Vitamins and minerals: efficacy and safety

John N Hathcock

ABSTRACT Safety and efficacy are crucial but separate issues for vitamin and mineral supplements. Misinterpretation of “safe and adequate” to mean “safety limit” would impose restrictions on vitamin and mineral intakes that are not needed to ensure safety. Substantial evidence indicates that intakes greater than the recommended dietary allowances (RDAs) of certain vitamins and minerals such as calcium, folic acid, vitamin E, selenium, and chromium reduce the risk of certain diseases for some people. Limitation of intakes to the RDAs would preclude reductions in disease risk from these nutrients. The margin of safety between the usual dietary intake and the intake that would produce adverse effects varies greatly among the different nutrients. Very high intakes of vitamins A and D, niacin, pyridoxine, and selenium have produced adverse effects. Many widely discussed putative adverse effects of vitamin C, vitamin E, and trivalent chromium have little factual basis. There is no evidence of adverse effects from β-carotene supplements except in current heavy smokers. Am J Clin Nutr 1997;66:427-37.

KEY WORDS Vitamins, minerals, benefits, efficacy, safety, adverse effects

INTRODUCTION Efficacy and safety are the health issues that determine whether dietary supplements should be recommended and consumed. Efficacy is the ability of a supplement to provide a health benefit related to either prevention of deficiency or a reduction in the risk of chronic disease (1-4). Safety is a reasonable certainty that there will be no adverse effects from excessive intake of a nutrient (1, 3, 5). Most consumers likely consider both by assuming safety and judging efficacy in their individual decisions. Moreover, safety related to avoidance of adverse effects of excessive intake and efficacy to provide health benefits are addressed separately under federal labeling and safety regulations. Nonetheless, the two concepts are sometimes treated in a manner that does not clearly separate them. For example, the Food and Nutrition Board has set estimated safe and adequate daily dietary intakes (ESADDIs) of selected vitamins and minerals as an alternative to recommended dietary allowances (RDAs) when the data are inadequate for setting an RDA (6, 7). Also, the term “safe and adequate” has been misinterpreted as “safety limit” by the Codex Alimentarius Commission (8). A more accurate definition of “safe and adequate” and the ESADDI would be “the recommended intake, an amount that is also safe” (5).

It has long been conventional wisdom that dietary supplements are not needed by persons who eat varied diets, and also that use of supplements may carry significant risk of adverse effects if intakes exceed the RDAs (9-11). The issue of need raises the question “Needed for what?” The potential benefits of nutrients in reducing the risk of diseases not recognized as classic deficiency diseases generally have not been considered thus far in setting the RDAs or ESADDIs. Recognizing the important role of some vitamins and minerals beyond that of preventing deficiency, the Food and Nutrition Board is now considering use of evidence for decreased risk of chronic disease in setting the RDAs. (11).

Safety is of course an important issue, especially at nutrient intakes well above the RDAs or ESADDIs. A safe intake of any substance is one that provides an adequate margin below amounts that cause adverse effects (4, 5). The Environmental Protection Agency’s reference dose concept of safe intakes has been applied to essential minerals (12). A similar approach that takes nutritional recommendations into account before calculation of a safety limit has been applied to both vitamins and minerals (4, 5). The Food and Nutrition Board is currently evaluating procedures and standards for identifying “safe upper limits” or “upper reference intakes” for nutrients.

For selected vitamins and minerals, this paper examined the scientific evidence for benefits other than meeting classical nutritional needs as well as the concepts and evidence related to safety concerns. The nutrients reviewed for safety were selected because they have been the source of practical safety problems or the subject of controversy about safety. Similarly, the nutrients reviewed for efficacy were selected because current evidence on them challenges the conventional wisdom that “the RDA is always enough.” The criteria for nutrient selection for safety and efficacy intersect in the conclusion that if there are benefits at intakes above the RDAs, the RDAs should not be used as safety limits.

EVIDENCE OF EFFICACY Calcium and osteoporosis

The role of dietary calcium in achieving higher bone mass and thereby reducing the risk or delaying the onset of osteoporosis is now well recognized (13) and a health claim on this nutrient-disease relation has been authorized by the Food and

1 From the Council for Responsible Nutrition, Washington, DC.
2 Address reprint requests to JN Hathcock, Council for Responsible Nutrition, 1300 19th Street NW, Suite 310, Washington, DC 20036-1009. E-mail: hathcock@crrusa.org.
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Drug Administration (14). Because bone loss accompanies the aging process, sufficient calcium intakes during early adulthood increase peak bone mass, thereby reducing the risk of osteoporosis decades later. Increases in calcium intake in postmenopausal women delay calcium loss from bone, thus lowering the risk of bone density declining to osteoporotic levels. Daily calcium intakes of 1000–2000 mg slow the decline of bone density, thus reducing risk of osteoporosis (13, 14). These amounts are well above the 800-mg RDA for nonpregnant, nonlactating adult women in the United States (7).

