

Is there a metabolic basis for dietary supplementation?¹⁻³

Steven H Zeisel

ABSTRACT To be efficacious, dietary supplements must either provide a nutrient that is normally undersupplied to cells or exert a pharmacologic effect on cellular processes. In the first case, optimal function is achieved when a nutrient required by the organism reaches a specific concentration within the cell. A supplement has benefit only when the normal intake of a bioavailable form of a nutrient is lower than the amount that would provide maximum benefit as judged from all biological perspectives. Metabolic, environmental, and genetic factors can make individual nutrient requirements differ from the estimated needs calculated from population-based data. For example, under certain circumstances intracellular antioxidants may be depleted and a dietary supplement might restore optimal antioxidant protection. In the second case, the dietary supplement contains a constituent that is normally not required by the cell, but this substance is capable of altering normal cell function. For example, herbal preparations may contain ephedrine (a drug), which might alter heart rate so that the amount of blood pumped by the heart is enhanced. An understanding of how the variation in nutrient requirements comes about and of the pharmacologic actions of nutrient supplements can help to identify which individuals are most likely to benefit from dietary supplements. *Am J Clin Nutr* 2000;72(suppl):507S-11S.

KEY WORDS Antioxidant, nutrient requirements, RDA, recommended dietary allowance, dietary supplements

DEFINING INDIVIDUAL NUTRIENT REQUIREMENTS

Many individuals use supplements to increase their intake of certain nutrients and active chemicals. Is there a strategy for deciding when these supplements are likely to be beneficial? If a person desires to optimize cellular function, he or she might take a dietary supplement for several reasons. One reason might be that delivery of the nutrient in the person's diet is inadequate because of low food intake. A second reason might be that a person's intake of nutrients may be dependent on official recommended allowances, and new scientific data indicates that these recommendations underestimate individual requirements. A third reason could be that special conditions at a certain point in the person's life cause requirements to change without corresponding changes in diet. A fourth reason might be that the supplement may have pharmacologic effects that correct cell functions that became abnormal as a result of a disease process.

The recommended dietary allowance (RDA) of a nutrient is calculated based on the needs of the entire population (1). These rec-

ommendations are based on observed food intakes by healthy individuals; on balance studies, in which optimal intake is defined as the amount needed before the nutrient begins to spill into urine; on biomarker studies, which determine the amount of the nutrient needed to maintain normal amounts of some chemical in tissues; and on deficiency studies, in which the amount of nutrient needed to correct a symptom of deficit is defined as optimal (1). Functional endpoints were used occasionally in the past, but they are proposed in this article as the best paradigm for developing future recommendations (1). By whatever method used, nutrition scientists hope to recommend an amount of nutrient that should permit optimal cellular function for most normal people.

The human population has normally distributed (bell-shaped distribution) amounts of dietary requirements and food intakes. Because genetic, developmental, lifestyle, environmental, normal aging, and pathologic conditions differ, the actual nutrient requirements for any given individual vary greatly from the RDA. In most cases the recommendation exceeds needs, but in some cases it falls short of requirements. If one looks at the intake for any large population, there will be an average amount that describes that population. It is assumed that if we recommend an amount that is 2 SDs above the average requirement, the recommended amount would be adequate for most of the population and would ensure that deficiency syndromes are avoided. Of course, this approach always leaves out a small group of individuals whose genetic makeup is such that they require >2 SDs above the average requirement for the nutrient (**Figure 1**). Requirements for <5% of the population are underestimated because of the manner in which scientists statistically describe any dietary requirement.

Because setting requirements for any individual on the basis of average human intake is imperfect, what should be used as the gold standard for defining recommended nutrient intake for a specific person? Do we, as nutrition scientists, define it on the basis of optimal function of the body and its constituent organs and cells? Do we define it to maintain a concentration of a nutrient measured in blood or tissue? Do we define it to prevent a specific nutrient deficiency syndrome? Do we define it on the basis of population-based concepts to reduce risk? All of these are reasonable

¹From the School of Public Health and the School of Medicine, University of North Carolina at Chapel Hill.

