Background Information
IOM/FNB Workshop on Dietary Reference Intakes
The Development of DRIs 1994-2004: Lessons Learned & New Challenges
September 18-20, 2007
Washington, DC

Information Compiled and Posted July 11, 2007

Purpose: To Provide Useful/Relevant Information for
Workshop Participants and Attendees

Opportunity for interested parties to comment electronically through August 11, 2007:
www.iom.edu/driworkshop2007

DOCUMENT REFERENCE:

International Harmonization of Approaches for Developing Nutrient-Based Dietary Standards
Food and Nutrition Bulletin, vol. 28, no. 1, 2007

INTRODUCTION
(Excerpted pp. S13-S15)

and

EXECUTIVE SUMMARY
(Excerpted pp. S3-S12)

Introduction

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The important roles of wholesome food supplies lead national governments or their designated agents to name expert groups periodically to derive and promulgate nutrient-based dietary standards, e.g., estimated average requirements, recommended intakes for individuals, and upper tolerable intake levels. Discrepancies often arise among diverse national efforts, in part because there is no global consensus regarding concepts and approaches for their derivation. These discrepancies create problems for health, trade, and other national authorities responsible for those sectors.

The lack of a global consensus on the most appropriate concepts and approaches for the determination of national standards makes it difficult to resolve differences that arise in setting national and international nutrition standards and public and clinical health objectives, designing national and international food policies, and enhancing the transparency of national standards to trade and other regulatory and normative activities with economic, health, and safety implications. Resolution of these differences is most problematic for developing countries that often have to sift through disparate recommendations without the needed infrastructures to make decisions.

Project objective

To address these discrepancies in dietary standards worldwide that lead to international discrepancies in health, food policies, and trade, a working group was convened *to harmonize concepts and approaches* (as opposed to deriving specific recommendations) for developing nutrient-based dietary standards. A major outcome of this effort is an improvement in the transparency of methods used to derive nutrient-based dietary standards and how to apply them to various functions.

Approach

The United Nations University (UNU) Food and Nutrition Programme in collaboration with the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) Nutrition Department for Health and Development commissioned 10 papers from leaders in establishing and applying nutrient intake recommendations. Each paper focused on distinct aspects of the process for developing harmonized nutrient-based dietary standards. A brief description of the papers follows.

King et al. [1] review the terminology used by various countries and regions for defining dietary standards. A general framework for establishing nutrient intake values is proposed and the rationale for the proposed framework is discussed. Aggett [2] reviews the approaches for identifying upper nutrient levels and proposes a framework for defining upper nutrient levels.

Yates [3] reviews the possible approaches for identifying physiological criteria for establishing dietary standards (i.e., determining what physiological functions requirements will satisfy). Important components of this paper are how to estimate the numbers of subjects needed to estimate function-specific nutrient requirements and interindividual variation, how to identify the basis for that variation, and the assessment of approaches for identifying the physiological states or ages for which data are required.

Murphy and Vorster [4] review the specific methologic approaches to plan and assess intakes for individuals and populations. The advantages of basing dietary

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assessments and plans on the NIV are discussed.

Atkinson and Koletzko [5] review the bases for extrapolation and interpolation among and between age groups, environments, and physiological states for which insufficient data are available.

Gibson [6] reviews the biological factors that influence recommended intakes of specific nutrients (e.g., composition of usual diets, bioavailability, biological value, interindividual variability, nutrient–nutrient interactions, etc.).

Stover [7] reviews the implications of expanding understanding of the human genome and the technological capabilities that have made that understanding possible. Special attention is focused on the role of population-wide versus individual recommendations and on the likely magnitude of inter- and intrapopulation genetically based differences that relate to nutrient requirements.

Vorster et al. [8] review the diverse applications of nutrient intake values (NIVs) for dietary assessment and planning. Examples of how to use NIV for food labeling, food fortification, and food-based dietary guidelines are provided.

Ramaswamy and Viswanathan [9] review regulatory and trade issues of importance to the harmonization of approaches for setting nutrient-based dietary standards and, ultimately, quantitative estimates of standards.

Smitasiri and Uauy [10] review principles and approaches for the translation of nutrient-based dietary standards to food-based guidelines, with special care being taken to address the multiple uses that food-based guidelines have served (e.g., consumer education and feeding programs).

Following an initial review and modification of the papers, the authors and staff from the UNU, FAO, WHO, and UNICEF met at the UNICEF Innocenti Center in Florence, Italy, in December 2005, to discuss the papers and develop the final report on harmonizing dietary standards. Following the December meeting, the authors revised their reports based on discussion and decisions regarding the framework, criteria, uses, and applications of dietary standards. The papers included in this supplement to the *Food and Nutrition Bulletin* are the final product of this process. An Executive Summary [11] is also included in the report that outlines the discussion and decisions made by the group.

