ABSTRACT The establishment of safe upper intake levels for micronutrients must consider the intake-response relations for both deficiency and toxicity. Limited data are available on the toxicities of most micronutrients, and few studies that meet the criteria considered essential for the risk assessment of other chemicals in food, such as pesticides and food additives, have been performed. In some cases, the application of large uncertainty factors, which are used to establish the amount of a chemical that would be safe for daily intake throughout life, could result in nutritionally inadequate intakes of micronutrients. As a consequence, lower than normal uncertainty factors have been applied to determine safe or tolerable intakes of many micronutrients. There is no clear scientific rationale, on the basis of the metabolism and elimination of micronutrients or the nature of the adverse effects reported for high intakes, for the use of reduced uncertainty factors for micronutrient toxicity. A review of recent evaluations of selected vitamins and minerals shows little consistency in the application of uncertainty factors by different advisory groups, such as the Institute of Medicine in the United States and the Scientific Committee on Foods in the European Union. It is apparent that, in some cases, the uncertainty factor applied was selected largely to give a result that is compatible with nutritional requirements; therefore, the uncertainty factor represented part of risk management rather than hazard characterization. The usual risk assessment procedures for chemicals in food should be revised for micronutrients, so that the risks associated with intakes that are too low and too high are considered equally as part of a risk-benefit analysis. J. Nutr. 136: 493S–501S, 2006.

KEY WORDS: • upper intake levels • micronutrient toxicity • risk management

Establishing upper safe or tolerable levels for vitamins and essential trace elements is the subject of considerable interest and activity at present. Because micronutrients are essential for a normal and healthy life, public perception seems to be that there is no risk associated with their intake at any dose, and proposals to restrict availability (1) can produce a highly critical public reaction. However, even the briefest of reviews of the available literature shows that, at very high doses, vitamins and minerals can be as toxic as other compounds present in the food and the environment. This is not unexpected, and to paraphrase Paracelsus (1493–1541), “In all things there is a poison and there is nothing without a poison. It depends only upon the dose whether a poison is a poison or not.”

A number of evaluations of the safety of high doses of vitamins and minerals have recently been conducted by both national and international bodies, with comprehensive reviews being undertaken in the United States (2–5), the European Union (6), and the United Kingdom (7). In addition, the safety of vitamins and minerals has been considered by the Nordic Council (8), the International Program on Chemical Safety (IPCS) (9) and French Ministries (10), as well as by associations of the manufacturers and producers of vitamins and mineral supplements, such as the Council for Responsible Nutrition (11) and the European Federation of Health Product Manufacturers Association (12), and consumer groups, for example, Consumers for Health Choice (13).

Assessment of the safety of non-nutrient chemicals present in foods is undertaken by identifying the adverse effect(s) produced at high intakes, defining the dose-response relationship for the effect(s), and then selecting an appropriate safety margin (such as a safety factor of 100) to establish levels of intake that can be consumed daily throughout life by humans without significant adverse health effects (14). In contrast, in the case of micronutrients, 2 dose-response relations need to be considered (Fig. 1). Adverse effects would be present at very low intakes because of a deficiency condition, which would decrease in severity with an increase in intake, and at high intakes because of toxicity, which would increase in severity with an increase in the dose. The relative positions of these 2 curves may vary widely between different vitamins and minerals. In most cases, the adverse effects associated with deficiency and toxicity are unrelated, and different adverse effects with different health implications are produced at very low and very high intakes.

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4 Abbreviations used: IOM, Institute of Medicine; IPCS, International Program on Chemical Safety; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; SCF, Scientific Committee on Foods.

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A major potential problem for establishing a safe upper level for vitamins and minerals is that, in many cases, the large uncertainty or safety factors that would normally be applied to toxic effects in experimental animals or humans, cannot be used because this could result in an intake below the dietary reference intake, or the intake necessary to avoid a deficiency syndrome. Therefore, safe upper intake levels that avoid both toxicity and deficiency must be established, and this may involve the application of a lower than normal margin of safety between exposure and the intakes that produce toxicity in humans or animals. Nevertheless, in principle there is no reason why the safety margin available to the public in relation to the intake of food supplements should be any different from that which would apply to other ingested compounds, providing that the maximum recommended intake was nutritionally adequate.

