Understanding Tolerable Upper Intake Levels

Introduction to the Workshop Proceedings1,2

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Beginning with its first Dietary Reference Intakes (DRI)4 report released in 1997 (1), the Food and Nutrition Board (FNB) of the Institute of Medicine introduced an updated framework of nutrient reference values to the nutrition community. As described in an overview of the history and evolution of the DRI, the series of DRI reports released from 1997 through 2004 replaces earlier periodic reports of the Recommended Dietary Allowances from the United States and the Recommended Nutrient Intakes from Canada (2). Four key DRI values are defined, including the Estimated Average Requirement (EAR), the Recommended Dietary Allowance (RDA), the Adequate Intake (AI), and the Tolerable Upper Intake Level (UL). [The macronutrient report (3) also articulates the Acceptable Macronutrient Distribution Range (AMDR) and the Estimated Energy Requirement (EER) as key guidance values.] In part because of past misunderstanding and misapplication of RDA values, there has been a strong effort to articulate the appropriate uses and interpretation of the new DRI, with reports devoted to their application in both dietary assessment (4) and planning (5). Nevertheless, revising the DRI and improving an understanding of their application is an ongoing process as new data emerge.

Including the UL in the DRI marks the first time a standard reference intake value has considered the potential toxicity of micronutrients. The most recent DRI report defines the UL as “the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all apparently healthy individuals in the specified life stage group. As intake increases above the UL, the potential risk of adverse effects may increase” (6, p. 27). The UL values for 14 elements and 8 vitamins are provided for at least some population subgroups. The UL concept and values were welcomed by many in the nutrition community as a way to address increasing concerns about the potential for the negative effects of over-consuming some nutrients, particularly with the widespread use of dietary supplements and fortified foods. In practice, however, the published list of UL values raises numerous challenges for nutritionists, regulatory agencies, and the food industry, as might be expected when a new guidance concept is introduced.

On April 23 and 24, 2003, the North American Branch of the International Life Sciences Institute (ILSI North America) Project Committee on Tolerable Upper Levels convened a workshop designed to outline the science behind the philosophy and the methods for deriving the ULs, to discuss how public health can best be served by the use of ULs, and to determine the research needs for advancing the science that is used to establish the ULs. Topics presented by speakers and workshop participants included discussions about the uncertainties inherent in deriving some ULs, particularly the issues of insufficient data and application of ULs to special populations, such as children; the challenges ULs bring to the nutrition community; the need for future improvements in the ULs; how to deal with practical and regulatory issues; and how to improve communication about ULs to risk managers and the public. Since the discussions in April, the Food and Nutrition Board initiated a series of open sessions with the nutrition community designed to inform the public of the existing DRI paradigm and to gather input about the future of the DRI process. These meetings have dealt with issues related to how and when future DRI nutrient panels might be initiated to review the science around individual nutrients so that nutrient reference values can be revised. The meetings also have been looking at the criteria for considering a nutrient or other food component for initial assessment within the existing DRI framework, and discussing ways to improve or modify the DRI process itself. Whereas the April ILSI North America workshop focused its discussions on issues surrounding the ULs, the other DRIs require parallel considerations. The UL proceedings make a contribution to the ongoing dialogue that will shape the next generation of DRIs.

Richard Lane, representing the committee that organized the workshop, introduced the meeting by summarizing the workshop intent: to determine how existing ULs may be appropriately applied to health, to examine the methods used to establish ULs, and to discuss how to improve them for future editions of DRI reports. Lane articulated 4 key areas of confusion or at least incomplete understanding. First, the nutrition community is not completely knowledgeable about or comfortable with the toxicological risk assessment approach used to
establish the ULs. In fact, some question the appropriateness of applying toxicology methodology to nutrients. It was proposed that a more complete risk-benefit analysis approach, that considers both the risks of excess intakes and the benefits of adequate intakes, is more suitable for nutrients and should be advanced for the development and application of ULs in forthcoming DRI revisions. Second, the language of the UL is confusing to some users. In fact, the use of “upper level” without the modifier “tolerable” [such as in the title of the DRI report, A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients (7)] is itself a potential point of confusion. In some cases, ULs are being misinterpreted as strict and safe “upper limits.” Lane proposed the acronym TUL or even TUIL as a replacement for UL. Third, there is confusion or skepticism regarding some of the specific UL numbers, either because typical intakes already exceed the UL for some population subgroups, or because the UL for one subgroup overlaps with the recommended intake for another. For example, the UL for zinc for children ages 1–3 is 7 mg/d, while the fiftieth percentile usual dietary intake based on the Continuing Survey of Food Intakes by Individuals 1994–1996 is estimated at 7.2 mg/day (8). How should a nutritionist interpret this finding? As another example, the UL for folate for children aged 4–8 y is 400 μg/d, which is also the RDA for adolescents and adults, as well as the current daily value for food labels designed for people ages 4 and older. Fourth, Lane identified shortcomings in communications to various stakeholders as a final source of confusion. In fact, communication is at the core of any confusion, because developers and potential end users of the ULs may not fully understand each others’ intentions, language, or issues. Thus, a series of presentations followed by discussions helped workshop attendees understand the philosophy and application of ULs, the scientific and communication challenges involved, and research needs and limitations; these discussions helped attendees provide recommendations to close the gaps.

