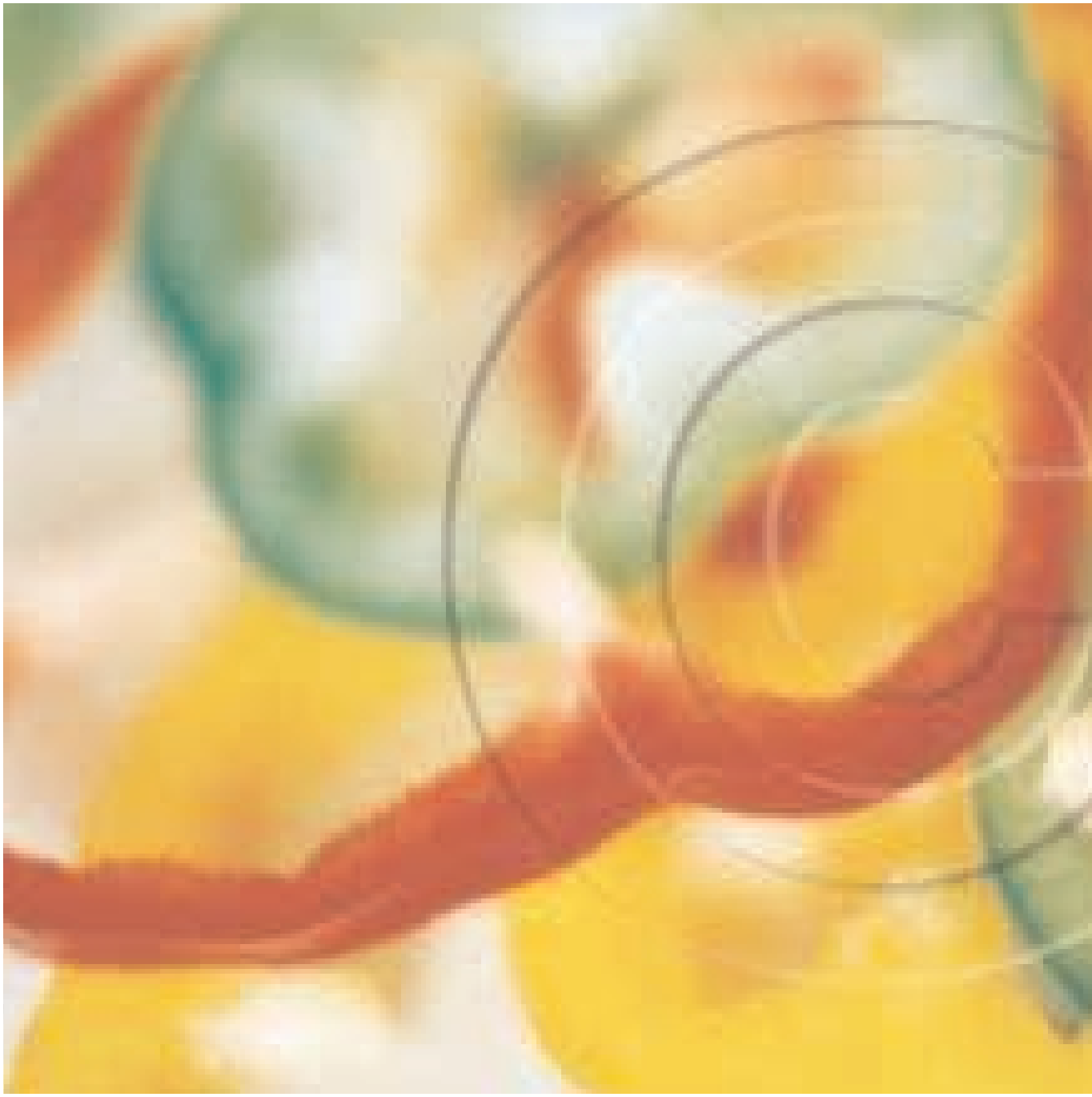
Safety of Vitamin and Mineral Supplements

Safe Levels Identified by Risk Assessment



John N Hathcock, Ph.D.

The International Alliance of Dietary/Food Supplement Associations (IADSA) brings together over forty associations of dietary/food supplement manufacturers and distributors from across the world. IADSA's central goal is to ensure a greater exchange of information about the science and regulation of dietary supplements and ingredients among scientists, regulators, industry and consumers.