This paper considers the nature of the uncertainties associated with the use of the available data to establish safe levels of human exposure and whether there is a scientific rationale for reducing the magnitude of the uncertainty factors in the case of micronutrients. The problems faced in deriving safe upper intake levels are illustrated with examples from recent evaluations by the Institute of Medicine (IOM), the Scientific Committee on Foods (SCF), and the Expert Group on Vitamins and Minerals (EVM).

Data available for assessment of hazards and risks from high intakes of micronutrients

For many vitamins and minerals homeostatic mechanisms ensure that the amounts present in the body are largely independent of intake at low levels. Such mechanisms may be overwhelmed at very high intakes, and this may indicate a nonlinear relation between intake and body burden. The intakes associated with saturation of homeostatic mechanisms have only rarely been defined, and therefore it is not possible to use this as a basis for establishing safe upper intake levels. Because the adverse effects associated with excessive intakes of micronutrients do not relate to the beneficial effects, there is no a priori reason to consider that these hazards are inherently different from the hazards caused by high intakes of a nonessential chemical. Indeed, micronutrients should be considered foreign compounds when the intake exceeds the homeostatic range.

For convenience, the data available on the toxicities of micronutrients may be divided into data from studies with humans and data from studies with animals.

Data from studies with humans. The available data on the effects of high exposure of humans to micronutrients arise from a variety of sources: clinical studies on nutritional need, clinical studies on interactions between nutrients, clinical studies for medical uses, epidemiological analyses, and anecdotal case reports. In most cases, the studies were not designed to establish safety at high doses but, rather, to establish benefit in relation to the prevention of deficiency by the use of low doses or to study a potential therapeutic benefit at very high doses. Each of these types of data has deficiencies and problems in relation to defining an upper safe level for micronutrients. Data on adverse effects are often reported from clinical trials for therapeutic indications, but such trials usually define the incidence of adverse effects at the therapeutic dose, which may be a gross exaggeration of nutritional intakes. The effects at lower doses, which would not produce the therapeutic effect, are not usually reported (the examples of niacin and pyridoxine are discussed below), but such information would be essential in establishing a safe upper intake level. In addition, such trials are often performed with highly selected patient groups, which results in problems of extrapolation of the findings from the trial to the general population. Epidemiological studies often suffer from confounding variables (for example, selenium and fluoride), and causation defined using recognized criteria (15) is rarely established. Anecdotal case reports are useful for hazard identification but frequently involve “abuse” dosages and cannot be used to define the incidence of the adverse effect.

Hazards identified from animal studies are rarely investigated systematically during human trials, so that the human data do not normally provide useful information related to the adverse effects identified in animal studies.

Data from studies with animals. In many cases, the hazard identification is based on animal experimentation, and in some cases the recognized hazards have then been investigated in studies with human volunteers. In the case of essential minerals, usually very few data are available from studies with humans, and therefore the hazard dose-response relation is derived largely from animal experimentation.

A defined set of studies is necessary to establish safe daily intakes of chemicals such as pesticides and food additives (Table 1); the studies involve different durations of intakes, and all major organ systems are assessed without any preconception of the hazard(s) that may be detected. The principal aim of such studies is to identify all possible hazards, recognize the nature of the uncertainties associated with the use of the available data to establish safe levels of human exposure, and whether there is a scientific rationale for reducing the magnitude of the uncertainty factors in the case of micronutrients. The problems faced in deriving safe upper intake levels are illustrated with examples from recent evaluations by the Institute of Medicine (IOM), the Scientific Committee on Foods (SCF), and the Expert Group on Vitamins and Minerals (EVM).