Members of the Working Group on International Harmonization of Approaches for Developing Nutrient-Based Dietary Standards

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References

1. King JC, Vorster HH, Tome DG. Nutrient intake values (NIVs): A recommended terminology and framework for the derivation of values. Food Nutr Bull 2007; 28(suppl):S16–26.
2. Aggett PJ. Nutrient risk assessment:Setting upper levels and an opportunity for harmonization. Food Nutr Bull 2007;28(suppl):S27–37.
3. Yates AA. Using criteria to establish nutrient intake values (NIVs). Food Nutr Bull 2007;28(suppl):S38–50.
4. Murphy SP, Vorster HH. Methods for using nutrient intake values (NIVs) to assess or plan nutrient intakes. Food Nutr Bull 2007;28(suppl):S51–60.
5. Atkinson S, Koletzko B. Determining life-stage groups and extrapolating nutrient intake values (NIVs). Food Nutr Bull 2007;28(suppl):S61–76.
6. Gibson RS. The role of diet and host-related factors in nutrient bioavailability and thus in nutrient-based dietary requirement estimates. Food Nutr Bull 2007;28(suppl):S77–100.
7. Stover PJ. Human nutrition and genetic variation. Food Nutr Bull 2007;28(suppl):S101–15.
8. Vorster HH, Murphy S, Allen LH, King JC. Application of nutrient intake values (NIVs). Food Nutr Bull 2007;28(suppl):S116–22.
9. Ramaswamy S, Viswanathan B. Trade and regulatory issues and nutrient intake values (NIVs). Food Nutr Bull 2007;28(suppl):S123–40.
10. Smitasiri S, Uauy R. Beyond recommendations: Implementing food-based dietary guidelines for healthier populations. Food Nutr Bull 2007;28(suppl):S141–51.
11. King JC, Garza C. Executive summary. Food Nutr Bull 2007;28(suppl):S3–12.

Executive summary

Harmonization of nutrient intake values

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Key words: Nutrient recommendations, nutrient requirements

The United Nations University's Food and Nutrition Programme, in collaboration with the Food and Agriculture Organization (FAO), the World Health Organization (WHO), and UNICEF, convened a group of international experts to review the harmonization of approaches for developing nutrient-based dietary standards. The group met at the Innocenti Center in Florence, Italy, and was charged to:

» Identify the concepts that must be harmonized to provide a foundation for generating nutrient-based dietary standards and to define the components and terms supporting these concepts;
» Harmonize guidelines for the elaboration of methods and approaches for developing nutrient-based dietary standards; and
» Consider specific aspects of the process for developing nutrient-based dietary standards that require adjustments for unique food patterns and lifestyles of specific populations throughout the world.
» The group reviewed the need for harmonization, agreed on the definitions of key terms, developed a framework for estimating average nutrient requirements (ANRs) and upper nutrient levels (UNLs), identified criteria for establishing ANRs and UNLs, evaluated key issues related to the derivation of such values (e.g., nutrient bioavailability, extrapolation of values among diverse life-stage groups, application of standard height and weights, categorization of life-stage groups, and effects of genetic variation), and considered their uses and applications, especially their roles in the development of dietary guidelines. The group's deliberations were based on papers developed for this review and published by the *Food and Nutrition Bulletin* [1–10]. The outcome of these deliberations is summarized below.

Why harmonize?

The group identified four basic reasons why it is important to harmonize approaches and methods for the development of nutrient intake values (NIVs), the term adopted to encompass all nutrient-based dietary standards derived from primary data. First, harmonization of the process will improve the objectivity and transparency of values that are derived by diverse national, regional, and international groups. Second, a harmonized process will provide a common basis or background for groups of experts to consider throughout processes that lead to NIV. Third, a harmonized process will permit developing countries, which often have limited access to scientific and economic resources, to convene groups of experts to identify how to modify existing NIVs to meet their populations' specific requirements, objectives, and national policies. Finally, a harmonized process will supply a common basis for the use of NIVs across countries, regions, and the globe for establishing public and clinical health objectives and food and nutrition policies, such as fortification programs, and for addressing regulatory and trade issues.

Harmonization of key terms

The group agreed to use the term NIV to encompass the set of recommendations based on primary data that are analogous to those developed by various regional groups, e.g., dietary reference values (DRVs) by the United Kingdom, nutrient reference values (NRVs) by Australia and New Zealand, reference values for nutrient supply by Germany/Austria/Switzerland, and

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dietary reference intakes (DRIs) by the United States and Canada. The term was judged to be sufficiently neutral and descriptive of these values' broad uses.

The group agreed to recommend only two NIVs, the average nutrient requirement (ANR) and the upper nutrient level (UNL). It recognized that groups charged with the development of such recommendations have derived other values, but that these other values usually are derived from estimates of nutrient-specific ANRs or UNLs.

The exclusion of lower recommended intakes, reference nutrient intakes, safe or adequate intakes, and population-level recommendations from tables summarizing NIVs, is put forward for the following reasons:

Lower reference nutrient intake (LRNI) or lower threshold intake (LTI). This value is derived from the ANR, i.e., it is equivalent to the ANR minus 2 SD of the requirement. Typically it is sufficient to meet the needs of only 2% of individuals, but countries may wish to use some other analogous value (e.g., values that meet the needs of 5% or 10% of a specified population) to evaluate the likelihoods of nutrient intake sufficiency and deficiency.

The principal rationale for the exclusion of such values rests on their limited usefulness for assessing the prevalence of undernutrition in populations, and concern that such values set too low an expectation for the adequacy of nutrient intake of individuals. Their use for planning purposes is similarly too limited.