**Folic acid and risk of neural tube defects and heart disease**

There is clear evidence that sufficient intakes of dietary folic acid before conception and very early in pregnancy decrease the risk of a baby developing neural tube defects (NTDs) that include spina bifida, anencephaly, and encephalocele (15). The daily intake of folic acid thought to be effective for a sensitive subset of the population is 400 μg (0.4 mg), an amount above the RDA in most countries. Although folic acid can reduce the risk for NTDs, these defects are not solely attributable to folic acid deficiency. Folic acid supplementation generally reduces the risk by 50–75%.

Increasing evidence suggests that sufficient dietary folic acid can decrease the plasma concentration of homocysteine, a substance that is gaining scientific recognition as a risk factor for heart disease (16–18). The data are not yet sufficient to make a reliable estimate of the amount of folic acid needed to generate this benefit, but the amount identified as possibly effective is in the same range as that shown to be effective against NTDs.

**Antioxidant nutrients and risk of cancer and heart disease**

**Vitamin E**

Results from several research approaches studying the effect of vitamin E on heart disease and its risk factors have shown protective effects associated with intakes well above the RDA (19–25). Epidemiologic evidence indicates a strong dose-response relation between decreased risk of heart disease and increased vitamin E intakes from both diet and supplements. Significant protection begins at daily intakes of 67 mg α-tocopherol equivalents (19). Low-density-lipoprotein (LDL)-cholesterol oxidation decreased significantly in blood taken from subjects receiving ≥ 400 IU/d but not ≤ 200 IU/d (21). In addition, a double-blind, placebo-controlled intervention trial showed a significant decrease in nonfatal myocardial infarcts in high-risk subjects consuming either 400 or 800 IU vitamin E/d as a supplement (23).

In comparison, another clinical trial did not observe any benefit on heart disease from a supplement of 50 mg all-rac-α-tocopherol acetate/d given for 5–7 y to middle-aged Finnish men who were long-term, heavy smokers (26). One recent epidemiologic study observed a decrease in heart disease with increased intakes from foods but not from supplements (27). The study population involved very few who took vitamin E supplements and there may have been insufficient statistical power to detect any effects of supplements. The preponderance of evidence contradicts these results. Considerable epidemiologic evidence also links vitamin E with a reduced risk of cancer (28). These data are supported by the results of animal experiments (29) but the evidence is not as strong as for the reduction of heart disease risk by vitamin E.

**Vitamin C**

Vitamin C inhibits chemical synthesis of nitrosamines (most of which are animal carcinogens) in the gastric contents, but inhibition is not complete until dietary intakes reach ∼1000 mg (30–33). Considerable evidence from both epidemiologic studies and clinical trials suggests that intakes of vitamin C much higher than the RDA may reduce the risk or risk factors for chronic diseases such as heart disease and cancer, especially when combined with higher intakes of vitamin E (34–39).

**β-Carotene**

Epidemiologic studies have shown that people with high intakes of β-carotene or high blood concentrations of this nutrient have a reduced risk of various diseases, including cancer and heart disease (40). The chemical abilities of β-carotene to quench singlet oxygen and inhibit peroxyl free radical reactions are well established (41). In addition to this antioxidant property, β-carotene and some other carotenoids may play an important role in facilitating normal cell-to-cell communication through gap junctions (42). Because many carcinogens inhibit gap junction communications (43), protection of this activity by dietary substances could be an important function in protection against cancer.

Recent clinical trials—the Physicians’ Health Study (PHS) (44), the Carotene and Retinol Efficacy Trial (CARET) (45), and the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study (26)—failed to find any benefit of β-carotene in reducing the risk of cancer or heart disease. In fact, the ATBC trial and the CARET found increases in lung cancer incidence in smokers who were administered β-carotene. The results of these highly publicized clinical trials were without a doubt disappointing to those expecting β-carotene to lower the risk of cancer, but the current data should not be overgeneralized. The results do not show that β-carotene has no anticarcinogenic effect under any circumstance. Because the ATBC trial and the CARET studied populations at very high risk of lung cancer, and because the duration of treatment was far shorter than the induction time for this cancer, these trials do not support, but also do not disprove, the hypothesis that β-carotene may be anticarcinogenic in early stages of cancer.

There are several credible reasons for hypothesizing that β-carotene might reduce the risk of cancer: 1) increased consumption of β-carotene is strongly associated with reduced risk of cancer (40), 2) β-carotene is a dietary antioxidant (41, 46), 3) antioxidants inhibit early stages of carcinogenesis (47), and 4) β-carotene reduces cancer in some experimental animal models (48).

For modifying cancer risk, the importance of early administration of an antioxidant in relation to the time of exposure to the initiating carcinogen is well established through studies with butylated hydroxytoluene and butylated hydroxyanisole (49, 50). It is widely thought that lung cancer requires two decades for development from the first initiating events to clinically diagnosed cancer. Thus, even with the most powerful known protective action against lung cancer, cessation of smoking, decreases in risk become significant only over a 10–15-y period (51).
Selenium

The epidemiologic association of higher selenium intakes with reduced cancer risk and the antioxidant role of selenium in glutathione peroxidase (as well as several other possible mechanisms) have provided a basis for research on possible anticarcinogenic effects of selenium. Several selenium compounds have antitumorigenic activities in a variety of animal models when administered at amounts greater than those associated with nutritional need (52).