### TABLE 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Nature of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Various genetic endpoints in bacteria and mammalian cells; screen for potential carcinogens</td>
</tr>
<tr>
<td>Acute</td>
<td>Usually single dose study</td>
</tr>
<tr>
<td>Short-term</td>
<td>Repeated daily doses for 14–28 d; identifies the target organ</td>
</tr>
<tr>
<td>Sub-chronic</td>
<td>Repeated daily doses for 90 d; gives dose-response, and used for dose selection in chronic studies</td>
</tr>
<tr>
<td>Chronic</td>
<td>Repeated daily doses for 2 y in rodents; used to investigate carcinogenicity; usual source of NOAEL for ADI</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Dosing occurs before, during, and after reproduction to investigate effects on fetal and neonatal development</td>
</tr>
</tbody>
</table>

1 Data from Renwick, 1999 (14).
2 ADI, acceptable daily intake.
the hazard of greatest concern (usually that which occurs at the lowest doses), and to define an intake that does not produce a detectable response, the so-called no observed adverse effect level (NOAEL). Studies used for risk assessment of pesticides and additives must be performed using recognized protocols and must meet the established quality criteria of good laboratory practice. In contrast, animal studies on vitamins and minerals are usually hypothesis driven and are limited in the ranges of tissues and effects studied. Frequently, adverse effects are reported at high intakes, but the dose-response relation is not studied and the NOAEL is often not defined. Such limited data would not be considered adequate to approve the use of a pesticide or a food additive, whereas in the case of a food contaminant, an additional uncertainty factor(s) would be applied to determine a safe intake.

The absence of an adequate safety database for most vitamins and minerals means that the scientific basis of hazard characterization is less secure than is usually the case, but the use of large uncertainty factors, as would traditionally be applied for nonessential compounds, could result in adverse effects due to a deficiency condition.

Rationale for the use of uncertainty factors in hazard characterization

Uncertainty factors allow for aspects of hazard characterization for which there are no compound-specific data. By definition, uncertainty factors are not precise, and the values selected are usually 1 log unit (10) or 0.5 log units (3). Uncertainty factors can be divided into those related to issues of database deficiencies and of extrapolation. For contaminants, database deficiencies, such as the absence of a NOAEL [in which case the lowest observed adverse effect level (LOAEL) has to be used as the starting point], or the absence of a chronic toxicity study, are often allowed for by the use of an extra 3- or 10-fold factor (16–18). Traditionally 10-fold factors have been used to allow for extrapolation issues, such as animal-to-human extrapolation, and to allow for human variability. There has been a long history of use of such factors (9,19), and their validity has been the subject of numerous reviews (20–29).

Renwick (24) suggested that the 10-fold uncertainty factors for interspecies differences and human variability should be subdivided to allow for toxicokinetic differences (4-fold) and toxicodynamic differences (2.5-fold). The aim of this subdivision was to allow chemical-specific toxicokinetic or mechanistic data to contribute quantitatively to the selection of the uncertainty factor (by the use of a combination of chemical-specific data and default factors). The principle of subdivision was accepted by an IPCS workshop on the derivation of guidance values and modified to allocate even 3.16 (10^0.5) factors for toxicokinetic and toxicodynamic differences in humans (17). IPCS has published guidance on the use of chemical-specific adjustment factors (30) to replace the toxicokinetic or toxicodynamic factors for interspecies differences or human variability (Fig. 2). There have been very few examples to date for which there are sufficient data of adequate quality to replace default uncertainty factors, but in principle, this subdivision could be used to refine the uncertainty factor used for vitamins and minerals. Although there are extensive human databases on vitamins and minerals, very few studies have defined species differences or human variability in the concentrations in plasma at high and potentially toxic intakes.

Differences between nonessential foreign compounds and vitamins and minerals

There are major differences between animal species and humans and between different human individuals in the fate of foreign compounds in the body. Coefficients of variation for human variability in the main pathways of elimination are typically about 35% (31–35). These differences provide a rationale and justification for the use of large (10-fold) uncertainty factors in the establishment of safe intakes of such compounds in human food. The high variability between species and between different individuals arises from protein-mediated processes, such as enzyme-catalyzed reactions, rather than physicochemical processes, such as passive diffusion, or physiological processes, such as glomerular filtration (35).

In contrast to foreign compounds, the concentrations of micronutrients in the body are controlled closely at low intakes and the body burden may be largely independent of intake. This supports the assumption of a low coefficient of variation [10% (2) or 15% (36)] that is used to define the 95th percentile daily requirement. High-dose toxicity with micronutrients probably occurs at intakes that saturate homeostatic control, and therefore, the fate at high doses and the variabilities in response would resemble those of a foreign compound. As a consequence, both species differences and similar person-to-person variations will exist at high intakes. Protein-mediated processes are of greater potential importance for micronutrients than for foreign compounds (Table 2), and therefore, there is no a priori rationale to assume that the variability associated with micronutrient toxicity is lower than that associated with foreign compound toxicity. As a consequence, in the absence of adequate compound-specific information, there is no scientific justification to use an uncertainty factor other than the usual default in the determination of an intake of a nutritional supplement that can be consumed safely by all members of society, every day throughout life.