Reference nutrient intake (RNI), recommended nutrient intake (also RNI), recommended dietary allowance (RDA), and recommended dietary intake (RDI). This number also may be derived from the ANR as the mean plus 2 SD of the mean requirement. The process for setting it or other values intended to guide individual intakes is described in subsequent sections of this summary. Typically, this value covers the index nutrient needs of 98% of individuals. Such values are also not recommended for inclusion in tables summarizing NIVs. The group has adopted the term "individual nutrient level" (INL_x) for these values. The x denotes the probability of nutrient adequacy for any single individual. This term is discussed below in greater detail.

The group concluded that it would be preferable to use a more flexible approach that enables expert groups to develop values analogous to the present RNI (or its equivalent) at points in the distribution of requirement deemed to be appropriate in specific countries and regions. Thus, some may wish to use 75%, 80%, 90%, etc., rather than the 98% used currently that reflects a risk of inadequate intake of approximately 2% for an individual.

Safe intake (same as the adequate intake (AI) or the lower end of the range of safe intakes). Because this value often is used when data are insufficient to set an ANR, the process for setting it is greatly subjective. Ideally, such a term will be used only to describe nutrient targets for infants (based on the nutrient content of breastmilk) or other exceptional situations. Exclusion of these values from NIV tables is recommended because of the great subjectivity inherent to their derivation.

The report also recommends that the NIVs *not include population-level recommendations,* such as the upper and lower limits of the population mean intake. These standards vary with the population's intake characteristics and require several assumptions. This topic is covered in more detail in the section below on uses and applications and in Vorster et al. [1] and Murphy et al. [4] in this volume.

The framework for estimating average nutrient requirements (ANRs)

The basic framework for estimating ANRs is based on distributions of nutrient intakes required to achieve a specific outcome in a specified healthy population [6]. If those intakes are distributed normally, the population's mean requirement is its ANR. When such intakes are not distributed normally, data should be transformed, thus enabling the resulting median intake to serve as the ANR. In many cases the distribution of requirements is unknown. Because this is not uncommon, substantial research is needed to define the distributions of nutrient requirements and to identify biological and environmental factors that influence them.

Groups charged with developing NIVs should determine which nutrients and food components to consider. The group agreed that NIVs should be established whenever possible for all nutrients and food components that are *essential OR have public health relevance.* Fiber is an example of a food component that has public health relevance but is not an essential dietary component. The group concluded that good food-composition data for a nutrient or food component are necessary to ascertain public health relevance, since such data are key to estimate exposures (or intake).

Acceptable macronutrient distribution ranges for carbohydrate, fat, and protein have been established by some groups. These ranges are derived primarily for promoting long-term health and preventing chronic (or noncommunicable) disease and will be described further in that context. Establishing an ANR for the total amount of carbohydrate and fat in the diet is not necessary. However, it is appropriate to establish ANRs for protein to achieve zero or appropriately positive nitrogen balance and for the essential fatty acids that have specific biological functions.

Population intake levels were established for some of the trace elements in the 1996 FAO/WHO report

[11]. These are levels of *intake* of a specific nutrient that can be used to plan diets or assess intakes of homogeneous populations, e.g., all girls of a similar age in a boarding school. Population intake levels for planning and assessment purposes should be derived from the ANR, assessments of the variation in nutrient requirements, and the targeted population's variation in nutrient intakes. Thus, such calculations reflect an application of the ANR. Also, assessing population intakes requires several assumptions that are not met easily. This application is considered in more detail in subsequent sections of this summary.

The group recognized that nutrient–nutrient interactions may alter nutrient requirements. Examples of such interactions are protein–energy, vitamin E–polyunsaturated fats, and calcium–protein–sodium. The potential impact of such interactions on average requirements should be considered and described whenever such interactions are likely. Ideally, such nutrient interactions should be characterized quantitatively, e.g., estimates of reductions in protein requirements with increasing energy intakes.

Finally, the group addressed the need to consider subpopulations with special needs, e.g., children with chronic diarrhea or smokers. The NIVs address the requirements of "apparently healthy" individuals. Individuals with special needs should be considered separately, and if enough data are available, NIVs may be established for them.

Framework for estimating UNLs

The second recommended NIV is the upper nutrient level (UNL) [7]. This value was defined as the highest level of habitual nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in the general population. As intake increases above the UNL, the potential for risk of adverse effects increases. Habitual intake was defined as chronic daily use and is usually based on the total intake of a nutrient from food (including fortificants), water, supplements, and, in some cases, medications.

As implied by the definition, the recommended process for deriving UNLs for all groups is the determination of a "no observed adverse effect level"* (NOAEL) or the "lowest observed adverse effect level"** (LOAEL). The group agreed that UNLs should be determined by applying an uncertainty factor to NOAELs or LOAELs and that the magnitude of uncertainty factors should be determined on a case-by-case basis. These considerations should include a careful review of the differences between values equivalent to the ANR plus 2 SD, and corresponding NOAELs or LOAELs and outcomes of a risk assessment's hazard identification and characterization. The group endorsed the use of a modification of the sequence of possible effects due to excess intakes proposed by Renwick et al. (2004) [13] to help estimate the magnitude of uncertainty factors:

1. Biochemical changes within the homeostatic range and without indication of adverse sequelae;
2. Biochemical changes outside the homeostatic range without knowing the sequelae;
3. Biochemical changes outside the homeostatic range that represent a biomarker of potential adverse effects due to excess;
4. Clinical signs and/or symptoms indicative of a minor but reversible adverse effect;
5. Clinical signs and/or symptoms of significant but reversible adverse effects;
6. Clinical signs and/or symptoms indicative of significant reversible organ damage;
7. Clinical signs and/or symptoms indicative of irreversible organ damage.