Only two clinical intervention trials published to date were designed to determine whether selenium in combination with other nutrients will reduce cancer risk. In one, 50 μg Se (in yeast) in combination with vitamin E and β-carotene moderately reduced the risk of total mortality, total cancer mortality, and stomach cancer mortality (53). In the other, inorganic selenium together with a wide spectrum of other minerals and vitamins did not significantly protect against cancer (54). An additional placebo-controlled, randomized clinical trial was stopped recently for ethical reasons after it became clear that treatment with 200 μg Se in yeast significantly decreased total lung cancer mortality and total colorectal and prostate cancer incidence (55–57). The amount of selenium used in the study was 200 μg, an amount nearly three times the RDA for adult males (7). The primary objective of the trial was to determine the effect of selenium on nonmelanoma skin cancer, but there was no effect, either negative or positive, on this disease—in contrast with effects on cancer at three other sites.

SAFETY: ISSUES AND EVIDENCE

Safety cannot be absolutely proven for any substance because such proof would require demonstration of a negative—that an adverse effect does not occur. Any substance would be expected to produce adverse effects if the intake were sufficiently high, and therefore safety or lack of it must be related to a specified intake. Published evidence is sufficient for safety assessment of vitamins and minerals over a range of intakes. This evidence is reviewed for some genuine and some bogus safety concerns for different vitamins and minerals.

Vitamin A

The potential for adverse effects from excessive vitamin A intake is well documented. Potential risk is based on the ingestion of excessive amounts of preformed vitamin A in the forms of retinol or retinyl esters, and not from provitamin A forms such as β-carotene or other vitamin A–forming carotenoids. Consumption of 7500–15 000 μg preformed retinol equivalents (RE) daily for periods of several months or more can produce multiple adverse effects, including liver toxicity and possibly birth defects (58). The smallest daily supplement of vitamin A reported to be associated with liver cirrhosis is 7500 μg RE (25 000 IU), which had been taken for 6 y (59). The smallest daily supplement generally considered to generate any risk of birth defects is also 7500 μg RE (25 000 IU) (58). One recent report, however, described a significantly increased risk of neural crest birth defects at daily supplement amounts of > 3000 μg RE (> 10 000 IU) (60). The average supplement intake by this group was 6509 μg RE (21 675 IU) but unfortunately the authors did not identify individual supplement intakes. Several issues have been raised about the validity of the defect classification scheme used and the resulting likelihood that the study overestimated the risk associated with vitamin A at the intakes identified in this study (61–63).

Some reports suggest that there may be some risk of vitamin A toxicity at supplement intakes < 6000 μg RE/d (20 000 IU/d). One report to the US Food and Drug Administration suggested a characteristic birth defect associated with maternal supplementation at 5400 μg RE/d (18 000 IU/d) (64). Another report found marginal indications in elderly subjects of adverse effects on the liver associated with chronic supplementation providing intakes of 1500–3000 μg RE/d (5000–10 000 IU/d) (65). However, the same laboratory was unable to repeat this finding in later research (66).

In summary, there is no evidence that vitamin A supplements of 3 000 μg RE (10 000 IU) are harmful to normal adults, including pregnant women and the elderly. Adverse effects of vitamin A are sometimes observed when supplement intakes reach 7500 μg RE (25 000 IU) and one report suggests that such effects may occur with somewhat lower intakes (60).

β-Carotene

β-Carotene is widely considered to be virtually nontoxic because humans tolerate high doses without apparent harm, and animal studies have also failed to find any toxic effects (58, 67, 68). There is no evidence that conversion of β-carotene to vitamin A contributes to vitamin A toxicity, even when β-carotene is ingested in large amounts (69).

The only consistent adverse or undesirable effect of high β-carotene intakes has been coloration of the skin related to hypercarotenemia, which occurs only at extremely high intakes. Doses as high as 180 mg/d have been given to humans for several months without observed adverse effects other than skin discoloration (70).

Because of the extensive safety record of β-carotene, major clinical trials have been designed with the implicit assumption that the only likely effects would be benefits. But subsequently, questions about the safety of β-carotene have been raised by the results of the ATBC trial (26) and the CARET (45), which observed significant increases in lung cancer risk in high-risk populations (long-term smokers or asbestos workers) given supplements of β-carotene (20 mg/d in the ATBC trial and 30 mg/d in the CARET). On the other hand, there was evidence in the CARET that β-carotene may reduce the risk of lung cancer in former smokers. In contrast with the results of the ATBC trial and the CARET, no increased risk was observed in the longer-term PHS (44), which included > 2000 smokers, or in three other shorter-term trials (53, 71, 72). Moreover, observational studies found no risk of lung cancer or other disease associated with increased β-carotene intakes (20, 73, 74).