"Safety of Vitamins and Minerals: Limits Derived by Risk Assessment" has been researched and drafted by Dr. John N. Hathcock, the Vice President for Scientific and International Affairs at the Council for Responsible Nutrition, Washington, DC, with the input from Dr. Hirobumi Ohama, Prof. David Richardson, and Dr. Derek Shrimpton.

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Objective

The objective of this document is to use scientific risk assessment procedures to identify the highest levels of supplemental vitamin and mineral intakes that could be confidently considered safe for long-term daily consumption by most people. The values identified do not represent recommended intakes.

Introduction

Vitamins and minerals are essential for life and/or health and supplements of these nutrients are helpful components of the total diet, with the supplemental intakes providing several established benefits for many persons, especially those in specific age and gender groups. Because of the tendency toward increased consumption by persons seeking to achieve the health benefits, as part of a greater emphasis on health self-care, several government institutions have developed recommendations on tolerable upper intake levels for nutrients, either as total dietary intake or as supplemental amounts.

The Food and Nutrition Board (FNB) of the Institute of Medicine, (a component of the U.S. National Academies), the European Commission's Scientific Committee on Food (SCF), and the United Kingdom's Expert Group on Vitamins and Minerals (EVM) have reviewed and published comprehensive risk assessments for vitamins and minerals. Regulatory strategies to specify maximums or other guidelines for vitamins and minerals in supplements are under consideration in several countries, the European Commission (EC) and the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU). The Codex guideline would have special application to international trade in these products, because of its recognition by the World Trade Organization (WTO).

As a voluntary self-regulatory action, the supplement industry has taken leadership for many years in assessing the safety of vitamins and mineral used in supplements, and providing this information to all interested parties. These efforts included the development and publication of (1) "Essential Nutrients in Supplements," by Dr. Derek Shrimpton, for the European Federation of Associations of Health Product Manufacturers (EHPM), (2) "Vitamin and Mineral Safety," by Dr. John Hathcock, for the Council for Responsible Nutrition (CRN USA), (6)"Vitamins and Minerals—A Scientific Evaluation of the Safe Range of Intakes," by Dr. Derek Shrimpton, the European Federation of Associations of Health Product Manufacturers (EHPM), (4) "Risk Assessment of Vitamins and Minerals," by the European Responsible Nutrition Alliance (ERNA), and (5) "The Safety of Vitamins and Minerals: An overview of the US Institute of Medicine's Risk Assessment," by ERNA.

IADSA Safety Methodology

Most of the approaches to upper safe levels are based on widely applicable risk assessment models similar to those used by FNB in its Dietary Reference Intakes documents published in 1997 and after (1-5). The FNB method and reviews are a formalization and extension of the quantitative methods widely used earlier in risk assessment of other substances, and by the supplement industry. Because of the systematic, comprehensive and authoritative character of the FNB risk assessment method for nutrients, this approach has gathered widespread support and adoption by others such as the SCF (7) and EVM (11), with some slight modifications. All current methodology emphasizes the concept of nutrient-appropriate, quantitative risk assessment, but the difference in the selection and interpretation of the available scientific literature on safety has sometimes resulted in differences in the safety values for various nutrients, as derived by the FNB, SCF, and EVM.

The safety evaluation method underlying this document is that in the updated and expanded Vitamin and Mineral Safety, 2nd Edition (by John Hathcock, CRN, Washington, DC, USA) (12), with the basic features from the methods of the FNB, SCF, and EVM. This document, like that of CRN USA, emphasizes the direct evaluation of the safety of supplemental intakes of nutrients, rather than total intakes from all sources, where such data are available.

Nutrient-Appropriate Scientific Risk Assessment for Vitamins and Minerals

The term “nutrient-appropriate” used to describe risk assessment for vitamins and minerals indicates that some risk assessment methods are not appropriate. Certain risk assessment methods use default uncertainty factors (sometimes called safety factors) that, although they are generally considered acceptable for identifying safe intakes of food additives and environmental contaminants, are unacceptably large for application in risk assessment of vitamins and minerals. That is, application of these factors leads to identification of “safety limits” that are below the recommended daily intakes for some nutrients for certain age/gender groups. For example, the Acceptable Daily Intake (ADI) and the Reference Dose (RfD) used by the U.S. Environmental Protection Agency (US EPA) involve arbitrary uncertainty factors that calculate ”safety limits” for zinc that are below the Recommended Dietary Allowance (RDA) for some groups.