The group concluded that the magnitude of uncertainty factors is likely to increase as observations progress from items 1 to 7 in the above sequence, and with the severity of sequelae to excess intakes. It acknowledged that the earliest potentially significant adverse effects would correspond to items 2 or 3 in the above sequence.

The group's recommendation of this sequence implicitly recognizes the need for biomarkers that anticipate adverse effects, rather than focusing solely on biomarkers that reflect an adverse effect's occurrence. The availability of such biomarkers was viewed as most supportive of the protection of the public's health and most likely to minimize the role of uncertainty factors in the estimation of UNLs.

In making these recommendations, the group recognized the paucity of dose–response data available for determining UNLs and describing interindividual variation and distributions. Estimates of index exposures, particularly exposures among the most vulnerable, e.g., pregnant and lactating women, children, and the elderly, also are inadequate. The seriousness of this data gap is evident in both industrialized and less wealthy countries. Furthermore, data needed to estimate values at the upper tails of intake distributions are almost always scanty for vulnerable groups in all settings.

* "Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure" [12].

** "Lowest concentration or amount of a substance, found by experiment or observation, which causes an adverse alteration of morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure" [12].

Criteria for selecting outcomes for establishing NIVs

NIVs should be based on specific outcomes related to functional capacities or the avoidance of disease or other adverse outcomes [2]. Ideally, outcomes for establishing NIVs should have the following characteristics:

» A demonstrated dose–response function;
» Responsive to inadequacy or excess of a single nutrient;
» Resistant to rapid (daily) changes in response to inadequate, adequate, or excessive intakes;
» Easily measurable or assessable with noninvasive methods;
» Not responsive to environmental changes other than nutrient intake from all sources.

Selecting outcomes that meet all of these characteristics is presently difficult; thus, research is needed that is designed to identify outcomes with these characteristics and to develop appropriate technologies for this purpose.

It is recommended strongly that a single outcome be selected for establishing NIVs for each nutrient in a specific age-physiological group. The basis for this recommendation is the likelihood that values based on more than one outcome will create confusion and unnecessary complexity. Multiple outcomes also present the risk of discriminatory application, e.g., to diverse socioeconomic or differentially privileged groups.

It also is important that experts explicitly recognize that diverse outcomes for setting requirement levels differentially affect resulting ANRs and very likely also affect their variances. For example, selecting "dark adaptation" or "saturation of liver deposits" as an outcome for setting the ANR for vitamin A will result in different ANRs and probably different variances and coefficients of variation. It also is likely that diverse diet-, host-, and environment-related factors will affect ANRs differentially. Thus, careful reviews of such influences are key to the estimation of ANRs. In practice, reliable estimates of population-specific variability are seldom available, and thus research on the determinants of variances should be a high priority.

The group stressed the importance of using all available published physiological data based on agreed-upon characteristics to determine outcomes on which to base NIVs. It did not recommend the independent development of such data by each group that is charged with estimating NIVs. The same data may be used by diverse groups as a basis for developing NIVs that are context-specific in terms of diverse population characteristics and environmental factors that may alter estimates of specific NIVs.

Acceptable distribution ranges for fat, carbohydrate, and protein intakes have been established by some groups. These ranges are derived primarily for promoting long-term health and reducing the long-term risk of noncommunicable disease. It is not necessary to establish an ANR for total dietary carbohydrate or fat. However, it is appropriate to establish ANRs for protein to achieve appropriate nitrogen balance at various life stages, and for the specific biological functions of essential fatty acids.

There is a need to be as specific as possible regarding "targeted" diseases when nutrient-based standards are recommended for disease prevention or control. Thus, for example, when targeting cancer, the site, tissue involvement, physiological stage at onset, etc. should be stated explicitly. This level of specificity is likely to support the development of biomarkers linked directly to outcomes of interest and exploitation of growing information regarding specific nutrient–gene interactions that modify the risks of diet-related long-term diseases.

Evidence linking diet to risks of long-term diseases is more often related to specific dietary patterns than to levels of intake of specific nutrients. Thus, the group stressed the need to link committees convened to develop diet-based strategies for the promotion of long-term well-being and reduction of risk of diet-related long-term diseases, with those convened to develop NIVs.

Issues related to study design and experimental errors also should be considered explicitly by groups setting NIVs. Sample size is among the more important design characteristics in this regard. For this purpose, it is necessary to consider the width of resultant confidence intervals and to minimize the likelihood of alpha or beta errors. For example, the probability of accepting a false negative conclusion with a sample size of 100 is 0.71 if an alpha value of 0.05 is used to determine statistical significance and a clinically significant difference between values of interest is set at 50%. Many nutrition studies, however, involve samples of 15 to 25 subjects rather than 100 and have a much higher risk of underpowering comparisons of interest. Such risks need to be addressed when selecting a database for estimating nutrient requirements.