The effects of alcohol or high intakes of retinol on the liver have been postulated to explain the adverse outcomes with β-carotene in the ATBC trial and the CARET (75). This hypothesis is supported by recently published subgroup analyses of the ATBC and CARET data, indicating that the promoting effects of β-carotene on lung cancer were seen primarily in subjects who consumed alcohol and smoked more (76, 77). All data available suggest that heavy concurrent smoking is a necessary condition for a promotional effect of β-carotene (78). Former smokers, whose tissues would presumably have been subjected to the mutagenic and carcinogenic effects of cigarette smoke, show decreased, not increased, rates of lung
cancer with β-carotene treatment (77). A review of all published evidence on β-carotene shows that the ATBC trial and the CARET suggest adverse effects but this conclusion is not supported by other clinical trials or epidemiologic data.

Nicotinic acid

The flushing reaction produced by nicotinic acid has been recognized for more than half a century (79). When taken on an empty stomach, crystalline nicotinic acid (but not nicotinamide) in doses as small as 10 mg may produce a mild but noticeable flushing reaction. Although not desirable, such reactions produce no known adverse consequences and they are seldom perceptible when small amounts of nicotinic acid are taken in tablet or capsule form or consumed with food.

Side effects such as liver toxicity and serious gastrointestinal reactions have occurred when gram quantities of nicotinic acid were taken to lower serum lipids (80). Gastrointestinal side effects include indigestion, nausea, vomiting, and diarrhea, and, in some persons necessitate discontinuation of nicotinic acid. Liver toxicity is most commonly manifested by increases in serum transaminase enzymes of liver origin released as a result of damage to liver cells. High doses have produced jaundice, fatigue, and, in at least one case, fulminating liver failure.

There is strong agreement between the minimum adverse effect level identified through clinical trials and that suggested by published case reports. Many severe reactions to nicotinic acid, especially liver toxicity, have involved ill-advised or inadvertent switching from unmodified to slow-release formulations (80). Most reported adverse reactions to niacin have occurred with intakes of 2–6 g/d. There are only two anecdotal cases reported in which intakes were <1000 mg, one for slow-release nicotinic acid at 500 mg/d and another for unmodified niacin at 750 mg/d (80). In a clinical trial two groups of adult subjects, one taking immediate-release and one taking slow-release nicotinic acid, were observed initially and for 6 wk at each dosage level: 500, 1000, 1500, 2000, and 3000 mg/d (81). The data showed no adverse reactions at 500 mg/d for either form of nicotinic acid, but significant effects beginning at 1000 mg/d (gastrointestinal effects with unmodified nicotinic acid and mild liver toxicity with slow-release nicotinic acid).

Many uncertainties exist in these cases about the accuracy of patient reports regarding the amount consumed and the presence or absence of preexisting or confounding conditions such as alcoholism or other conditions that compromise liver function (80). For these reasons, the clinical trial data are useful for safety and risk evaluations of nicotinic acid. From the clinical trial data it can be concluded that an intake of 1000 mg/d carries significant risk and that an intake of 500 mg/d carries no identifiable risk (81). Note, however, that the adverse reactions to 1000 mg unmodified nicotinic acid/d were gastrointestinal effects, which generally have less potential for serious outcomes compared with the liver toxicity that can result from 1000 mg slow-release nicotinic acid/d. The risks associated with ≥1000 mg nicotinic acid/d may be tolerable when it is used as an antihyperlipidemic drug under the care and monitoring of a physician, but such risks are not acceptable for unsupervised, self-selected use by consumers.

Pyridoxine

Deficient and excess intakes of pyridoxine can produce neurologic disturbances (82). The first report of pyridoxine neurotoxicity in humans described a sensory neuropathy of the extremities in women with daily intakes of 2000–6000 mg, mostly taken in an attempt to control premenstrual symptoms (83). The neuropathy slowly but perhaps incompletely regressed after cessation of the elevated dose (84–86). Most cases of sensory neuropathy have resulted from intakes >600 mg/d but some evidence suggests that neuropathy may result from doses as low as 300–500 mg/d in some individuals (82, 87, 88). The total dose over an unspecified time may give a better prediction of the potential for neurotoxic response than either the daily dose or the duration of the high intake (88).

There is controversy over the validity of the single report of adverse effects at daily intakes of ~100 mg or less (89). Although this report is often cited as evidence that pyridoxine intakes <100 mg/d can cause sensory neuropathy, the data showed an average intake of 117 mg/d among women with symptoms and an identical average intake (116 mg/d) in the control group. The group with symptoms had taken pyridoxine longer (an average of 2.9 y) than those without symptoms (1.6 y). Some women in each group had intakes ≤50 mg/d. Possible inaccuracies in the telephone survey method and a lack of objective neurologic assessment could have introduced bias.

The symptoms observed had no dose-response relation to pyridoxine intake but did show a time-response relation.

Some reports suggest that high intakes of pyridoxine may cause the development of oxalate kidney stones, but the reported cases may have been associated with the drug pyridoxilate (a combination of pyridoxine and glyoxalate) (90), and a recent prospective epidemiologic study found the relative risk of oxalate renal stone development to be decreased for men consuming >40 mg pyridoxine/d compared with those consuming <3 mg/d (91).