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³Address reprint requests to SH Zeisel, Department of Nutrition, School of Public Health and School of Medicine, CB#7400, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7400. E-mail: steven_zeisel@unc.edu.

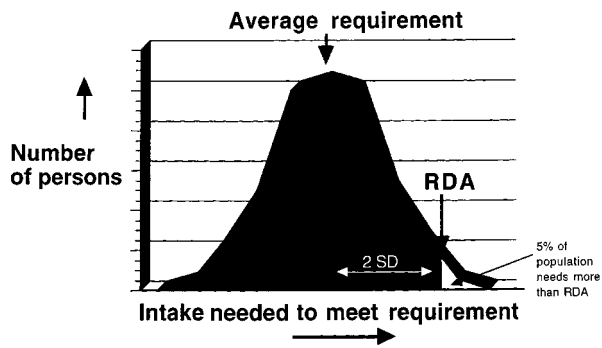


FIGURE 1. Distribution of dietary requirements in a population. Dietary requirements usually vary among individuals and are distributed in a classic bell-shaped pattern. The recommended dietary allowance (RDA) is usually defined as the intake meeting the requirements of 95% of individuals (2 SDs above the average requirement). Modified from reference 2.

choices. Nutrition scientists are moving away from recommending dietary intakes that are calculated to prevent deficiency symptoms and moving toward recommending intakes that reduce a population's risks. This approach, too, has its problems. We might observe that in a whole population, a high intake of soy protein is associated with a lower risk of cardiovascular disease or cancer and thereby define a recommended soy protein intake based on a risk reduction strategy. This would improve the health of the population but might not necessarily benefit any given individual.

In view of the increasing use of dietary supplements, nutrition experts should define a recommended minimum and maximum intake of a nutrient (an upper safe limit beyond which the intake of a nutrient supplement may increase rather than reduce health risks). If we construct a curve for the risk of disease in a population compared with changing intake of a nutrient, clearly a region of this curve will be associated with low dietary intakes of the nutrient and greatest risk of deficiency or of suboptimal bodily function (**Figure 2**). As nutrient intake increases, the risk of deficiency is reduced until there is a minimum level of risk for the population. Thereafter, as nutrient intake increases, risks associated with excessive intake begin to accrue. It is not possible to identify a risk-free intake for all individuals; rather, nutrition scientists indicate intake amounts that are unlikely to pose risk for most members of the population. There are usually some people with a genetic predisposition or disease that makes them vulnerable to more modest amounts of nutrient intake. For a more complete discussion of upper limits, see the recent National Academy of Sciences publication on dietary reference intakes (2).

CHANGING NUTRITION SCIENCE

Nutrition scientists try to establish RDAs that match the amount that most individuals must ingest to achieve optimal body function and to minimize the risk of disease. As mentioned earlier, these recommendations are inadequate for a certain segment of the population who significantly deviate from mean requirements. These estimates also fall short when available scientific information is incomplete. For example, as yet undiscovered information may show a function for a nutrient, or a risk reduction associated with the nutrient, that was previously not imagined. A recent example is the observation that women

ingesting amounts of folate that fell within the low but adequate range of the recommended intake of this vitamin had an appreciably increased risk of giving birth to a baby with a defect in neural tube (brain and spinal cord) formation, and national nutrition policy was adjusted (3, 4). Before this new observation was made, it was reasonable to estimate that women of childbearing age needed less folate than what turned out to be optimal because they did not develop anemias characteristic of folate deficiency. Once this new information became available, the RDA for folate for women of childbearing age was increased.