Ian Munro, chair of the DRI Subcommittee on Upper Reference Levels of Nutrients, described the risk assessment model, including the considerations used to establish the no-observed adverse-effect levels, the lowest observed adverse effect levels, and the uncertainty factors in the derivation of ULs. In addition, he commented on alternate approaches considered by the committee, and why they did not choose them. Munro summarized the key reasons for using the risk assessment process, but cautioned that applications to nutrition “are only as good as the data.” Andrew Renwick added to the understanding of the risk assessment model applied to nutrients, including a consideration of how nutrients and non-nutrient toxicants differ in terms of adverse effects. He provided insight into the derivation of uncertainty factors and explained how different expert groups using the same risk assessment models may arrive at different uncertainty factors (as he related by comparing the United Kingdom and the European Union experiences with those of the United States and Canada).

John Milner and Stanley Zlotkin addressed the challenges in deriving useful ULs for various populations because of genetic diversity among individuals in populations and individuals’ different stages of life. Milner provided examples of differing thresholds among members of the general population and discussed the parallel concerns that will come about if and when UL guidance is given for nonnutrient functional food components. Milner envisioned that the development of early biomarkers will allow better personalization of ULs. Zlotkin raised many questions about ULs derived for children and criticized the practice of extrapolating values for adults and applying them to children merely on the basis of body weight. As he pointed out, intakes of some nutrients, such as zinc, routinely exceed the ULs for many children, without evidence of adverse health effects. He challenged the risk assessment model used by the committee that established the ULs and suggested that the use of an evidence-based approach might be a more realistic method of establishing ULs.

To use a UL to characterize population nutrient intakes, nutritionists need to know the actual usual intake of the nutrient. Alicia Carriquiry, a pioneer in the development of a method widely used to adjust intake data obtained on limited days to reflect the “usual” intake, described the Iowa State University method and showed how the upper tail of intake is particularly skewed if it is based on just a few days of data. She highlighted that the major problem the United States and other countries have in accurately assessing nutrient intake is due to the limited amount of available data on supplement use, and because food composition data are quickly outdated as new products appear on the market.

Finally, John Vanderveen and Sanford Miller highlighted the gaps in current knowledge and theory and outlined key considerations for moving forward. Vanderveen pointed out that the idea that certain essential nutrients may be harmful when consumed in sufficient quantities is still hard for some to grasp. He noted the particular challenges with determining UL values for nutrients because there is often a biological regulation of absorption, metabolism, or excretion that impacts the level at which a nutrient manifests toxicity. Nutrient–nutrient interactions can also impact the level at which a nutrient may be harmful. Miller called attention to the need to better define and differentiate the science of risk assessment vs. the concept of safety, which reflects society, culture, politics, economics, and other factors, in addition to science. The science itself, however, suffers from a lack of information regarding the dose-response relation for nutrients, the acute vs. the chronic effects of excess nutrient intakes, and the relevant endpoints for characterizing the risk of inadequacy versus the risk of excess. Miller offered a new twist on the real-estate mantra “location, location, location” to capture the essence of how the relevance of, and confidence in, UL values can be improved: “data, data, data!” Significant resources are needed to advance the ultimate goal of improving and protecting public health.

The papers included in this supplement summarize presentations by Munro, Renwick, Zlotkin, Carriquiry (with Camano-Garcia), and Vanderveen. These authors provide their individual insights and interpretations of the complex issues surrounding the derivation and use of ULs. In addition, workshop discussion sessions among speakers and guests yielded insightful ideas, summarized in the final paper. We hope that this supplement stimulates further discussion and research on ULs to improve their applicability as the Food and Nutrition Board considers new data and approaches to deriving DRI and refining the DRI process.

LITERATURE CITED