Bioavailability

Bioavailability is an important factor to consider when estimating NIVs for selected nutrients (e.g., iron, zinc, carotenoids, vitamin A, folate, protein, calcium, and magnesium). The definition of bioavailability accepted by the group was proposed by Hurrell in 2002 [14] and modified by Gibson [5], the "proportion of the ingested nutrient absorbed and utilized through normal metabolic pathways. Bioavailability is influenced by dietary factors and host related factors." Bioefficacy is the efficiency with which ingested nutrients are absorbed

and converted to an active form [15]. Both of these terms reflect the broader concept of bioequivalence of nutrients or their precursors in defining nutritional status and function. These concepts also encompass various steps in metabolic and utilization pathways of nutrients (i.e., absorption, metabolic conversion, utilization, retention, secretion, and excretion). There are multiple factors that influence the bioequivalence of nutrients and their precursors: competition for absorptive systems; role of enhancers or inhibitors of absorption; metabolic conversion efficiency in the intestine, liver, kidney, or other tissues; and interactions between or among nutrients, chemical form, and others. Also, it is important to remember that food processing, treatment, and/or preparation practices at the household level influence nutrient bioavailability.

The roles of infection (bacterial and parasitic) and the nutritional and physiological status of the host also are of key importance in defining bioequivalence of nutrients and should be considered when the impact of infections can be described quantitatively for specific populations of interest.

The importance of considering bioequivalence is especially relevant for iron and zinc, where specific approaches have been developed based on dietary components that enhance and/or inhibit absorption. Algorithms predicting the bioavailability of iron and zinc have been developed based on the amounts of enhancers and inhibitors in the diet, the nutrient's chemical form, e.g., iron, and the nutrient status of the individual. However, the validity of these models needs to be evaluated in practice and considered in setting reference values only if quantitatively significant. Retinol, tocopherol, and folate equivalents are examples in which specific conversion values depend on the relative content of precursors, the chemical form of the nutrient, the food matrix that serves as a "delivery system," and the host's physiological and health condition. Digestibility of protein sources is the key factor affecting absorbed amino nitrogen, and amino acid composition determines protein retention and urea excretion.

Data on the efficiency of the biological conversion of carotenoids and various tocopherols into their bioactive forms have significant variability; however, the practical implications of this variability have not been elucidated completely. In many cases, food-composition data are scant, limiting the assessment of bioequivalence. Recent progress in FAO's data system to assess food availability (FAOSTAT II) represents an advance in this matter. The capacity to define the nutritional adequacy of local diets will remain very limited, unless efforts to improve information systems on food-composition data are strengthened. Efforts should be encouraged to advance progress in developing the International Food Data Systems Project (INFOODS) as a tool to improve the derivation of NIVs and related values.

Derivation of life-stage groups, standard heights and weights, and NIV estimation by extrapolation

Derivation of life-stage groups

NIVs are developed for specific life-stage groups [3]. There is no consensus, however, as to how to establish those groups. Three different options exist: chronologic age, use of functional characteristics (e.g., growth and puberty), or potential purposes for which NIVs might be used (e.g., complementary feeding programs). As an illustration of the last alternative, one might want to establish life-stage groups for infants and young children so that all children requiring complementary feeding are included in one group. It is likely that a combination of options most often will be used to establish life-stage groups. Growth and type of feeding may be used for infants and children, whereas chronologic age might be used for young, mature, and elderly adults. The same life-stage groups, however, should be used for all nutrients included in the NIV; it would be inappropriate and confusing to use one life-stage group for calcium and another for riboflavin, for example.

Pregnancy and lactation do not need to be divided into various stages such as trimesters of pregnancy or early and late lactation, because physiological adjustments in nutrient utilization generally compensate for shifts in nutrient requirements that occur at different stages of gestation or lactation. Furthermore, having more than one NIV for pregnancy and lactation is essentially impossible to implement; advising women to eat one diet during early pregnancy and another in late pregnancy is impractical.

Standard heights and weights

Standard weights and heights should be established for each selected life-stage group to define the general characteristics of the population and to permit extrapolations of ANRs to other life-stage groups based on body size. For infants and children between 0 and 5 years of age, the new WHO growth standards are recommended as the basis for normalizing NIVs when adjustments based on weight are appropriate. For all other age groups, data from the National Center for Health Statistics/World Health Organization (NCHS/WHO) can be used to derive a standard weight and height [16]. The group recommended, however, that the average weight of men and women at 18 years of age be used throughout the adult years rather than reflecting the typical secular increase in body weight with age. It is uncertain whether this secular increase is consistent with good health. It is important to downwardly adjust energy NIVs when expressed per kilogram of body weight or per day for overweight

or obese individuals with body-mass indexes greater than 25. For all other nutrients, standard body weight uncorrected for overweight status is appropriate for estimating NIVs.

Extrapolation

It is preferable to use original research for estimating nutrient requirements of various life-stage groups [3]. However, due to the paucity of data for some subgroups, it is often necessary to extrapolate information from other groups. Extrapolation should always be a second choice, and scientists are encouraged to develop innovative, noninvasive methods or to use existing methods (e.g., stable isotopes) to determine nutrient requirements of understudied groups, e.g., pregnant and lactating women, infants, children, and the elderly.