Examples of apparent discrepancies in the setting of safe upper intake levels by different groups

The examples below illustrate how recent evaluations in the United States, the European Union, and the United Kingdom have reached similar or different conclusions about tolerable...
upper intake levels (the United States and the European Union) or safe upper levels (United Kingdom) for selected vitamins and minerals. A problem that all 3 groups faced was that for some micronutrients there were concerns about safety but inadequate data for derivation of a numerical tolerable or safe upper intake level, whereas for others there was limited information but the available information did not raise safety concerns. In the United Kingdom a guidance level was set for some micronutrients as an indication to risk managers of an intake that was likely to be without adverse effects but for which the database was not adequate to set a clear safe upper level.

**Vitamin A.** Vitamin A may be consumed either as preformed vitamin A (retinyl esters and retinol) or as provitamin A, such as the carotenoids (e.g., β-carotene). Each may be obtained from dietary sources and by taking vitamin supplements. In addition, β-carotene may be consumed from its use as a food additive. The toxicities of preformed vitamin A and β-carotene differ markedly, because preformed vitamin A has potential teratogenic activity, whereas this has not been reported for β-carotene. As a consequence, each was evaluated separately. Preformed vitamin A and other retinoids are well-recognized animal teratogens at high doses. 13-cis-Retinoic acid, a metabolite of retinol, has been used as an oral treatment for acne and has been nontoxic and is not associated with teratogenicity. Because of its antioxidant properties it has been used as a chemoprevention agent to reduce the risk of development of cancer in high-risk groups, such as cigarette smokers. The hypothesis for this was that oxidative stress contributes to cancer development and that prevention of oxidative damage may delay or prevent the development of lung cancer.

Four major β-carotene intervention trials have been conducted, and 3 of these were performed using subjects with adequate β-carotene intakes. The studies differed slightly in their designs and differed significantly in their outcomes [a review has been presented by Woutersen et al. (49)]. The ATBC trial (α-tocopherol β-carotene prevention study) investigated a total of 29,133 male smokers who were given α-tocopherol (50 mg), β-carotene (20 mg), α-tocopherol plus β-carotene, or placebo. At the end of the study (after an average of 6 years) there was a significant increase in the incidence of lung cancer in subjects given supplemental β-carotene. A similar outcome was found in the CARET study (β-carotene and retinol efficacy trial), which included 18,314 male and female smokers and asbestos-exposed workers who were given retinol (25,000 international units) plus β-carotene (30 mg) or placebo. The PHS study (United States Physicians’ Health Study) administered aspirin (325 mg), β-carotene (50 mg), aspirin plus β-carotene, or a placebo to 22,071 healthy American male physicians, of whom 11% were smokers. There was no measurable.

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**TABLE 2**

*Differences between foreign compounds (xenobiotics) and micronutrients*¹

<table>
<thead>
<tr>
<th>Process</th>
<th>Foreign compound</th>
<th>Micronutrient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>PD of lipid soluble form</td>
<td>Carrier-facilitated uptake at low conc; PD at high conc.</td>
</tr>
<tr>
<td>Blood transport</td>
<td>Free or bound to albumin</td>
<td>Free or bound to specific carrier proteins</td>
</tr>
<tr>
<td>Entry into tissues</td>
<td>PD of lipid soluble form</td>
<td>Carrier-facilitated transport at low conc; PD at high conc.</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Enzymes with low specificity and high capacity</td>
<td>Often specific enzymes with low capacity</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>Glomerular filtration + passive reabsorption + tubular secretion</td>
<td>Specific reuptake transporters + glomerular filtration + passive reabsorption + tubular secretion</td>
</tr>
</tbody>
</table>

¹ Note that processes mediated by interactions with proteins, such as enzymes and transporters are italic. PD, passive diffusion; conc, concentration.
effect on cancer incidence: neither an increased risk, as found in the other 2 studies, nor the decreased risk predicted at the onset of the study.