Such reengineering of estimates does not always result in steadily increasing amounts of recommended nutrient requirements. In the case of iron, the Food and Nutrition Board [a scientific panel of the National Academy of Sciences that advises as to intake recommendations (5)] increased the recommendation for iron in 1960, reflecting new knowledge about iron deficiency anemia and iron needs in humans. Recently, this board began to reduce their recommendation because new science has suggested that risks are associated with higher iron intake (6). As knowledge changes, recommended intakes change, and new recommendations in turn change the calculation of whether a supplement to normal dietary intake is appropriate.

CHANGING REQUIREMENTS RELATED TO LIFESTYLE AND LIFE CYCLE

Special conditions occurring during an individual's life span may increase the requirements for a particular nutrient. For example, exercise results in the production of reactive oxygen derivatives, which are damaging to cells, and thereby creates an increased demand for dietary antioxidants (7). Ultraviolet radiation from the sun forms previtamin D in the skin, and at skin temperature this is converted to an active form of vitamin D. Scientists discovered rickets, or vitamin D deficiency syndrome, in England during the Industrial Revolution. Air pollution during this period increased to the extent that the sun's ultraviolet light was obscured and sunlight deprivation became a major problem for the population. Today, sunscreen users who follow medical recommendations to protect their skin against the damaging effects of ultraviolet radiation can dramatically decrease the amount of vitamin D made in the skin (8). Increasing age also

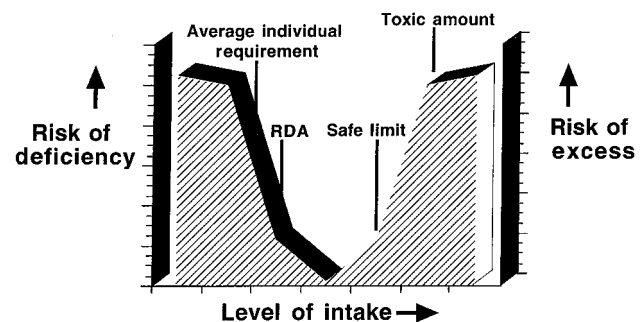


FIGURE 2. Relative risk and dietary intake. At very low intakes of a nutrient, there is substantial risk of deficiency symptoms. As intake increases, this risk diminishes. The recommended dietary allowance (RDA) is usually set at close to the amount associated with minimum risk. At higher intake of a nutrient, risk starts to increase. At the point where these risks become significant, the maximum safe intake is defined. At very high intakes, obvious toxicity develops. Modified from reference 2.

modifies vitamin D requirements. Given 15 min of sun, the skin of young adults makes much more vitamin D than does the skin of the elderly (8). Therefore, a supplement to dietary intake (as a fortification of diet, a pill, or a change in food choice) is important for the elderly to prevent the consequences of vitamin D deficiency (osteoporosis and rickets). Another example of age-related changes in dietary requirements is the greater need for dietary vitamin B-12 in the elderly. This vitamin is bound to proteins in foods and for the vitamin to be absorbed, acid in the stomach must break these bonds. A significant portion of people over the age of 60 y have insufficient stomach acid to accomplish this and require either more foods that contain vitamin B-12 or a supplement of the unbound vitamin (9).

Pregnancy also changes dietary requirements because not only must tissue mass be sustained, but a fetus must be formed. As discussed earlier, pregnant women have a special requirement for folate because of the critical period during early fetal development when folate availability is essential for brain formation. It is likely that other critical periods are associated with various nutrients. Two sensitive periods occur in the development of the rat brain during which treatment with supplemental dietary choline results in long-lasting enhancement of spatial memory. The first occurs during embryonic days 12–17 and the second during postnatal days 16–30 (10–12). The 2 sensitive periods correlate with neurogenesis of cholinergic neurons (the formation of nerve cells, which occurs during the prenatal period) and with synaptogenesis (the completion of connections with other nerve cells, which occurs during the postnatal period) (13–16). The effects of supplementing the mother's diet with choline can be detected as improvements in memory in her offspring throughout their lives (10, 11, 17–19). Choline supplementation also influences the electrical properties and structure of the memory center (hippocampus) of their brains (20).