Ascorbic acid

Many hypothetical adverse effects of high intakes of vitamin C have been cited for decades (92–94). Most, with the exception of mild and transient gastrointestinal effects, seem to have little or no known factual basis (82).

Conditioned scurvy

Although this supposed phenomenon has been so widely cited in review articles that it has become conventional wisdom (92–94), detailed review and bibliographic tracing provide no substantiation. Only a very few original sources can be located; most references are secondary sources, and subsequent interpretation frequently reached conclusions not supported by the original data. The original hypothesis grew out of two cases of infantile scurvy (95). The mothers of these infants had taken vitamin C supplements during pregnancy and the author speculated that this might have conditioned the infants for rapid clearance of vitamin C resulting in scurvy. High intakes of vitamin C can result in accelerated clearance but this does not result in blood concentrations lower than normal (96, 97). Oral scurvy due to withdrawal from high vitamin C intakes has been reported but the diagnosis was not confirmed, the time to onset was suspiciously short, and no plasma vitamin C measurements.
were made (98). Conditioned scurvy has been widely discussed and speculated, but not substantiated.

**Oxalate kidney stones**

Reported large increases in urinary oxalate concentrations during periods of high vitamin C intakes appear to be an artifact of analysis due to oxalate production from ascorbic acid in an analytic procedure that involves heat (99). A more recent report involving better assay methods indicated a significant increase in oxalate excretion (still within the normal range) by persons consuming 1000 mg ascorbic acid/d (100). It is not clear whether this increased excretion of 10–15 mg oxalate/d was due to the instability of ascorbic acid in the urine during collection, storage, or analysis. Some reports assert that ascorbic acid is a risk factor for calcium oxalate kidney stones (101).

Other research involving alternative sample handling procedures found no increase with a different preparation of ascorbic acid at intakes of up to 8 g/d (102). One study found that oxalate was produced only in vitro in the urine sample itself with daily oral ascorbic acid intakes up to 10 g (103). The contribution of high ascorbic acid intakes to urinary oxalate is not established (104), and the suggestion that oxalate kidney stones are caused by high ascorbic acid intakes remains speculative (105). Indeed, epidemiologic evidence suggests a decreased risk of oxalate kidney stones with increased intakes of vitamin C. For example, a recent prospective epidemiologic study found the relative risk of oxalate renal stones to be decreased for men consuming ≥ 1500 mg vitamin C in comparison with those consuming < 250 mg (91). These data provide further support for an earlier retrospective that produced similar results (106).

**Proxidant effects, excessive iron absorption, or excessive iron release**

A potential for harm by high intakes of ascorbic acid through proxidant effects has been discussed widely (107, 108). An original research paper (109) has been cited in a review article (108) as showing that an ascorbate-driven free radical reaction damages cells. The study used in vitro assays with phagocytes and found that the release of iron from senescent erythrocytes in the medium had adverse effects only at abnormally high ascorbic acid concentrations. These concentrations were > 10 times the highest plasma ascorbic acid concentrations of subjects consuming 1000–2500 mg ascorbic acid/d (100). The hypothesis that high intakes of ascorbic acid will produce direct proxidant effects is not consistent with the data on iron release, and contrasts with the antioxidant effects of vitamin C observed under a wide variety of conditions (110). The concept that enhanced iron absorption by ascorbic acid leads to excess iron-related disease has been suggested (108) based on the hypothesis that increased serum ferritin concentrations cause heart disease (111, 112). The hypothesis that excessive iron causes heart disease is not supported by subsequent evidence and evaluation (113–118). Ascorbic acid intakes of 2 g/d for 2 y did not cause excessive iron uptake (119), providing additional evidence that a high ascorbic acid intake is unlikely to produce any iron-related increase in heart disease. Intakes of up to 10 g/d for up to 3 y without observed side effects have been evaluated in clinical trials (120).

**Gastrointestinal distress**

The most common adverse effects of high vitamin C intakes are gastrointestinal symptoms such as nausea, abdominal cramps, and diarrhea (121). When these symptoms occur, the vitamin C dosage is usually > 2 g/d but a few individuals report such symptoms at intakes as low as 1 g. These symptoms seem to be a direct osmotic effect because they can usually be avoided by taking the vitamin as a buffered salt rather than as a free acid. The symptoms usually disappear within a week or two with no further consequences. At least some of the diarrhea reportedly caused by ascorbic acid supplements may have been produced by other components such as sorbitol (122).

**Folic acid**

Three major concerns have been identified as possible adverse effects from excessive folic acid intakes: 1) the masking of pernicious anemia, thus allowing the neurologic disease of vitamin B-12 deficiency to progress unchecked; 2) the disruption of zinc function; and 3) the antagonism of medications, especially antifolate agents.