Given the enormous sample sizes of these studies and the adverse outcomes in 2 of the 3 intervention trials, it is unlikely that there will be future studies on the dose-response relation for β-carotene and its adverse effects on the development of lung cancer in cigarette smokers. As a consequence, a risk assessment must be made on the basis of the present data. Recent studies with a ferret model (50) have indicated that β-carotene has short-term effects on the ferret lung, and this may provide information on the dose-response relationship, which can then be extrapolated to humans.

In the United States, the IOM concluded that the safety of supplements containing β-carotene could not be ensured. The European SCF (51) concluded that a tolerable upper intake level could not be set because of the absence of suitable dose-response data. In the United Kingdom, the EVM (7) established from the findings of the large supplementation trials a safe upper level based on a LOAEL of 20 mg/d and an uncertainty factor of 3 because a NOAEL was not identified.

Pyridoxine. Pyridoxine (vitamin B-6) is an essential cofactor, in the form of pyridoxal phosphate, for a number of enzymes involved in transamination, deamination, decarboxylation, and desulfuration reactions. Pyridoxine deficiency leads to retarded growth, acrodynia, alopecia, and skeletal changes, as well as neurological effects such as seizures and convulsions. The daily requirement for pyridoxine is related to protein intake and is equivalent to ~2 to 3 mg/d (36).

The principal hazard associated with pyridoxine is neurotoxicity and neuronal degeneration, which were initially identified from the results of studies with experimental animals. Doses associated with toxicity in animals are >25 mg/kg of body weight/d, indicating a wide safety margin (about 500) between normal dietary intakes and potentially toxic doses.

However, pyridoxine illustrates the problems that can arise when vitamins are used at very high doses for the treatment of clinical conditions. Pyridoxine has been used to treat a number of conditions at doses up to and exceeding 1 g/d, and these clinical uses have given rise to anecdotal reports of neurotoxicity in humans. The first report (52) described 7 patients who had been taking 2–6 g/d of pyridoxine daily for between 2 and 40 mo. Subsequent anecdotal reports described cases with daily intakes of 200 mg or more (53,54). These data cannot be used to define the dose-response relationship, because the number of subjects taking such doses is unknown and the incidence cannot be calculated. Berger et al. (55) gave either 1 or 3 g/d of pyridoxine to 5 volunteers until signs of clinical or laboratory abnormalities were detected. That study showed sensory symptoms and quantitative sensory threshold abnormalities in all subjects. Under these controlled high-dose conditions, sensory and neurological effects were not detected until after many months of treatment. There was an inverse relationship between the dosage and the duration of intake before the onset of symptoms. This inverse relationship was also apparent in the original report by Schaumburg et al. (52).

A number of publications have reported no adverse neurological effects in patients receiving <500 mg/d of pyridoxine (56–63). Many of these studies were of short duration (<6 mo), which would be insufficient time to produce toxicity even at higher doses, and therefore do not provide evidence of the safety of low intakes. Brush (58) reported a low incidence of possible pyridoxine-related side effects (3 subjects with tingling or numbness, or both) in a cohort of 336 subjects who had taken 200 mg/d, but the duration of treatment and other details were not given. Only 1 subject in this cohort reported side effects at an intake of 100–120 mg/d. The main evidence raising doubts about the safety of doses <200 mg/d comes from a study in which a group of 172 women, who were receiving pyridoxine for premenstrual syndrome, were subdivided into those who reported altered sensations in their limbs or skin or had muscle weakness or pain (n = 103) and those who did not (64). Comparison of the 2 subgroups showed that those who reported symptoms had been taking pyridoxine for a significantly greater duration (2.9 y) than those without symptoms (1.6 y). There was no significant difference in the average intakes of vitamin B-6 between the 2 groups (117 and 116 mg/d, respectively), although a higher proportion of patients with symptoms (70%, compared with 55% of patients without symptoms) had serum vitamin B-6 levels >34 μg/L. This study has been heavily criticized because of the absence of an appropriate control group and the subjective nature of the symptoms described. However, it is difficult to ignore these data given the long duration of intake by those patients who reported symptoms and the reversal of symptoms on the cessation of intake. Some of the patients in the study had intakes <100 mg/d, and therefore, if the data are taken at face value, an intake of 100 mg/d was not equivalent to a no-effect level (in this study).