Until data are available for all life-stage groups, extrapolation from one group to another is necessary. Frequently, this involves extrapolation from adults to children and adolescents and from younger adults to older adults. The rationale or scientific basis for the method chosen should be completely transparent and thoroughly described for each nutrient and life-stage group. It is likely that different approaches will be used for different nutrients, or different extrapolations for diverse life-stage groups for a single nutrient. There is no one "correct" method for extrapolation, and thus scientific judgment is required. Examples of extrapolation methods that are used include body size (weight or metabolic weight), energy intakes for age, or factorial estimates of requirements for growth, pregnancy, and lactation. When the factorial approach is used, it is important to be completely transparent in describing the databases used to estimate components of the estimate, such as milk volume and composition during lactation, or composition of weight gain during pregnancy.

Effects of genetic variation on nutrient intake values

The primary nucleotide sequence of the human genome varies by approximately 0.2% to 0.4% among humans [8]. Variations in a DNA sequence that are enriched in populations are referred to as polymorphisms, which constitute a primary molecular basis for human phenotypic variation. Human mutations expand in populations as a result of natural selection or through random drift. Historically, the nature and abundance of the food supply are among several environmental selective pressures that enabled the expansion of polymorphisms within human populations. Genetic variants that enable survival in challenging nutrient environments become enriched in populations through the process of natural selection. This process may confer differences in food tolerances or intolerances, could develop into metabolic disease alleles in different environmental contexts, and has the potential to alter NIVs. Because many human populations have existed for many generations in unique, isolated, and challenging nutrient environments, relatively rare gene variants that influence NIVs may be highly prevalent in isolated populations. Gene variants associated with human lactose intolerance and alcohol intolerance display genomic signatures of positive selection in specific geographic regions. These signatures indicate that these variants offered survival advantages related to an index food component itself and/or more broadly to the metabolic network key to a food component's broader role. Computational approaches are identifying numerous gene variants associated with nutrient transport and metabolism that display signatures of positive selection. To date, no gene variant has been demonstrated to affect nutritional requirements sufficiently to warrant genotype-specific recommendations, although the effect of the MTHFR A222V variants on folate requirements has been considered. Because polymorphisms can confer both health benefits and risks, depending on the outcome of interest, and these outcomes may respond differentially to nutrient intake levels, it may be important to consider the effects of genetic-specific recommendations on all known health outcomes. For example, the MTHFR A22V polymorphism confers increased risk for developmental anomalies but protection from colon cancer; the impact of individualized ANRs on both health outcomes should be considered for this genetic minority.

The impact of a gene variant on nutrient requirements will be dependent on its prevalence and penetrance. Penetrance is the probability that a gene variant will express a phenotype from a given genotype at a given time. In most cases, penetrance varies inversely with prevalence. Few gene variants are anticipated to be sufficiently penetrant to affect variation of ANRs to a greater degree than environmental factors. However, the identification of highly penetrant gene variants may require the derivation of more than one ANR or UNL for genetic subgroups. It is unlikely that gene–gene interactions will be a major consideration in the determination of NIVs because of the low prevalence associated with highly penetrant gene–gene interactions. Furthermore, because chronic diseases are polygenic complex traits, individual SNPs are unlikely to impact NIVs that target the reduction of diet-related risk of long-term disease.

Thus, the group concluded that other than that for folate, no other specific polymorphisms have been identified that should be considered in the derivation of NIVs beyond those subsumed in estimates of interindividual variation. This field is, however, progressing

very rapidly and our understanding of human genetic variation is expected to improve steadily in the near and mid-term future. Linking specific gene variants to known nutrient-sensitive ethnic or geographic populations, such as salt sensitivity in African Americans, may enable population-specific recommendations for genetic subgroups. Therefore, advances in understanding the impact of genetic variation on NIVs merit the close attention of all groups charged with their derivation.

Methodological approaches and applications of NIVs

The term "uses" frequently has been used to refer to all of the various applications of a set of NIVs. The group felt, however, that it is important to distinguish between the terms "uses" and "applications." Common uses of NIVs are for planning diets (of groups and individuals) and assessing intakes (of groups and individuals). The group decided to refer to this set of uses as "methodological approaches [4]." "Applications," then, refers to specific ways in which methods can be applied to various tasks (e.g., setting fortification levels, developing food-based dietary guidelines) [1, 9, 10].

Theoretical approaches to using the NIV for assessment of dietary intakes for individuals requires calculating the probability of an inadequate intake using the ANR and its distribution. At any intake on the x-axis one can calculate the probability of inadequacy for an individual. For example, if the intake equals the ANR, then the probability of inadequacy for an individual is 50%. For the assessment of groups, the prevalence of inadequacy can be estimated as the percentage of the population below the ANR if certain criteria are met.*

For planning diets for individuals, one must first establish a "recommended intake" or individual nutrient level (INL_x, where x indicates the likelihood of meeting an individual's nutrient requirement, historically 98%). The group suggests that the INL_x should be based on the ANR adjusted for the level of acceptable risk for deficiency. For example, if 2 SD of the requirement are added to the ANR, then the likelihood of meeting an individual's needs is 98%, or conversely the individual's risk of inadequacy is 2%.