People sometimes undertake behaviors that alter their intake of essential nutrients in the belief that these behaviors will increase their overall health. For example, many persons who consciously reduced their dietary intake of fats have, as a result, changed their intake of fat-soluble vitamins. If this trend continues and individuals reduce dietary fat intake to 10–20% of energy in their diet, as some nutritionists advocate, the dietary intake of fat-soluble vitamins, eg vitamins A, K, E, and D, will be very low. The need to supplement daily intake of these vitamins may therefore change. Another example of the influence of a lifestyle choice on nutrient requirements is smoking, which increases an individual's exposure to oxidant damage and causes the consumption of endogenous antioxidants, thereby depleting protective reserves (21). Thus, smoking may increase the demand for dietary supplementation with antioxidants.

MORE IS NOT ALWAYS BETTER

Recent information on the effects of dietary and supplemental vitamin C, α -tocopherol, and provitamin A carotenoids in preventing heart disease (22) has led many individuals to supplement their diets with large doses of these vitamins. Other individuals take these supplements to prevent cancer. Oxygen free radicals can react with DNA, forming damaged DNA that is misread when copied. This can result in mutations that cause cancer. Antioxidants can soak up oxidants and prevent DNA damage. Is the ingestion of more of these antioxidants therefore likely to be uniformly helpful?

In heavy smokers, increased intake of β -carotene and vitamin E was shown to increase the incidence of lung cancer (23, 24). How can this be? Perhaps the explanation is that antioxidants interfere with important processes needed to kill cancer cells. In normal tissues, apoptosis (an internal program that allows damaged or obsolete cells to commit suicide) provides a physiologic way to eliminate terminally differentiated, damaged, or genetically altered cells, thus facilitating tissue remodeling after cell injury (25). Apoptosis is an important defensive barrier that inhibits carcinogenesis by eliminating initiated (mutant) cells (26, 27). Reactive oxygen species are intermediate messengers in several apoptosis signaling pathways (28–30). A suggested mechanism of action for Bcl-2, an apoptosis suppressor protein, is that it regulates an antioxidant pathway at sites of free radical generation (31). Administration of antioxidants inhibits apoptosis (28, 32). Therefore, scientists and concerned individuals must address the wisdom of inhibiting apoptosis that eliminates cancer cells. It is easy to be excited by new discoveries in nutrition, but experience indicates that there are positive and negative effects that occur whenever we appreciably alter diets. Before advocating increased intake of antioxidants, we need to consider whether the individual is likely to have already damaged their DNA (for example, by heavy smoking). If they have, antioxidants will not prevent or repair this damage and they will inhibit the apoptosis mechanisms that are needed to eliminate these damaged cells. Thus, more is not always better. Antioxidant-depleted diets diminished tumor size and increased apoptosis rates in cancer cells in mice with brain tumors (33).

PHARMACOLOGIC ACTION OF DIETARY SUPPLEMENTS

Sometimes the effects of a dietary supplement mimic the actions of drugs. When is a dietary supplement acting as a drug rather than a nutrient? Obviously, when an herbal supplement is taken for its ephedrine-like effects, there is no problem understanding that we are dealing with a pharmacologic agent (34). However, some supplements are clearly nutrients when ingested in amounts that could be found in the diet but are drugs when ingested in amounts that could never be achieved in the diet. For example, 5 or 10 y ago tryptophan was widely prescribed for insomnia (35, 36). Persons taking a large dose of tryptophan fell asleep as much as 15–20 min sooner (35). In this example, a compound was administered in doses that exceeded dietary requirements to obtain a pharmacologic response. The normal metabolism of nutrients includes many regulatory protection mechanisms that make adjustments for modest changes in intake of the nutrient. Often when a nutrient or chemical is ingested in amounts that greatly exceed those to which the body is normally exposed, these safeguards are overwhelmed. When supplements are ingested for their pharmacologic effects, it is reasonable for consumers to think of them as drugs and to consider the benefits and risks much more carefully than they would for foods. There should be compelling evidence for efficacy and for safety.