**Masking pernicious anemia**

Administration of high intakes of folic acid to patients with pernicious anemia can mask the anemic manifestations while allowing the neurologic disease (posterolateral spinal cord degeneration) to progress. Although there are a few reports of the masking effect related to amounts of folic acid ≤ 1 mg (results based almost entirely on studies with injected folic acid), the effect is unusual at such low doses and predictable only at doses ≥ 5 mg (123).

**Folic acid–zinc interactions**

Certain folic acid–zinc interactions are well documented, including the malabsorption of food folates in zinc deficiency due to insufficient activity of the folate conjugase enzyme that must convert food pteroylglumatates to the monoglutamate form before absorption (124). The crucial question for folic acid safety in relation to zinc is whether higher intakes have adverse consequences through a disruption of zinc bioavailability or function, and, if so, what are the intakes of folic acid that are associated with such effects. Some reports suggest that as little as 350 μg of supplemental folic acid can adversely affect zinc nutriture (125–127), but more recent reports indicate no adverse effects of folic acid at even higher intakes on zinc uptake or function (128, 129). The suggestion that folic acid intakes < 400 μg/d cause adverse outcomes of pregnancy through the antagonism of zinc functions (125) has not been supported by subsequent larger, multicenter studies involving intakes that were either 4 mg (130) or 800 μg (131) before and throughout pregnancy.

It is difficult to resolve differences in the scientific literature regarding a possible adverse effect of folic acid on zinc nutriture. These apparently incompatible results are likely attributable to the widely different experimental approaches used. In general, methods based on uptake rate and plasma concentration tend to show effects at lower folic acid intakes, whereas zinc balance methods tend to show effects only at higher intakes. Large, well-conducted clinical trials have found no adverse effects of folic acid on pregnancy through zinc antag-
onism or any other mechanism, although they have shown a clear benefit in reducing the risk of NTDs (130, 131).

Folic acid–drug interactions

At high intakes, folic acid has been reported to interfere with the effectiveness of anticonvulsant drugs such as Dilantin (diphenylhydantoin; Parke-Davis, Division of Warner Lambert, Morris Plains, NJ), used to control epilepsy (124). Folic acid doses of 5–30 mg orally have produced some evidence of increased frequency of seizures in epileptics, but there is no evidence of such effects at lower intakes of folic acid. It might be expected that increased folic acid intakes could interfere with actions of folate-antagonizing drugs such as methotrexate. In contrast, administration of 1 mg folic acid/d for 6 mo in patients with rheumatoid arthritis treated with low-dose methotrexate actually decreased methotrexate toxicity without affecting its efficacy for therapy (132).

Selenium

Excess selenium intake from consumption of seleniferous plants by animals produces a wide range of adverse effects (133). Chronic signs of toxicity in livestock include cirrhosis, lameness, hoof malformations, hair loss, and emaciation. In laboratory animals the signs commonly include liver cirrhosis. The minimum dietary intake of selenium recognized to produce adverse effects in farm animals is 4–5 μg/g dry wt of diet (133).

An episode of human poisoning by selenium involved a manufacturing error that resulted in a dietary supplement product that actually contained 182 times the amount of selenium declared on the label (134, 135). Adverse effects occurred within a few weeks and included effects on hair, nails, and liver. Human selenium poisoning in a high-selenium area of China also produced adverse effects on nails, skin, the nervous system, and teeth (136). These adverse effects occurred in some persons with intakes > 910 μg/d. No adverse effects have been associated with lower intakes, but the ratios of plasma selenium to erythrocyte selenium have been found to increase with dietary intakes > 750 μg/d (137, 138). Surveys in seleniferous areas of the United States have failed to find any signs of selenium intoxication in persons with intakes of up to slightly > 700 μg/d (139). In the Chinese population with an average lowest observed adverse effect level (LOAEL) of 910 μg Se intake, the lower 95% confidence limit for the LOAEL was 600 μg/d (140). Because the chemical forms of selenium in foods grown in seleniferous areas are not completely known, the human data on adverse effects from chronically high intakes apply only to total dietary selenium and not to any specific form. No adverse effects were observed in a 10-y clinical trial at daily supplemental intakes of 200 μg Se in selenized yeast (55–57).

Chromium

No credible data or reports have shown adverse effects of Cr⁶⁺ in humans, and animal data also suggest that orally administered Cr⁶⁺ is extremely innocuous (5, 141, 142). In addition, the MEDLINE database (National Library of Medicine, Bethesda, MD) lists no published cases of adverse reactions in humans. In contrast, chromate (Cr⁷⁺) is clearly established as a work-related etiologic agent in lung disease, including lung cancer, in chromate and stainless steel workers (143).

One report described clastogenesis (chromosome breakage in vitro) from high concentrations of chromium picolinate added directly to Chinese hamster ovarian cells in culture (144). Because Cr⁶⁺ can be biologically reduced to Cr⁵⁺, Cr⁴⁺, and Cr⁴⁺, but Cr⁴⁺ is not oxidized to the higher valence states, the authors suggest that Cr⁴⁺ could be the actual carcinogen. This suggestion seems to conflict with their data that indicated clastogenic effects of chromium picolinate and picolinic acid, but not chromium chloride, chromium nicotinate, or nicotinic acid (144). Also, other data from the same research group were interpreted to show that Cr⁵⁺ is the genotoxic and presumably carcinogenic species of chromium (145–148). Moreover, the criteria of the Environmental Protection Agency (EPA) for interpreting in vitro clastogenesis data in cancer risk assessment specify that evidence of clastogenicity is meaningful only if there is confirming mutagenicity data, and that these together are sufficient only to recommend an animal bioassay to evaluate possible carcinogenicity (149–151).

