A Perspective on Mineral Standards

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ABSTRACT History has shown that the consumption of a balanced diet in adequate amounts is consistent with survival of mankind. This fact demonstrates that for each essential nutrient there is not one, but a range of safe and adequate intakes. In the past, the determination of the two endpoints of that range, one bordering on deficiency, the other on toxicity, has been sought independently by nutritionists and toxicologists. Refinement of the criteria of adequacy and safety during the past few decades has tended to raise estimates of requirements and to reduce those of toxicity, narrowing and in some cases, eliminating the range of safe and adequate intakes. The Herndon Conference in 1992 suggested some common principles, potentially useful to establish both endpoints of the ranges of safe and adequate intakes for essential trace elements. Some perspectives of implementing these are discussed. J. Nutr. 128: 375S–378S, 1998.

KEY WORDS: • nutrient recommendations • upper limits of intake • safe ranges of intake

HISTORIC DEVELOPMENTS

An early personal experience in the laboratory shaped my perspectives on mineral standards. After the identification of chromium as an essential element in 1959, we tried to improve its modest stimulation of glucose uptake in vitro by increasing the dosage. The results proved to be the opposite of what we had expected: To improve the response, we had to reduce the chromium concentration; increasing it would abolish the effect. In those years when the literature referred to the concentrations used as “nondetectable” or even “zero,” it was hard intellectually to accept increasing effects resulting from reduced dosages. This led to our concern with the “total dose-response curve” of nutrients and to the recognition that the upper range of that curve is as important to the nutritionist as the lower end (Mertz 1976). The discovery that the great French scientist Gabriel Bertrand (1912) had firmly established and mathematically formulated dose-response curves for trace elements around the beginning of the 20th century came as a welcome relief.

During the 80 years after Bertrand’s publications, however, the main concern of nutritionists remained the determination of requirements with only occasional and sometimes faulty statements concerning the safety of higher intakes (WHO 1973). The 9th edition of the Recommended Dietary Allowances finally established a new approach with the introduction of ranges of Estimated Safe and Adequate Daily Dietary Intakes (ESADDI) for three vitamins, three electrolytes and six trace elements (NRC 1980). Although the RDA committee modestly ascribed the new recommendations to the “more tentative and evolutionary” data category, the ESADDI can be considered the first approach to the total dose response that recognizes the homeostatic regulations of the organism and sets upper limits of intakes. In 1990, an Expert Consultation of FAO/IAEA/WHO agreed in Geneva to follow a similar approach for setting its recommendations in Trace Elements in Human Nutrition and Health (WHO 1996). Two years later, the efforts of nutritionists to define the total dose-response curve of nutrients were joined and complemented by the expertise of toxicologists in the historic Herndon Conference (Mertz et al. 1994). The conference presented and reconciled the different principles and approaches of the two fields to the definition of safe and adequate intakes and stimulated much activity nationally (Institute of Medicine 1994) and internationally (Nordberg and Skerfving 1993).

SCIENTIFIC ASPECTS

Standards for essential nutrients, including mineral elements, are based on the definition of the “total dose-response curve” of these substances. That bell-shaped curve describes biological function as depending on the degree of exposure, and it consists of five segments (WHO 1996): the two extremes, representing deficient and toxic exposure, are incompatible with life. Increasing exposure beyond deficiency and reducing it below toxicity improve function. Between these two dose-dependent segments is a plateau that represents a range of exposures in which homeostatic regulation of the organism can maintain optimal function. The exact definition of that range, termed “range of safe and adequate intakes” is the ultimate goal of nutritional and toxicological research.

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Although the past few years have brought agreement between toxicologists and nutritionists on these principles and on the need for collaboration, several basic tenets of each group remain to be reconciled. Nutritionists generally accept an intake of a nutrient at or reasonably above the RDA and as a component of a balanced diet as safe. They rely on the results of many modern epidemiologic studies and on the historic experience that such intakes have not interfered with the survival of mankind. Toxicologists, on the other hand, emphasize that it is difficult, perhaps impossible, to prove the safety of any environmental substance, including nutrients, and therefore set as their goal the determination of “minimal risk” rather than “safety.” These differences of terms are more than semantic; they markedly influence the approaches to setting the respective standards.

The toxicological approach. Its main objectives are to define health risks created by excessive exposure to environmental chemicals, to quantify these risks for different exposures (time and concentrations) and to determine conditions resulting in minimal or tolerable risk. In applying that approach to nonessential compounds, toxicologists, with complete justification, have used the most stringent standards. These are reflected in uncertainty factors, in extreme cases of up to four orders of magnitude, that are applied to less than satisfactory data to arrive at a minimal risk level. In addition, standards are set for the most vulnerable groups in a population, which is also justified for nonessential chemicals. When, on the other hand, this stringent approach is applied to some essential nutrients, a striking dichotomy in the interpretation of one and the same exposure level appears: what is considered essential for life by nutritionists can carry a degree of risk for toxicologists.