The case of pyridoxine illustrates well a problem with the available data on adverse effects in both animals and humans and their interpretation in relation to the safety of high doses of vitamins. It is clear from any analysis that the normal dietary intakes would be without adverse health effects; however, it is less clear that intakes of 100–200 mg/d would similarly be without adverse effects. Given the available data, an upper level could be selected somewhere within the range of 10–100 mg/d (the range spanned by the recent recommendations from the IOM and the United States). A detailed review of all the data indicates that the influence of duration of intake was not given similar weightings in the different evaluations.

In the United States, the IOM set a tolerable upper intake level of 100 mg/d on the basis of a NOAEL of 200 mg/d from a number of short-term studies showing no adverse effects and a 2-fold uncertainty factor because of deficiencies in the studies. The IOM highlighted a number of methodological weaknesses in the study of Dalton and Dalton (64) and concluded that the findings were inconsistent with the weight of evidence pertaining to the safety of higher doses of pyridoxine. The report identified a NOAEL of 200 mg/d largely on the basis of the findings of 2 studies (57,65), supported by additional studies that reported no cases of neuropathy among hundreds of individuals given pyridoxine doses of 40–500 mg/d (60,66–68). Careful scrutiny of these reports shows that the study durations were too short to have been able to detect the slowly developing neuropathy produced by pyridoxine. Bernstein and Lobitz (57) reported data for 16 patients who received doses of 150 mg/d with a duration of intake of up to 6 mo (only 5 subjects were studied after 5 mo), whereas Del Tredici et al. (65) studied 24 patients for 4 mo. The large number of subjects evaluated in the other studies used to support the NOAEL of 200 mg/d was largely due to the work of Brush and colleagues (60) (which was not unequivocally without possible adverse effects; see above), whereas Ellis et al. (66) reported on the findings for 22 subjects [Ellis (69) discusses data for 35 subjects], Mitwalli et al. (67) gave detailed data for only 7 subjects (but these subjects had been treated for 2.8 y), and Tolis et al. (68) provided information on 9 patients.

The European SCF (70) set a tolerable upper intake level of 25 mg/d on the basis of the average intake in the study of Dalton and Dalton (64) with an uncertainty factor of 4 to allow...
for the fact that the intake was a possible effect level (2-fold) and for deficiencies in the database (2-fold). In the United Kingdom, the EVM (7) considered that none of the human data were adequate for the establishment of a numerical upper level and derived a safe upper level of 10 mg/d by using the LOAEL from a study with dogs (50 mg/kg of body weight/d) with a 300-fold uncertainty factor to allow for LOAEL-to-NOAEL extrapolation (3-fold) and for the use of data from animal studies to predict a safe intake for humans (100-fold).

Niacin. Niacin is a term used to describe nicotinic acid and nicotinamide, both of which have biological activities. Niacin is a precursor of the essential cofactors NAD and NADP, which are involved in a vast array of redox reactions. Niacin is not a true vitamin, since it can be produced in vivo by humans from the catabolism of the essential amino acid tryptophan, and there is no absolute requirement for preformed niacin in the diet. There are interesting parallels between niacin and pyridoxine because experiments with animals revealed a hazard, in this case, hepatotoxicity (71), and the use of very high doses of niacin for therapeutic purposes gave rise to anecdotal reports of severe hepatic toxicity in treated patients. As with pyridoxine, the doses associated with this toxicity were generally many times the nutritional intake; most clinical trials used up to 3 g/d (72).

A second minor adverse effect reported at doses of 50 mg or more was the production of flushing and hypotension (3). This phenomenon was seen only with nicotinic acid and not with nicotinamide, and was found to a greater extent when nicotinic acid was taken on an empty stomach. As a consequence, the interpretation of the safety of high doses of niacin is complicated by the difference in chemical forms taken and the influence of food on the generation of the adverse effect.