The Tolerable Upper Intake Level (UL) method used by the US Food and Nutrition Board

Because of the general validity and widespread acceptance, a safety evaluation approach closely resembling the UL method by the US FNB, with the adaptations by the EC SCF and UK EVM has been adopted. The approach in the IADSA risk assessment, however, includes modification to emphasize preference for direct evaluation of supplement safety from data related to supplemental use of those nutrients, rather than total intakes from all sources. Thus, IADSA has identified Upper Levels for Supplements (ULS values), which are defined and selected to represent amounts of vitamins and minerals known to be safe for supplemental intake by healthy adults who eat typical diets.

The UL method involves the following major steps:

- *Hazard identification:* Preferably from human data but using animal data when necessary, identify a hazard related to excess consumption of a vitamin or mineral, using the guidelines and procedures described in the UL method. Biochemical or other indirect indicators are judged to represent a hazard only if they are surrogate markers for pathological conditions. If no hazard can be identified, do not proceed with the additional steps in the UL method. Apply the criteria for causality, including the strength of association, consistency of association, specificity of association, dose-response relationship, temporal relationship plausibility, biological plausibility, and overall coherence.

- *Dose-response assessment:* Identify a No Observed Adverse Effect Level (NOAEL) from human data if possible. Alternately, identify a Lowest Observed Adverse Effect Level (LOAEL) if the data are appropriate but do not support a NOAEL. Use animal data only if appropriate human data are not available.

  Assess the uncertainties and assign a numerical uncertainty factor (UF) that applies to the overall database and the specific data used to establish the NOAEL or LOAEL. If a LOAEL is used, select an uncertainty factor appropriate to the conversion to a NOAEL. If the NOAEL or LOAEL are identified from animal data, appropriate uncertainty factors are assigned to the extrapolation to UL values for humans.

- *Derive the UL:* Calculate the UL, as UL = NOAEL ÷ UF (or UL = LOAEL ÷ UF).

European Commission's SCF UL Values and EC Proposal for Setting Maximum Amounts of Vitamins and Minerals in Supplements

The European Commission's SCF has published UL values for several vitamins and minerals, using methodology (7-9) similar to that developed by the US FNB. The EC Food Supplements Directive requires the identification of maximums for vitamins and minerals in supplements, apparently through application of a difference method (7-10). The approach specified in the Directive would include the following steps:

Step 1

- Use the EC SCF UL values identified through a method almost identical to the one developed by the US FNB.
- Consider intakes from other dietary sources.

Step 2

When applying step 1, also give "due account" to population reference intakes (equivalent to the RDAs).

This proposal seems to identify maximums for supplements as the difference between the UL and the intake from other sources. That is, the supplement maximum would be the UL minus the expected intake from conventional foods. The population reference intakes, referred to in Step 2, could be used to assure that the risk assessment is not excessively conservative, and thereby produce a UL below the RDA.

At the time of this publication (April 2004), the EC has not released any proposed maximums for vitamins and minerals in food supplements.

UK's Expert Group Report on Vitamins and Minerals - Risk Assessments

The UK's EVM report (11) on their evaluations of vitamin and mineral safety is based on the UL method developed by the FNB, but assigned the term Safe Upper Level (SUL) to the value derived by this method. Although the EVM applies the term SUL, these values are identified by the same UL methodology developed by the FNB and adopted by the SCF. The EVM stated that for certain nutrients the databases were not sufficient to set a SUL, and a "guidance level" was identified. Nonetheless, the "guidance level" was often derived and used for overall safety evaluation and discussion in the same manner as a SUL value. For a few nutrients, the EVM report takes an additional step toward risk management recommendations for supplements. For specific nutrients with appropriate data, the EVM report uses either the SUL or a "guidance level" for supplemental intakes, in contrast to total intake from all sources. A safety value based on supplemental intake effects could be logically used to identify maximum contents of products marketed and regulated as supplements. EVM assumes daily consumption throughout the adult lifetime (16 years to death), whereas the FNB and SCF are not explicit on this issue.

