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INVITED REVIEW

Harmonisation of micronutrient-based dietary standards globally: Challenges and future developments

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Abstract

Aim: The terminology and frame work for setting nutrient-based dietary standards (NBDS) varies across countries leading to discrepancies in health, food policies and trade. Hence, harmonising approaches for NBDS warrants investigation.

Methods: A working group reviewed the terminology used to define NBDS and upper levels, statistical approaches for their use for individuals and populations, criteria to establish requirements, extrapolate and interpolate missing data, bioavailability issues and the potential impact of inter-individual variations other than life-stage and gender on nutrient requirements.

Results: The group proposed the term—nutrient intake values (NIVs)—that include the average nutrient requirement (ANR) and upper nutrient level. An individual nutrient level (INL_x) based on the ANR was also proposed, the *x* representing the percentile for an acceptable risk for inadequacy for an individual. To assess nutrient adequacy and plan diets for groups, use of the ANR cut-point or probability approach was recommended. In the future, NIVs may be set that take into account inter-individual differences in lifestyle, environment, health, genotype and epigenetics.

Conclusions: Use of the proposed terminology and framework for NIVs has global potential for evaluating nutrient intakes and diets for individuals and populations and for use in several aspects of food and nutrition policy.

Key words: average nutrient requirement, dietary standards, individual nutrient level, micronutrient, nutrient intake values.

Introduction

Many countries set nutrient-based dietary standards. They are used to assess nutrient intakes and plan diets of individuals or groups, as well as in food and nutrition policy, food regulation and trade. However, both the terminology and framework used for setting nutrient-based dietary standards vary markedly among countries leading to discrepancies in health, food policies and trade. As a result, in 2007, a working group was convened to consider harmonising nutrient-based dietary standards.[1] This group proposed that a new term—nutrient intake values (NIVs)—should be used to embrace values derived from a statistical evaluation of data on nutrient requirements and nutrient toxicities. Two of the values are the average nutrient requirement (ANR) and the upper nutrient level (UNL). They should be applied to all nutrients and food components known to be essential or to have public health relevance. The group also suggested that another more flexible value—the individual nutrient level (INL_x)—could be derived from the ANR, the *x* representing the level of adjustment for the INL considered to be an acceptable risk for inadequacy by a particular country.

Average nutrient requirement (ANR) is defined as the intake that will be adequate for half of the healthy individuals in a particular life-stage and sex group. A single uniform criterion of adequacy was suggested[1] to establish the ANR for each nutrient in a specified life-stage group to avoid confusion and to simplify the process. Where possible, a physiological functional criterion should be chosen to establish an intake that not only prevents a nutrient deficiency but also optimises health and reduces risk of chronic disease.[2] Countries should use the same physiological data from the literature to select the criterion, and ensure that the data meets recognised quality standards.

The ANRs are derived from the physiological requirements for *absorbed* nutrients and, for some (e.g. iron, zinc and vitamin A), the physiological requirements are adjusted to give the dietary requirements or ANRs. Theoretically, these adjustments should take into account all the biological factors known to influence dietary requirements. In practice,

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factors that affect requirements have not always been identified, are difficult to measure, or their impact is unknown. Hence, the appropriate adjustments cannot always be made.

The key biological factors that should be considered include bioavailability, bioefficacy, inter-individual variability and nutrient–nutrient interactions. Their relative importance for the NIVs depends on the environment and the type of diet consumed. Hence, the ANR for a micronutrient in a specified life-stage group may differ markedly across populations, even though the physiological requirements may be similar. Clearly, the diverse impact of these biological factors across countries and regions is a major source of uncertainty that needs to be better understood when harmonising NIVs.

Bioavailability and bioefficacy are particularly important for nutrients such as iron, zinc, folate, protein, calcium, magnesium, carotenoids and vitamin A.[1,2] The working group defined bioavailability as the proportion of the ingested nutrient absorbed and utilised through normal metabolic pathways.[3] Bioefficacy is the efficiency with which ingested nutrients are absorbed and converted to an active form.[4] In many countries, fixed bioavailability and bioefficacy factors have been assumed, even though both are influenced by diet- and host-related factors that vary widely.

Of the diet-related factors, those most often considered are the dietary composition, the chemical form of the nutrient (e.g. haem *vs* non-haem iron), the amount consumed, interactions with other nutrients or dietary components and food pretreatment during preparation and/or processing. Hence, appropriate diet-related adjustment factors for setting ANRs globally require accurate information on micronutrient intakes, local food consumption patterns and food preparation and processing practices.[2]

The impact of the host-related factors on the absorption and utilisation of micronutrients is less well characterised and often overlooked when setting ANRs, even though these factors additionally modify micronutrient bioavailability along with the dietary factors discussed above. Host-related factors include intestinal factors such as atrophic gastritis that influences the efficiency of digestion, absorption or bioconversion of micronutrients, and systemic factors such as age, sex, physiological state, host nutritional status, genotype and coexisting illness because of infections.