The EPA has reviewed all relevant data on chromium toxicity and calculated a reference dose, a safety limit involving a margin of safety below the levels with evidence of adverse effects, for Cr⁷⁺ and also for Cr⁴⁺. Application of a composite safety factor of 1000 to the animal data for Cr⁷⁺ gives a reference dose of 1.47 mg/kg (142), which with downward rounding converts to 70 mg/d in adult males. The reference dose for Cr⁴⁺ (70,000 μg) is 350 times the upper value of the ESADDI of 50–200 μg for adults (7). Thus, trivalent chromium has an extraordinarily wide margin of safety. In contrast, hexavalent chromium—a form not normally found in the diet—has significant toxic potential, and accordingly the reference dose for Cr⁶⁺, calculated by the EPA for a 70-kg man, is only 335 μg/d (142).

There is no evidence of toxicity in humans from orally ingested trivalent chromium, and 1000 μg Cr/d as chromium picolinate produced no adverse effects in a clinical trial (R Anderson, N Cheng, N Bryden, et al, unpublished observations, 1996). Extrapolation from animal data corroborates human data that trivalent chromium is extraordinarily safe but its benign character should not be confused with the established toxicity of hexavalent chromium.

CONCLUSIONS

The potential benefits of nutrients in reducing the risk of diseases that are not recognized as classic deficiency diseases have not been used thus far in setting the RDAs or ESADDIs. Recognizing the important role of some vitamins and minerals beyond that of preventing deficiency, the National Academy of Science, in contrast with past practices, is now considering use of evidence for decreased risk of chronic disease in setting the RDAs (1). Evidence is rapidly accumulating that intakes above the RDA for some micronutrients provide benefits in reducing the risk of chronic disease, and these effects are moving toward acceptance as an appropriate basis for future RDAs (1, 152). Also, it is well recognized that higher intakes of nutrients necessitate careful evaluation of the safety of those intakes (1, 5).
Efficacy

**Calcium**

The benefits of calcium in reducing the risk of osteoporosis are recognized by health claims authorized by the US Food and Drug Administration for intakes of 1000–2000 mg/d, but the current RDA for most women is only 800 mg (Table 1).

**Folic acid**

The intake of folic acid recognized by the Food and Drug Administration to reduce the risk of NTDs is 400 µg/d, but the RDA for adult males is 10 mg (15 IU) (Table 1).

**Vitamin E**

Intakes of 67–300 mg α-tocopherol equivalents (100–400 IU) of vitamin E have been shown to reduce oxidation of LDL cholesterol and lower the risk of heart disease, but the RDA for adult males is 10 mg (15 IU) (Table 1).

**Selenium**

A recent clinical trial found reduced cancer risk with a selenium intake of 200 µg/d, but the RDA for adult males is 70 µg/d (Table 1). Limiting this nutrient to the RDA precludes benefits from higher intakes, and such limitations are not necessary for safety.

**Safety**

Safety limits should be based on a standard other than the RDA, ESADDI, or other recommendations related to nutritional policy or beneficial effects. Use of a direct scientific approach to identify safe upper levels does not impose false safety limits related to the RDA or ESADDI.

**Vitamin A**

Most evidence of adverse effects is associated with intakes ≥ 7500 µg RE (25 000 IU). There is no evidence of adverse effects from consumption of < 6500 µg (21 600 IU). An intake of 3000 µg (10 000 IU) is known to be safe for adults, including pregnant women and the elderly. These amounts are well above the RDA of 3000 µg RE for adult men (Table 2).

**β-Carotene**

β-Carotene is widely considered to be virtually nontoxic because humans tolerate very high doses without apparent undesirable effects, other than skin discoloration, and animal studies also failed to find any toxic effects. There is no evidence that conversion of β-carotene to vitamin A contributes to vitamin A toxicity, even when β-carotene is ingested in large amounts. Two clinical trials involving β-carotene found increased lung cancer in smokers, but others found no adverse effects. An intake of 25 mg is safe for most adults except for heavy smokers.

**Nicotinic acid**

When taken on an empty stomach, crystalline nicotinic acid in doses as small as 10 mg may produce a mild but noticeable flushing reaction. Liver toxicity and serious gastrointestinal effects can occur in persons consuming ≥ 1000 mg nicotinic acid/d, but clinical trials have found no adverse reactions at intakes of 500 mg/d, an intake well above the RDA for adult males (Table 2).