WHEN SHOULD DIETARY SUPPLEMENTS BE USED?

There are 2 reasons for using dietary supplements. The first is to optimize cellular function, which might be justified if delivery of the nutrient in the diet is low because of inadequate food intake or poor selection of foods, or if genetic diversity and special conditions cause the requirements for the nutrient to increase without



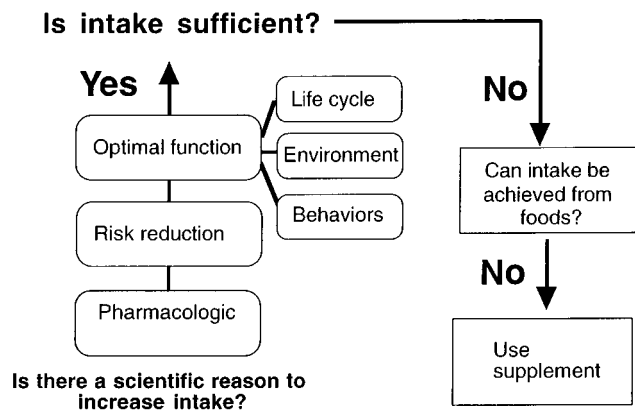



FIGURE 3. Approach to dietary supplementation. The determination of whether dietary intake is sufficient is based on consideration of several factors discussed in the text. If it is deemed that intake is insufficient, decisions have to be made as to whether normal foods can be eaten to increase intake or whether a dietary supplement is required.

corresponding changes in diet. How is an individual to know whether his or her own requirement for a nutrient differs from that of the population? At this time, nutrition scientists have limited answers. Laboratory tests for nutritional adequacy (called biomarkers) are still quite crude. Many of these tests measure amounts of the nutrient but not its functional effects. Scientific identification of the genes that control requirements for nutrients is just beginning. For example, we are just learning that some individuals are at greater risk for heart disease because they express the *APOE*E4* allele, which is involved in the transport and distribution of cholesterol (37). Research that refines our understanding of appropriate biomarkers and gene expression will greatly improve the ability of health care providers to make individually tailored recommendations for nutrient intake. This research needs to be assigned national priority.

The second reason for using dietary supplements is to obtain a pharmacologic effect that corrects cell function that is abnormal as a result of a disease process. As discussed earlier, this use of supplements involves exposure to a nutrient or chemical in amounts that are greatly in excess of those to which an individual might normally be exposed. Justification for this type of supplement use is no different from that for the use of pharmaceuticals. If there is proven efficacy that promises benefit in excess of risks, then the use of these supplements is warranted. Careful research must be conducted so that adequate data are available before such choices are made.

Figure 3 consists of a flow chart suggesting how scientists and individuals might think about choosing nutrients and determining when a supplement is needed. First, a health provider or an individual must assess whether there is adequate mechanistic research supporting the role for the nutrient in optimizing cellular function. Usually this requires data from human clinical trials or epidemiologic data complemented by basic science studies. Then it is reasonable to ask whether an individual's dietary intake of the nutrient is sufficient, based on an assessment of stage in the life cycle, genetic polymorphism, normal aging, exposure to environment, personal behaviors, and so forth. Sometimes available biomarker tests are not optimal for making this decision. If this is the case, it should be determined whether there is evidence of suboptimal function in certain individuals or increased risk in a particular population. If so,

there is reason to believe that individuals could benefit from supplementation with a nutrient or a food constituent. A second question concerns whether people can achieve this benefit by changing their diets to increase intake of normal foods. If this is not possible, then individuals are justified in considering supplements. 

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