Some nutrient–nutrient interactions also alter requirements and their potential impact on ANRs should always be considered. Examples include calcium-protein-sodium, protein-energy, and vitamin E-polyunsaturated fats.[1]

Individual nutrient level (INL_x) is used as the target for an individual's nutrient intake, and hence is used for assessing intakes or planning diets for individuals. It is derived from the ANR and its distribution. The subscript *x* refers to the percentile chosen and deemed to represent an acceptable risk for inadequacy within a specific country or region. The $INL_{97.5}$ is analogous to the value typically set at the ANR + $2SD_{ANR.}$ (i.e. the recommended nutrient intake) and covering the needs of most (i.e. 97.5%) individuals of the population. Based on this example, individuals whose intake is equal to $INL_{97.5}$ have a 97.5% probability that their intake meets their needs. The working group suggested that, depending on the country, the INL_x might be set at a level where it covered the needs, for example, of 75, 80 or 90% of the population. The lower the value of x, the lower the probability that intake at that level would be adequate for an individual.[5]

Unfortunately, in many cases, the distribution of the ANR for micronutrients is unknown. Instead, the distribution is assumed to be symmetrical and to have a coefficient of variation of 10%. However, this assumption needs to be examined more critically prior to use in harmonising nutrient-based dietary standards. Estimates for the distribution of requirements for certain nutrients may also require modification as understanding of inter-individual variation from genetic variation improves.[6]

Upper nutrient level (UNL) is defined as the highest level of habitual daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in a specified life-stage group.[7] It is defined by using a specific indicator of excess, when available. The habitual intake refers to the total intake of a nutrient from all sources, including food, fortified food, water, supplements and, in some cases, medications. As intake increases above the UNL, the potential for risk of adverse health effects increases. The expert group recommended that the UNLs should continue to be based on risk assessment methodologies. In this approach, an uncertainty factor is applied to a 'no observed adverse effect level' or to the 'lowest observed adverse effect level'; Aggett[7] and WHO/FAO[8] give further details. The estimate for the magnitude of the uncertainty factor should be based on the approach of Renwick *et al*.[9]

Future developments in setting NIVs

Currently, life-stage group and gender are the major adjustments made for individual differences when setting NIVs. Although standardising the life-stage groupings across countries was not recommended, the group did advise using the same life-stage groupings for all nutrients, and one ANR for pregnancy and one for lactation. They urged scientists to generate more data to avoid extrapolation for the 'understudied' life-stage groups (e.g. infants, children, pregnant and lactating women, and the elderly). When necessary, the methods and factors used for extrapolation (e.g. body size, lean body mass, energy intakes, activity levels) should be transparent and consistent.[10] The WHO growth standards[11] were recommended for normalising the NIVs for children between 0 and 5 years of age. For all other age groups, the NCHS/WHO data[12] should be used, although for adults, use of weight at aged 18 years was recommended in view of the uncertainty about whether the secular increase in body weight with age is consistent with good health.

In the future NIVs, based on different characteristics other than life-stage groups and gender, may be required to take into account inter-individual variations in requirements for certain subgroups and individuals. Examples are summarised below.

Environmental conditions can modify nutrient requirements. For example, (i) the extent of endogenous synthesis of vitamin D in the skin because of exposure to ultraviolet

light from the sunshine; (ii) exposure to pesticides such as dioxin-type compounds in toxic amounts in foods can result in hyperlipidemia, loss in body weight, changes in carbohydrate metabolism and lipid peroxidation; (iii) exposure to high altitude may induce cachexia and weight loss.[13]

Lifestyle factors influence requirements through occupation or discretionary physical activity. For example, requirements for energy, thiamine, niacin and riboflavin are affected by variations in physical activity, and iron requirements for athletes engaged in intense exercise may be 30% to 70% above those of normally active persons. Requirements for vitamin C, tocopherol, retinol and folic acid may be altered by smoking, and those for iron and zinc by a vegetarian diet.[13]

Chronic health problems can modify nutrient requirements even among individuals considered healthy. For example, higher requirements for vitamin C may be necessary for asthmatic patients.[13]

Moderately malnourished children have higher nutrient requirements than normal children to replenish tissue losses or for catch-up growth during convalescence from illness, and to strengthen their resistance to infection. An expert group is now compiling nutrient requirements for moderately malnourished children.[14]

Genetic variation may necessitate the derivation of more than one ANR or UNL for certain genetic subgroups. Examples include the effects of (i) *MTHFR* (methylene tetrahydrofolate reductase) and A222V variants on folate requirements; and (ii) *HFE* polymorphism and iron overload on the UNL for iron intake. The prevalence of these two polymorphisms varies widely with specific ethnic groups.[6]

Epigenetics refers to the inheritance of traits that are not linked to DNA sequence but rather to modification of DNA. Epigenetics might influence requirements of certain micronutrients (e.g. choline) through permanent damage to the genome, which can be measured at both the molecular and cytogenetic level.[15] Hence, in the future, it may be possible to define the optimal intake of micronutrients individually or in combination (nutriomes) that are needed to protect against DNA damage events. The latter are a fundamental cause of developmental and degenerative disease.[16]

Uses of NIVs for assessing intakes and planning diets

New statistical approaches have been developed to determine if the nutrient intakes of an individual or group are meeting the needs of that individual or group. Using these approaches, the probability of inadequate or excessive intakes for an individual, and the prevalence of inadequate or excessive intakes within a group, can be calculated. The methods can also be used to plan diets for a low probability of inadequacy while at the same time minimising the potential risks of excessive intakes. At the individual level, the INL_x value derived from the ANR should be used, with the *x* representing the level of risk for deficiency considered acceptable. At the group level, the ANR should be used to estimate the prevalence of inadequate intakes using the probability approach or the cut-point method based on the ANR. Additionally, where defined, the Upper Level (UL) can be used to estimate the proportion at potential risk of adverse effects from excessive intake. When planning diets for groups, the ANR or the UL is used in combination with the usual nutrient intake distribution to plan for an acceptably low prevalence of inadequate or excessive intakes. Otten *et al*.[17] provide further details.

Conclusion

Some progress has been made towards harmonising the development of nutrient-based standards. However, many challenges still exist, of which the most notable is uncertainties in inter-individual variations in requirements that are separate from those explained by the more conventional characteristics such as gender and life-stage groups. Advances in our understanding of these differences may lead to the derivation of special ANRs or UNLs for those with certain lifestyles, chronic health problems, genotypes and for individuals susceptible to DNA damage events.

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