The IADSA Approach to Supplement Safety

Safety evaluation for dietary supplements is properly determined on a case-by-case basis through nutrient-appropriate risk assessment, not as arbitrary multiples of the RDA, as described below:

Nutrient-appropriate risk assessment requires the safety evaluation to depend on identification of a hazard related to excessive intake, assessment of the dose-response relationship for the identified hazard, consideration of uncertainty, and finally derivation of a supplementation level that is not only safe but includes a reasonable margin of safety.

In the identification of a hazard related to excessive consumption of a nutrient, care must be taken to distinguish between effects that represent a genuine hazard and those that are merely a nuisance. For example, the minor gastrointestinal distress that can occur when supplements are taken on an empty stomach should not be considered equivalent to any risk of a serious effect, such as liver toxicity.

Levels for supplements that can be expected to be safe can be identified by either of two related but different methods. The direct method, the preferred option, is subject to less uncertainty because it contains fewer steps.

Option 1: Direct Safety Evaluation of Supplemental Intakes: If appropriate data on supplemental intakes of a specific vitamin or mineral are available, the tolerable upper intake level from supplements (ULS) may be determined directly from those data related to supplemental intakes. If the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Option 1, the direct method, identifies the NOAEL and ULS from data related to the use of *supplemental amounts* of the vitamin or mineral, above and beyond the amounts contributed by the diet, and therefore do not require any additional consideration of amount contributed by consumption of conventional foods. That is, the

- ULS = human supplemental intake NOAEL (conservatively selected to justify a UF of 1.0)

OR

Option 2: Indirect or Difference Method for Supplement Safety: If appropriate data on supplemental intakes of a vitamin or mineral are not available, a *difference* procedure, similar to that identified by the EC, may be used.

The difference method involves:

- Determination of the tolerable upper intake level (UL) for total intake from all sources
- Identification of the usual intakes from conventional foods (ICF) from appropriate food intake surveys and food composition tables, taking consumption of fortified foods into account, and
- Calculation of the tolerable upper intake from supplements (ULS) as a difference. That is, ULS = UL – ICF.

In contrast to Option 1, this approach identifies NOAEL and UL for total intake of the vitamin or mineral from all sources, including conventional foods and dietary supplements, thereby requiring subtraction of the expected contribution of conventional foods, if this amount is not trivial compared with the NOAEL, in calculation of the ULS for supplemental intake.

OR

Option 3: Observed Safe Level: For some nutrients, without established hazard at high intakes, the toxic potential is so low that there is no credible evidence of adverse effects at any level of intake that has been widely consumed or used in a clinical trial. For such nutrients, the maximum level with sufficient evidence of safety can be identified as an Observed Safe Level (OSL), and this OSL can be used as a ULS. That is,

- ULS = OSL (the highest level with convincing evidence of safety, if there are no established adverse effects at any level)

In some ways the approach in the IADSA risk assessment differs and goes beyond both the FNB UL method and the EC proposal. For some nutrients, the IADSA and EVM methods are the same. For other nutrients, IADSA and EVM use different approaches.

IADSA's approach differs from the US FNB, EC reports and food supplements directive, and UK EVM methods in the following ways. Specifically, this method:

1. Gives preference to data on effects of supplemental intakes, rather than total intakes, thereby eliminating any need to correct for intakes from conventional foods.
2. Gives stronger preference to use of human data rather than animal data, thereby avoiding the uncertainties involved in extrapolation between species.
3. Gives stronger preference to clinical trial data from human studies, if available, rather than other types of human data.
4. Gives stronger preference to identifying NOAEL values, rather than LOAEL values, thereby eliminating the uncertainty related to extrapolation from the LOAEL.
5. Considers only effects that represent a true hazard (i.e. risk of impaired health), rather than nuisance effects.
6. Preferentially uses direct evidence of adverse effects, if available, rather than biochemical markers or other indirect indicators.
7. Utilizes history of use data, if necessary, to identify an OSL and ULS when adverse effects in humans have not been identified for a nutrient. This approach relies on previous experience by humans, when consistent with the scientific evidence that for some nutrients includes an indication of a high-order of safety.
8. Conservatively selects human NOAEL values that justify selection of an uncertainty factor of 1.0.
9. Recognizes that supplement use is an independent choice for the consumer, and does not impose increased intake on anyone who does not select it, in contrast to food fortification programs that require the consumer to carefully read labels to obtain or avoid increased intake of nutrients.