**Pyridoxine**

Daily intakes of 2000–6000 mg pyridoxine can cause sensory neuropathy. The neuropathy slowly and perhaps incompletely regresses after cessation of the elevated intake. There is controversy over the validity of the single report of adverse effects at daily intakes of ~100 mg or less. A pyridoxine intake of 500 mg/d carries some risk of neurotoxicity. There are no reliable reports of adverse neurologic effects with intakes of 200 mg/d. Both the NOAEL (no observed adverse effect level) and the LOAEL are far greater than the RDA (Table 2).

**Ascorbic acid**

Intakes up to 1000 mg vitamin C, far above the RDA for adults, have been consumed daily without any known adverse

### TABLE 1

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>RDA</th>
<th>Beneficial amount</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg)</td>
<td>800</td>
<td>1000–2000</td>
<td>13, 14</td>
</tr>
<tr>
<td>Folic acid (µg)</td>
<td>180</td>
<td>400</td>
<td>15–18</td>
</tr>
<tr>
<td>Vitamin E (mg α-TE)</td>
<td>10</td>
<td>67–300</td>
<td>19–25</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>70</td>
<td>200</td>
<td>56–58</td>
</tr>
</tbody>
</table>

1 Recommended dietary allowance (7) selected for comparison with the beneficial effects listed in the next column: calcium, 800 mg for nonpregnant, nonlactating women; folic acid, 180 µg for nonpregnant, nonlactating women; vitamin E, 10 mg α-tocopherol equivalents (TE) for adult males; and selenium, 70 µg for adult males.

2 The range for adult women recognized in regulations for food labeling health claims as being beneficial in reducing the risk of osteoporosis.

3 The folic acid intake for adult women recognized in regulations for food labeling health claims as being beneficial in reducing the risk that a pregnancy will be affected by a neural tube defect. The RDA of 400 µg for pregnant women is not an appropriate comparison because the neural tube closes at ~28 d of pregnancy, a time before prenatal care usually begins (15).

### TABLE 2

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>RDA or ESADDI</th>
<th>NOAEL</th>
<th>LOAEL</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg RE)</td>
<td>1000</td>
<td>3000</td>
<td>6500</td>
<td>58–66</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>20</td>
<td>500</td>
<td>1000</td>
<td>80, 81</td>
</tr>
<tr>
<td>Pyridoxine (mg)</td>
<td>2</td>
<td>200</td>
<td>500</td>
<td>83–88</td>
</tr>
<tr>
<td>Ascorbic acid (mg)</td>
<td>60</td>
<td>1000</td>
<td>Unknown</td>
<td>82, 99–105</td>
</tr>
<tr>
<td>Folic acid (µg)</td>
<td>180</td>
<td>1000</td>
<td>5000</td>
<td>123, 124, 129–132</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>70</td>
<td>200</td>
<td>910</td>
<td>136–140</td>
</tr>
<tr>
<td>Cr3+ (µg)</td>
<td>50–200</td>
<td>1000</td>
<td>Unknown</td>
<td>142, 143</td>
</tr>
</tbody>
</table>

1 The highest recommended dietary allowance for any age or sex group, except for pregnant or lactating women, or the upper value of the estimated safe and adequate daily intake (7).

2 The no observed adverse effect level, based on the absence of a convincing pattern of effects shown in human data or observations; an intake that may be considered safe.

3 The lowest observed adverse effect level, based on convincing adverse effects as shown in human data or observations; an intake that is not safe for all consumers.

4 RE, retinol equivalent.

5 Includes unpublished observations by Anderson et al. 1996.
effects (Table 2). Most of the purported adverse effects attributed to vitamin C have no factual basis.

**Folic acid**

Folic acid is nontoxic but concern has been raised about high intakes masking pernicious anemia. This effect is established only at intakes ≥ 5000 µg. Intakes of 1000 µg (1 mg) total folic acid plus food folates are without identifiable risk of any known adverse effects. This intake is well above the RDA for women (Table 2).

**Selenium**

The margin of safety for selenium is relatively narrow. Adverse effects have occurred at intakes of 910 µg/d. Some risk of adverse effects may occur with total dietary intakes as low as 600 µg/d. Daily supplemental intakes of 200 µg have been shown to be safe (Table 2).

**Chromium**

No credible data or reports have shown adverse effects of dietary trivalent chromium in humans, and animal data also suggest that orally administered trivalent chromium is extremely nontoxic. Reports of DNA damage by chromium do not apply to oral intakes of the forms found in foods and dietary supplements. The benign character of oral trivalent chromium should not be confused with the established toxicity of inhaled hexavalent chromium, which is associated with workplace-related lung cancer. Hexavalent chromium is not normally found in foods and is not used in dietary supplements. There is sufficient experience with intakes of trivalent chromium, as chromium picolinate, up to 1000 µg Cr/d, along with the wide margin of safety in animal studies, to establish the safety of trivalent chromium at this intake (Table 2).

REFERENCES


79. Bean WB. Some aspects of pharmacologic use and abuse of water-


Erratum


The legends to Figures 1, 2, and 3 on pages 1029, 1030, and 1031 should read as follows in part: 40% (■) and 60% (○).