The nutritional approach. It is the mirror image of the toxicological efforts, sharing with the latter many problems, such as the interpretation of incomplete data or the difficulty of determining the first, marginal deviations from normal. What divides the philosophy of the two mirror images is the acceptance by nutritionists of the safety concept for balanced diets. Balance refers to the relative distribution of nutrients approximating those recommended in the RDA values. Excluding by definition extreme dietary practices and extreme influences of the geochemical environment (areas of high F, Se, Cd and As), it states that the consumption of a balanced diet is safe when it maintains normal body weight. This may be the reason for the much smaller “safety factors,” usually two standard deviations of the recommended levels, used in the RDA values.

CRITERIA FOR ADEQUATE AND SAFE (MINIMAL RISK) INTAKES

From the time of the first efforts to set recommendations, the criteria of adequacy and safety have continuously increased in their stringency, together with striking advances in biochemical technology and analytical chemistry. These developments extended the goals from the prevention of acute health effects of deficient or excessive exposures to the maintenance of health throughout the lifetime (Institute of Medicine 1994). Modern techniques have made it possible to identify and measure biological functions such as intellectual development and immune competence as highly sensitive risk indicators whose application has raised adequate intake estimates while reducing those of minimal risk. This has not only narrowed the range of safe and adequate intakes as estimated by nutritionists, but has led to a conflict between nutritional and toxicological recommendations for an essential trace element, zinc (Smith 1994). It is neither likely nor desirable that the stringent criteria of risk assessment be relaxed in the future; therefore it will be increasingly necessary to agree on those measured parameters that affect health and those that do not. Fluorine can serve as an example. It is a “beneficial” (if not essential) element for nutritionists, because it prevents caries and may have some beneficial effects on bone health within a small range of intakes, but the spectrum of adverse effects begins right there with mottling of the teeth to end at the severe pathology of skeletal fluorosis. Even a carcinogenic potential of high, long-term exposure is under discussion again (Grandjean et al. 1993). Should mottling of the teeth be regarded as the first indicator of risk or should it be judged to have only cosmetic importance? The answer depends on judgment and will strongly influence risk management decisions.

There are other, more general problems of risk assessment in which judgment plays a substantial role. One relates to the relevance for health of nutrient-specific enzyme activities, i.e., to the question whether maximal activity confers any health benefits. The 10th edition of the Recommended Dietary Allowances (1989) and the WHO document, Trace Elements in Human Nutrition and Health (1996), base their recommendations for selenium on maximal saturation of the selenium enzyme, glutathione peroxidase, even though measurable risks to the health of populations exhibiting less than full saturation of the enzyme, for example, in New Zealand, have not been demonstrated (Robinson and Thomson 1983). The interpretation of changes due to homeostatic regulation presents another problem. The efficiency of an element’s absorption and/or excretion, the degree of saturation of its carrier protein and the total body pool are functions of habitual intake; moderate deviations from “normal” reflect efficient homeostasis, but not necessarily a health risk. Here again, scientific judgment must determine at which point these adjustments begin to produce undesirable effects, for example, by interfering with the utilization of other elements.

Impairment of immune functions caused by inadequate or excessive intakes is rightfully accepted as an indicator of risk even in the absence of immediate clinical consequences, as are changes in cognitive or emotional status and development. The diagnosis of all of these changes requires sophisticated methods that are now available and whose application may have a growing influence on the setting of safe and adequate levels of intakes.

Who is covered by recommendations of safe and adequate intakes? The nutritional and toxicological standards for adequacy and minimal risk, respectively, apply to “practically all healthy persons”; they exclude conditions of disease and medical interventions such as high calcium or fluoride prescriptions to individual patients in the treatment of osteoporosis. Beyond this agreement, however, there is an important difference in the definition of the target population: the traditional toxicological standards for minimal risk exposure are set for the most vulnerable groups among the healthy population, such as infants, children and pregnant women, resulting in an extra margin of safety (and perhaps unnecessary restrictions) for the remaining age and sex groups. The Recommended Dietary Allowances and other national recommendations, on the other hand, have set their standards separately for each age and sex group, so that vulnerable groups are protected, without imposing their standards on the rest of the population.

MODIFYING FACTORS

Any standard of safe or adequate intakes is valid only for the conditions under which it was determined, because there are many modifying factors that affect the reaction of the
organism to a given exposure. The most important factors are the chemical form of the nutrient, the route and timing of intake, and dietary interactions. Each of those can change an intake that is adequate under one condition to a deficient or excessive intake under another.