In the United States, the IOM set a tolerable upper intake level of 35 mg/d for both nicotinic acid and nicotinamide, on the basis of a LOAEL of 50 mg for nicotinic acid–induced flushing and an uncertainty factor of 1.5 to allow for LOAEL-to-NOAEL extrapolation. The European SCF (73) set different tolerable upper intake levels for nicotinic acid (10 mg/d on the basis of a LOAEL for flushing at 30 mg and an uncertainty factor of 3) and nicotinamide (900 mg/d on the basis of a NOAEL of 25 mg/kg of body weight/d from a number of studies with children that gave assurance about possible hepatic effects and an uncertainty factor of 2 because adults might eliminate nicotinamide more slowly than children). In the United Kingdom, the EVM established a guidance level for nicotinic acid of 17 mg/d on the basis of a LOAEL for flushing at 30 mg and a 3-fold factor to allow for the use of a LOAEL and a guidance level for nicotinamide of 500 mg/d using the same NOAEL as the SCF, but with a 3-fold uncertainty factor.

Selenium. Selenium is a commonly occurring micronutrient that is present in enzymes such as glutathione peroxidase. Intakes <10 μg/d have been associated with selenium deficiency, known as Keshan disease, an endemic juvenile cardiomyopathy occurring in the Keshan region of China. The amounts of selenium present in different geographical areas vary widely, and some areas have high selenium intakes (74), whereas other areas, for example, in China, have much lower intakes.

The adverse effects reported among subjects living in selenium-rich areas include brittle hair, new hair with no pigments, and thickened and brittle nails with spots and streaks, a condition known as selenosis (75). The data available to define a dose-response relationship for selenium-related adverse effects arise from epidemiological studies and from clinical investigations in which selenium supplementation has been given intentionally. Epidemiological studies (76,77) indicated adverse effects with selenium intakes from foods of ~900 μg/d, whereas Longnecker et al. (74) reported no adverse effects for intakes up to about 700 μg/d. A clinical study on the effect of selenium in patients with cancer (78) reported no signs of selenosis at an intake of 200 μg/d (in addition to the normal dietary intake).

In the United States, IOM (4) set a tolerable upper intake level of 400 μg/d using a NOAEL of 800 μg/d on the basis of the findings from the studies of Yang et al. (76,77) and Longnecker et al. (74) with an uncertainty factor of 2 to allow for possible human variability in sensitivity compared with that of the study populations. The European SCF (79) set a tolerable upper intake level of 300 μg/d on the basis of a NOAEL of 900 μg/d from the study of Yang et al. (77) and an uncertainty factor of 3 for general uncertainty about the study data. In the United Kingdom, the EVM (7) set a safe upper level of 450 μg/d on the basis of a NOAEL of 900 μg/d in the studies of Yang et al. (76,77) and an uncertainty factor of 2 to allow for the use of a LOAEL for humans that was close to the NOAEL.

Future directions for combined consideration of risks and benefits of micronutrients

It is clear from the descriptions given above that there has been flexibility in the choice of the uncertainty factor used to establish a safe or tolerable upper intake level, and it is equally clear that there has been little consistency in the approaches adopted. To some extent this reflects the generally inadequate nature of the available data, which were not derived for the purposes of risk assessment, but it also reflects the need to ensure that the resulting safe level is nutritionally adequate.

Human variability in different biological parameters is best represented as log-normal distributions rather than normal distributions. The data from a single observation of the incidence of response in a group of subjects related to either a requirement (benefit) or an excess (toxicity) can be modeled, provided that an assumption regarding the coefficient of variation that represents human variability in sensitivity is made (Fig. 3). The optimum intake is that which minimizes the percentage of the population that is at risk of deficiency or toxicity, and this risk can be expressed in terms of a threshold intake or in terms of a threshold toxicity. The threshold intake is the optimum intake, provided that the nature of the deficiency and the toxicity are of equivalent adversities (see text). ED50, the dose that gives a 50% incidence; CV, coefficient of variation.

![Figure 3](image-url)
incidences of both deficiency and toxicity (provided that the effects are of similar severities).