RDA-Based Safe Upper Levels Have No Scientific Validity

Recommended Dietary Allowances (RDAs) have sometimes been used by national regulatory authorities as the basis for setting safe upper levels for vitamins and minerals. However, it is important to note that the RDA and the UL are determined by two completely different conceptual approaches. There is now increasing scientific consensus that upper safe levels should be established by scientific risk assessment based on generally accepted scientific data, and that safe upper levels based on arbitrary multiples of RDAs have no scientific validity. For example, at its 2003 meeting the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) dropped any further consideration of RDA-based limits.

RDA values are set on a very similar basis from one country to another—that basis is the consensus of scientific opinion on the quantities of these nutrients needed to confidently assure the performance of recognized physiological functions related to their essentiality. Thus, the RDA values are related to avoidance of classical nutrient deficiency signs and symptoms. Although this basis for the RDA may be appropriate for undernourished populations, the needs are different for well-nourished and over-nourished populations. A significant fraction, such as 15 percent, of the RDA can be used appropriately to set lower limits for vitamins and minerals in supplements.

RDA-based values are not valid for judging safety because:

1. The RDA is not defined or identified to describe safety or represent a safety limit for total or supplemental intake.

2. RDA-based limits are not possible for nutrients without established RDA values. For example, no RDA has been set for lutein, lycopene, boron, and many other important substances with nutritive value. These substances have beneficial effects, but the available evidence has not been judged sufficient to identify RDAs, although that may occur in the future. Risk assessment can be used to identify appropriate safety limits for these important nutrients, whether or not an RDA has been set.

3. Arbitrary limits at or near the RDA may preclude certain benefits of some nutrients. For example, well-documented benefits of nutrient quantities above the RDA include:

   a. Folic acid, vitamin B_6 and vitamin B_{12} which help control plasma homocysteine concentrations. Homocysteine is not yet accepted as a recognized risk factor for heart disease, but there is an ever-increasing body of scientific evidence to support this finding. Supplementation with these three vitamins definitely helps control plasma concentrations of homocysteine, and is likely to be proven to reduce risk of heart disease.

   b. Supplementation with 200 micrograms of selenium to diets containing about 100 micrograms has been shown in a long-term, well-conducted clinical trial to reduce the incidence of three important types of cancer. A confirmatory clinical trial is underway that, if positive, would justify a widespread public health policy to increase selenium intake in many populations. In the meantime, there is no reason to deny accurate information about the state of the current evidence and to restrict selenium supplements to the RDA.

   c. Supplementation of diets containing less than 40 micrograms of chromium with additional 200 to 400 micrograms helps maintain normal blood glucose levels and minimize the signs and symptoms of type II diabetes. Clinical trials confirm the safety of up to 1,000 micrograms of supplemental chromium.

4. The imposition of RDA-based upper limits is a disproportionate restriction on supplement products, compared with conventional foods. Certain conventional foods contain many multiples of the RDA of some nutrients. For example, the natural amounts of vitamin B_{12} in conventional foods such as liver and some shellfish can approach 100 micrograms per 100 gram serving. The adult RDA for this vitamin is commonly set at approximately 1.4 to 2.5 micrograms. Thus, these ordinary conventional foods may contain upwards of 40 to 70 multiples of the RDA of vitamin B_{12}. There is no known toxicity of oral vitamin B_{12} in humans. Thus, RDA-based upper limits are not rational, serve no useful purpose, and are a disproportionate response to any hypothetical safety concern about this vitamin.

5. Labeling, not limits, can address proper usage. Labeling can provide information on contents, benefits related to RDA or other measures of benefit, and draw attention to limits imposed on a safety basis, as identified by risk assessment.

Fat-Soluble Vitamins

Safety Summaries for Individual Vitamins and Minerals

The data on which this risk assessment depended in these sections have been reviewed and summarized in the listed publications by FNB, SCF, EVM, and CRN (2nd edition). See the reference list for these sources.
The conclusions reached in this document are supported, with detailed references, by The Council for Responsible Nutrition's Vitamin and Mineral Safety, 2nd Edition, which can be ordered on line at www.crnusa.org.