Chemical form. The valence of a metal determines bioavailability as well as toxicity, a fact that has been known for many years and is being applied in nutritional recommendations (Fe, Cu, Cr, Se, As and Hg). The valence state of chromium determines whether this element is a carcinogen (hexavalent) or an essential nutrient (trivalent). Furthermore, large differences result from the form in which an element is bound. The higher bioavailability of organically bound iron than that of inorganic forms contrasts with the greater toxicity of inorganic arsenic, compared with the organically bound element. These and several other examples not discussed here emphasize the need to specify the chemical form of elements for which standards are set.

Route and timing of intake. This nutritional discussion excludes exposure by inhalation, but even the oral intake presents two different situations with different levels of risk: An element may be consumed as part of the daily food or apart from food as a constituent of drinking water or as a supplement. Experience has shown that the risk of micronutrient toxicities even from high intakes of balanced diets is minimal or negligible. (The risk of obesity from excessive energy intake is not the subject of this paper.) On the other hand, the irritation of the gastrointestinal tract by supplements of iron or zinc taken separately from food is well known, as is the diarrheal action of certain magnesium salts at amounts that are innocuous as normal constituents of a diet. Such differences were recognized by the Environmental Protection Agency when it included extensive epidemiologic data on the toxicity of waterborne manganese for drinking water standards, but not for its determination of the oral reference dose of that element (Velazquez and Du 1994). There are many possible reasons for these differences. Absorption efficiency may be one; disturbances of elemental balance in the diet by individual supplements may be another.

Dietary interactions. Interactions among the constituents of a diet exert a very strong influence on the translation of absolute requirements (the amounts required by the organism) into dietary requirements (the amounts that must be present in the diet). Depending on the nutrient and the composition of the diet, the two requirements may be nearly identical (e.g., I and Cl) or may differ by one or even two orders of magnitude (e.g., Fe and Cr). For this reason, a given dietary allowance for inorganic micronutrients is valid only for a certain type of diet, not for others. The RDA values, for example, assume an average 10% iron availability in the U.S. diet. The World Health Organization (1973 and 1996) had to recommend three different levels of zinc intake to cover the needs of populations worldwide, consuming diets of different zinc availability. It is to be expected that dietary interactions influence the upper limits of safe intakes as well, so that the whole range of safe and adequate intakes can be distinctly different among populations with different dietary habits. Of the hundreds of known interactions, only those of iron and zinc are sufficiently quantified for application to nutritional recommendations.

EXPRESSION OF UPPER AND LOWER LIMITS

As absolute numbers. RDA committees traditionally have set their allowances in terms of the amount of the daily nutrient intake for each age and sex group, and upper limits could be expressed the same way. Advantages and disadvantages of this method have been amply discussed in the past. The method presents two major problems. One is the separation of recommendations for individual nutrients from the total diet intake. There is no recommended allowance for energy. This raises the question whether a certain intake of a micronutrient is safe and adequate for the wide range of energy intakes typical for a small, sedentary person compared with one performing heavy work. In reality, there is a strong relation between the consumption of energy and that of micronutrients. The other problem is the lack of a common denominator, such as energy intake, that would assure balance among the recommended intakes of individual nutrients.

On the basis of body weight. The reference dose (RfD) values of the Environmental Protection Agency are expressed on the basis of kilograms body weight (Dourson 1994). Because they address the most vulnerable population, they do not have to specify age or sex groups. Although there is some relation between body weight and food consumption, this method does not distinguish between the safety of certain micronutrient levels consumed by an obese, sedentary person and those consumed by a highly trained athlete of the same weight with a much higher food intake.

On the basis of energy intake. The evaluation of the nutritional value of diets on the basis of their nutrient density (the concentration of nutrients/1000 kcal or kJ) offers the important advantage that it considers the individual nutrients in relation to all others and to energy intake. It thus emphasizes balance and is consistent with the consumption of the same meals by all but the very youngest family members, differing only by the amounts eaten (Sorensen et al. 1976). Its use for expressing the recommended dietary allowances was proposed to the 9th RDA committee (Hansen and Wyse 1980) but not implemented then. The nutrient density concept would offer distinct advantages over the above-mentioned alternatives as a basis for recommending both lower and upper limits of safe and adequate intakes. The nutrient density concept prescribes a certain relation among individual nutrients and between those and the energy content of diets. This relation is maintained at all levels of consumption, reducing the risk of adverse dietary interactions. It is consistent with the lack of reports of adverse effects of individual nutrients eaten as part of a balanced diet, even at high intakes. It could serve well as a guideline for fortification policies and for the design of food analogs.

CONCLUSIONS

My interpretation of the facts discussed above suggests the following conclusions: 1) The consumption of a balanced diet in amounts to maintain desirable body weight presents no risk or negligible risk of adverse health effects. 2) A balanced diet is best described as the relation of all recommended nutrients and micronutrients to its energy content. 3) Individual supplements of micronutrients, especially of minerals and trace elements, can produce different health effects and risks, depending on chemical form and dosage. They require separate risk assessment and possibly separate upper limits.

LITERATURE CITED

