and hypopharynx and total cancer rates in an epidemiological study, and d) hypersensitivity, which was rare, at 1 mg/day (IOM, 1998b). At the time there were about 100 reported cases of neurological damage with supplemental folate consumed at $\geq$ 5 mg/day, while there were only 8 well-documented cases at < 5 mg/day. Based on this LOAEL, the Uncertainty Factor (UF) was chosen as 5, due to the severity of the neurological complications and their irreversibility. However, it was not higher than 5 because there were uncontrolled observations in millions of people taking 1/10th the LOAEL of 5 with no reported harm. Similar DRI UL reviews were done for all 37 vitamins and minerals evaluated.

Since the DRI reports were released beginning in 1997, other groups have undertaken in-depth risk assessments of nutrients for upper levels using similar methodologies. The most extensive were conducted by the European Union Scientific Committee on Foods (2000, 2002) subsequently now under the European Food Safety Authority (EFSA, 2004) and the United Kingdom's Expert Group on Vitamins and Minerals (EVM, 2003). Not surprisingly, resulting ULs have differed, even when using the same datasets, due to different choices of adverse effects upon which to base a UL, and different UFs based on committee consensus. A comparative analysis of the three approaches (DRI, EVM, and UK) has been published (IOM, 2007).

Other possible reference value approaches have been proposed. One approach proposed in 2006 at the FAO/WHO Technical Workshop on Nutrient Risk Assessment (FAO/WHO, 2006) for use when there is little NOAEL or LOAEL data upon which to conduct a risk assessment is to establish the Highest Observed Intake (HOI), derived only when no adverse health effects have been identified. The HOI is the highest level of intake observed (or administered as reported within a study of acceptable quality); this could be the 90th or 95th percentile of estimated intakes in a population with no apparent adverse effects. However, it is important that the HOI should be overtly differentiated from the UL to prevent its misinterpretation or use.

The FAO/WHO report also highlighted the critical issues faced when developing ULs for nutrients: that nutrient substances are subject to complicated homeostatic mechanisms that may control and alter absorption, utilization, storage, and/or transport which may typically not occur with contaminants or additives, and that there are few valid *causally* associated biomarkers that are known surrogates for adverse effects. Thus the likelihood of being able to establish an UL based on risk assessment, particularly for bioactive components in the diet which are less well characterized, becomes quite difficult. Long-term or habitual intake data are required to determine both the relation between the biomarker and adverse effect and to characterize risk. Thus the HOI could provide guidance on where to limit intake for substances such as bioactives when valid risk assessments can't be obtained.

3. Application of toxicology decision-making

The main steps involved in developing tolerable upper intake levels (ULs) are 1) identification of the critical effect, 2) determination of the point of departure (POD) of the dose response curve, and 3) application of appropriate uncertainty factors (UFs) to the POD. Although risk assessors often focus on the second and third points, identification of the critical effect is of utmost importance, as an UL predicated on a non-critical effect may not protect the consumer against toxicologically relevant effects.

To determine the critical effect of a food or dietary supplement ingredient, risk assessors should review studies with oral exposure. Human data are preferable to animal data and intervention studies (particularly randomized, double blind, placebo controlled) are more useful than observational. Information from animal species whose biological responses are most similar to humans is more valuable than other animal data, but usually studies in rats or mice, which may not be the best models are used to derive an UL when reliable human data are not available.

Lewis and coworkers (2002) provided three pointers to help toxicologists select the data set that identifies the critical endpoint. First, *is there a difference compared to control?* Usually this is identified by an appropriate statistical analysis. Second, *is the difference an effect of treatment?* A difference is more likely to be an effect of