When planning diets for groups, one should aim for a distribution of intakes that results in an acceptably low prevalence of inadequacy (estimated as the proportion below the ANR) and also a low prevalence of nutrient excess (estimated as the proportion above the UNL). To reduce the prevalence of inadequacy, one could either shift the entire intake distribution to a higher level, or change the shape of the intake distribution by improving the intakes of those at the lower end. Either way, the goal is to identify an intake distribution that represents an acceptable level of inadequacy, such as only 2% to 3% of the population being below the ANR. This may be achieved through education in relevant nutrition practices or by a targeted food supply (e.g., fortification of staple foods) to ensure that the intake distribution curve has only a small proportion of the population below the ANR or above the UNL. For most groups, it is not appropriate to use the INL_x as the target for the group's mean intake. Due to significant interindividual differences in high variance individuals in a group, targeting mean group intakes at an INL_x usually results in a high prevalence of inadequacy (as much as 25% to 30%, for some nutrients, even when INL_{98} is targeted) because of commonly high levels of interindividual differences in nutrient intakes. For this reason, intake distributions should be examined, not just group mean intakes.

In summary, NIVs should form the basis of planning and assessment of diets, and this requires at a minimum an ANR and a UNL. The INL_x is derived from the ANR by adding a factor to cover a specified percentage of the population (x). The specific application of the INL will drive the x factor that is applied [6]. Graphs and charts illustrate the relationship among the ANR, UNL, and INL_x and the appropriate use of these NIVs for nutrient assessment and dietary planning purposes**.** Groups charged with developing NIVs may choose to include values for INL_x in basic tables, but this latter value is derived basically from the ANR and its distribution.

Trade and regulatory issues

The group agreed that issues related to international and domestic trade, and the important roles played by the Codex Alimentarius Commission and the World Trade Organization (WTO), should be considered when developing harmonized processes and approaches for deriving NIVs [9]. Also, it is important that scientific advice regarding nutrient requirements and their applications be made available to specific groups of the Codex Alimentarius Commission, such as the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) and the Codex Committee on Food Labeling (CCFL). Information on developing dietary guidelines for health and consumer protection also should be provided to these specific groups. It is crucial to understand the important role

*Among these criteria is that requirements must have a reasonably normal distribution; thus, the estimated average requirement (EAR) cutpoint method that is the basis for estimating the prevalence of nutrient adequacy or inadequacy in a targeted population cannot be used for assessing iron intakes of menstruating women, because the distribution of iron requirements for this group is highly skewed to the left.

that the Codex Alimentarius Commission plays in setting food standards and guidelines for protecting consumer health and ensuring fair practices in domestic and international trade.

Food labeling is an important component of trade and regulatory nutrition issues. Harmonizing label procedures also will improve trade opportunities within regions and worldwide. The process of developing food labels can be harmonized among regional, national, and international groups. To establish food labels, some have used the INL_x weighted by the distribution of the various life-stage groups in populations as a basis for food labels. Others have used the highest nutrient level recommended for individuals in a population.

Food fortification is another application of NIVs relevant to trade and regulatory issues. Food fortification may be mandatory or voluntary. Fortification programs should be designed so that the prevalence of intakes of target nutrients that are below the ANR or above the UNL is low [17]. This will ensure that very few individuals have either inadequate or excessive intakes of targeted nutrients.

Application of NIVs to dietary guidelines

Explicit food-based dietary guidelines (FBDGs), or similar recommendations, have been developed by many countries [10]. In some countries, such as the United States and Canada, FBDGs are the basis for national nutrition education activities and food assistance programs. FBDGs generally provide a comprehensive set of guidelines that are intended to reduce long-term disease risk and improve general health. In addition to specific guidelines regarding the intake of fruits, vegetables, whole grains, and dairy foods, statements often are included regarding physical activity, food safety, and the types of carbohydrate and fat for reducing long-term disease risk. Thus, FBDGs serve as the basis for healthy lifestyles. In most countries, resources for disseminating information embodied in FBDGs are inadequate and their use and implementation by the general public are limited. Thus, not surprisingly, direct evidence that dietary guidelines are an effective means to improve the overall health of a population is lacking in practically all countries.

It is not possible to harmonize food-based dietary guidelines across countries, cultures, and regions, because these guidelines stem from social influences on food patterns, culturally sensitive issues regarding food within a country or subpopulation, and nutrition and health problems of a specific population. However, *methods* for developing dietary guidelines can be harmonized around the world. As is the case for food labeling and fortification programs, NIVs form the basis for FBDGs. A harmonized method for developing FBDGs based on ANR, INL_x, and UNL values is described by Vorster et al. [1].

Summary

The conceptual framework for the various NIVs is depicted in **figure 1** along with the methodological approaches and applications. The NIVs consist of two values derived from a statistical evaluation of data on nutrient requirements, the average nutrient requirement (ANR), or nutrient toxicities, the upper nutrient level (UNL). The individual nutrient $level_x$ (INL_x) is derived from the distribution of average nutrient requirements. The percentile chosen is often 98%, which is equivalent to 2 SD above the mean requirement. Concepts underlying the NIVs include criteria for establishing a nutrient requirement, e.g., ferritin stores, nitrogen balance, or serum vitamin C. Once the requirement for the absorbed nutrient is determined, it may be necessary to adjust the value for food sources, i.e., bioavailability, or host factors, such as the effect of infection on nutrient utilization. Other concepts that committees may want to consider when establishing NIVs include the effects of genetic variation on nutrient requirements and the role of the nutrient in preventing long-term disease.

Two fundamental uses of NIVs are for assessing the adequacy of nutrient intakes and for planning diets for individuals and populations. Establishing the NIV using the statistical framework proposed in this report improves the efficacy of the values for identifying risks of nutrient deficiency or excess among individuals and populations. NIVs also are applied to a number of aspects of food and nutrition policy. Some examples include regulatory issues and trade, labeling, planning programs for alleviating public health nutrition problems, food fortification, and dietary guidance.