The European Branch of the International Life Sciences Institute (ILSI Europe) Expert Group on Risk-Benefit Analysis for Nutrients Added to Foods has developed an approach that integrates both of the intake-response relationships shown in Figure 3 into a risk-benefit analysis (80). There is an established method for the derivation of the dietary reference intake, which is based on the average requirement plus 2 standard deviations. For the prevention of a deficiency, a coefficient of variation of 10% has a history of use by IOM in the United States for the establishment of dietary reference intakes, whereas a value of 15% has been used by SCF in Europe; this difference will affect the position of the optimum (Fig. 3). A similar approach was proposed by the ILSI Europe Expert Group in relation to the dose-response for toxicity at high intakes, with the incidence of adverse effects determined a log-normal distribution with a coefficient of variation of 45% to reflect human variability [see (80) for details]. Data on variability relevant to the specific micronutrient would be used when available, but in the absence of such data, a value of about 45% would be a suitable default, because it represents the average for a number of pathways of foreign compound elimination (81), which are probably relevant to the elimination of micronutrients at intakes that exceed the homeostatic range (see above).

Derivation of an optimum range from the graphical representation given in Figure 3 would require determination of a suitable cutoff on the log-normal distribution. A complete absence of both deficiency and toxicity on the basis of this model is impossible, as they will result from intakes of infinity and zero, respectively. As outlined above, a value of 2 standard deviations (95th percentile) has been used for benefit (the prevention of a deficiency), but selection of a suitable cutoff for toxicity would need to take into account the nature and the level of adversity of the effect. A 5% incidence of subjects with a sensitive biochemical parameter outside the normal range might be acceptable, but a 5% incidence of a potentially irreversible effect such as teratogenicity or neuropathy would not be acceptable. The publication of the ILSI Europe Expert Group (80), proposes that the advice provided to risk managers should indicate the incidences of both deficiency and toxicity predicted for different intakes, combined with a description of the severity of the health effects on which the incidence data are based. In this way, the acceptability of a particular incidence can be a risk-management decision that takes into account societal and other considerations, which are not strictly parts of risk characterization. An additional benefit of a structured risk-benefit analysis is that risk assessors will not be asked to set a safe or tolerable upper intake level, which requires risk management considerations in order to balance a precautionary approach to toxicity with a pragmatic approach to maintaining benefit.

Conclusions

Unlike food additives and pesticides, which require prior approval before they can be used, there is no requirement for the formal toxicity testing of high doses of micronutrients. Application of the procedures used for other chemicals in food to vitamins and minerals could in some cases result in an increase in the incidence of adverse effects if the inappropriate application of large uncertainty factors were to result in an acceptable intake that caused deficiency.

The major problem for groups undertaking risk assessments of micronutrients with the aim of establishing safe or tolerable upper intake levels is that there is a requirement to provide risk managers with advice on both the risks of excessive exposure and the risks associated with deficiency. As a consequence, the normal risk assessment paradigm for food additives and contaminants should be replaced by some form of risk-benefit analysis to prevent adverse effects from arising from inappropriate advice. Recent reviews have used very low uncertainty factors in some cases; but there is no scientific rationale for low uncertainty factors and the logic for their derivation is not clear. In some cases the uncertainty factors used simply seem to be a means of getting from the doses that characterize the adverse effect to a reasonable and practical intake that will not lead to excessive toxicity or deficiency. In such cases the application of an uncertainty factor, which is a part of hazard characterization (82), is being used as a part of risk management. Micronutrients with a narrow range between essentiality and toxicity would be handled more clearly by a descriptive narrative to the risk manager rather than as a pseudonumerical estimate. In some cases lower than normal uncertainty factors have been applied to an adverse effect, despite a very wide separation of the two intake-response curves in Figure 1. It is unclear what nutritional benefit there is to consumers by such an approach, and, indeed, it gives the risk of apparently approving therapeutic uses of vitamins and minerals without the normal requirements of establishing safety, quality, and efficacy.

The risk assessment of micronutrients requires the establishment of a new approach that considers the risks of both deficiency and toxicity. The output of risk assessment should provide the risk manager with sufficient information and advice on the predicted incidences and natures of the adverse health effects that would result from low intakes and from high intakes (80). The determination of an acceptable range of intake could then be based on the available scientific data and their interpretation (risk characterization), combined with consideration of what would be an acceptable incidence of adverse health effects (risk management).

LITERATURE CITED