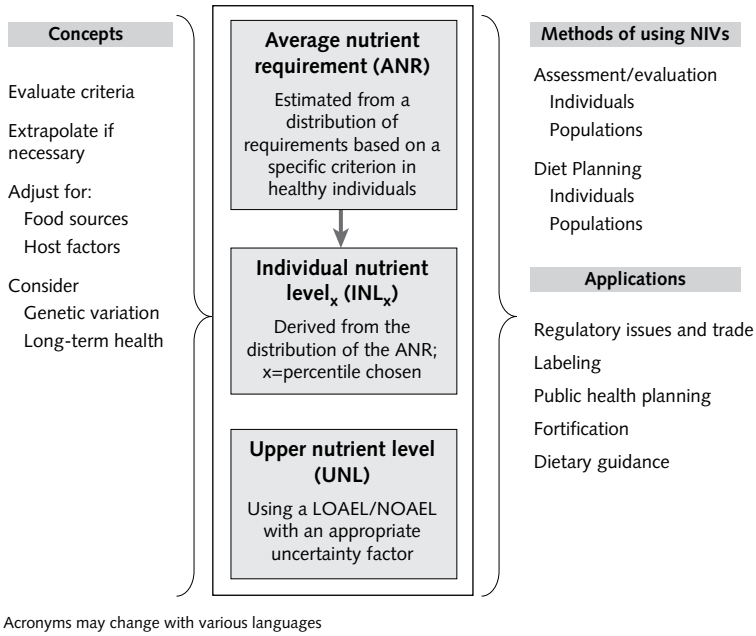

FIG. 1. The two nutrient intake values (NIVs) are the average nutrient requirement (ANR) and the upper nutrient level (UNL). Other NIVs may be derived from these two values, i.e., the individual nutrient level$_x$ (INL$_x$), which is the ANR plus some percentile of the mean used for guiding individual intakes. The ANR and UNL are derived from estimates of amounts needed for a specific physiological criterion, e.g., tissue stores, metabolic balance, or a biochemical function. The NIVs are modified for population differences in the food supply, host factors such as infection, genetic variations, and needs for sustaining long-term health. The methods of using NIVs to assess/evaluate intakes of individuals and populations differ from that used for planning diets for individuals and populations. NIVs are the basis for a number of policy applications. Examples include food labeling and fortification, food-based dietary guidance, planning public health nutrition programs, and establishing food regulatory policies.

References

1. Vorster HH, Murphy SP, Allen LH, King JC. Application of nutrient intake values (NIVs). Food Nutr Bull 2007;28(suppl):S116–22.
2. Yates AA. Using criteria to establish nutrient intake values (NIVs). Food Nutr Bull 2007;28(suppl):S38–50.
3. Atkinson SA, Koletzko B. Determining life-stage groups and extrapolating nutrient intake values (NIVs). Food Nutr Bull 2007;28(suppl):S61–76.
4. Murphy SP, Vorster HH. Methods for using nutrient intake values (NIVs) to assess or plan nutrient intakes. Food Nutr Bull 2007;28(suppl):S51–60.
5. Gibson RS. The role of diet- and host-related factors in nutrient bioavailability and thus in nutrient-based dietary requirement estimates. Food Nutr Bull 2007;28(suppl):S77–100.
6. King JC, Vorster HH, Tome DG. Nutrient intake values (NIVs): A recommended terminology and framework for the derivation of values. Food Nutr Bull 2007;28(suppl):S16–26.
7. Aggett PJ. Nutrient risk assessment: Setting upper levels and an opportunity for harmonization. Food Nutr Bull 2007;28(suppl):S27–37.
8. Stover PJ. Human nutrition and genetic variation. Food Nutr Bull 2007;28(suppl):S101–15.
9. Ramaswamy S, Viswanathan B. Trade, development, and regulatory issues in food. Food Nutr Bull 2007;28(suppl):S123–40.
10. Smitasiri S, Uauy R. Beyond recommendations: Implementing food-based dietary guidelines for healthier populations. Food Nutr Bull 2007;28(suppl):S141–51.
11. World Health Organization. Trace elements in human nutrition and health. Geneva: WHO, 1996.
12. McNaught AD, Wilkinson A. IUPAC Compendium of Chemical Terminology. The Gold Book. 2nd Edition. 1997. Blackwell Science.
13. Renwick AG, Flynn A, Fletcher RJ, Muller DJ, Tuijtelaars S, Verhagen H. Risk-benefit analysis of micronutrients. Food Chem Toxicol 2004;42:1903–22.
14. Hurrell R. Bioavailability—a time for reflection. Int J Vitam Nutr Res 2002;72:5–6.

15. West CE, Eilander A, van Lieshout M. Consequences of revised estimates of carotenoid bioefficacy for dietary control of vitamin A deficiency in developing countries. J Nutr 2002;132(9 suppl):2920S–6S.
16. World Health Organization. Measuring change in nutritional status: guidelines for assessing the nutritional impact of supplementary feeding programmes for vulnerable groups. Geneva: WHO, 1983.
17. World Health Organization. Guidelines on food fortification with micronutrients for the control of micronutrient malnutrition. Geneva: WHO, 2006.