Vitamin A (as retinol and its esters)

Supplements of 3,000 µg of preformed retinol or its esters are safe for people with low food retinol intakes. For users of large amounts of fortified foods or food naturally high in retinol, a ULS of 1,500 µg is appropriate. These values are identified on the following basis:

- The LOAEL for birth defects is at least 25,000 IU (7,500 µg) of retinol, and there are no credible data to suggest that it is likely to be lower than 21,675 IU (6,500 µg) RE).
- The FNB selected a retinol NOAEL of 4,500 µg (15,000 IU), but conservatively applied an uncertainty factor of 1.5 to derive their UL of 3,000 µg (10,000 IU).
- The intake of retinol and retinyl esters from sources other than supplements is likely to be less than 1,000 µg.
- There is a long history of safe use of dietary supplements containing 5,000 IU, 8,000 IU and 10,000 IU (1,500 µg, 2,400 µg, and 3,000 µg, respectively)
- The FNB NOAEL equivalent to 4,500 µg and the highest likely intake of 1,000 µg from sources other than supplements are compatible with a supplements limit (ULS) of 3,000 µg.
- The possible effects of retinol on bone fragility are based on epidemiological evidence and remain speculative and unconfirmed, but the clinical trials needed to confirm or deny such possibility are not likely to be performed because of ethical constraints on dosing with large amounts of retinol.
- Persons, for example those who regularly consume liver or other organ meats, with likely high intakes of retinol should consume supplements that contain vitamin A activity as beta-carotene and should limit consumption of preformed vitamin A.
- A large number of companies are voluntarily decreasing the maximum amount of retinol in multivitamin products to 1,500 µg or less to avoid the unsubstantiated concerns about bone fragility or retinol intakes from conventional foods such as liver.
- If the emerging data on bone fragility become generally accepted, the safety evaluation of retinol will need to be based on these effects, and a supplement maximum might need to be 1,500 µg or less.

IADSA safety values for vitamin A (a retinol and its esters)	
Low users of retinol-rich foods	3,000 µg
High users of retinol-rich foods	1,500 µg

Comparison of safety values for vitamin A	
FNB UL, total intake	3,000 µg
EC UL, total intake	3,000 µg
UK EVM, Guidance Level, total	1,500 µg

Beta-Carotene

Extensive data show that beta-carotene supplements of 50 mg every other day (equivalent to 25 mg per day) can be taken for more than a decade without harm in a large group of mostly non-smokers. An intake of 25 mg per day is therefore selected as the OSL for non-smokers. Skin discoloration may occur with larger amounts, but this effect should be considered potentially undesirable rather than adverse. It is harmless and self-correcting with intake reduction.

The only evidence of adverse effects of beta-carotene comes from the ATBC and CARET studies and involved long-term heavy smokers or asbestos workers. These data suggest a LOAEL of 20 mg per day for smokers or asbestos workers, but disparity between the ATBC and CARET results and other data prevents a confident identification of any LOAEL for beta-carotene. Smokers and asbestos workers should first of all control those health risks, and then consider whether beta-carotene supplements are safe for them.

IADSA safety value for beta-carotene	
ULS (OSL method)	25 mg (non-smokers; no supplement for smokers)

Comparison of safety values for beta-carotene	
FNB UL, total intake	Reviewed but not set; not for smokers
EC UL, total intake	Reviewed but not set; risk for smokers
UK EVM, UL (LOAEL ÷ 3), supplemental	7 mg (none for smokers)

Vitamin D

Recent data indicates that the NOAEL may be as high as 100 µg. Thus, from the available data, the LOAEL is greater than 100 µg per day in relation to its hypercalcemic effects. The US FNB and UK EVM estimate vitamin D intakes from all non-supplement sources to be in the range of 9 µg or less. The majority of dietary supplements that include vitamin D contain10 µg or less. There are no reports of adverse effects at this level of intake. The ULS is identified as 60 µg, based on the absence of adverse effects in a clinical trial. The FNB identified a NOAEL of 60 µg based on these data, but applied an uncertainty factor of 1.2. The database for an intake of 100 µg is highly supportive of a NOAEL at that level, but not yet replete enough to warrant setting the NOAEL that high. However, the data at 100 µg strongly reduces any uncertainty about the safety at a 60 µg intake. Indeed, in comparison, the SCF identified the NOAEL at 100 µg but considered the uncertainty sufficient to warrant application of a factor of 2 in calculation of the UL from that NOAEL.

With the confidence in the safety at the 60 µg intake level increased by the data related to 100 µg intake, a NOAEL of 60 µg does not to need be adjusted by application of an uncertainty factor. Thus, ULS is set at 60 µg, based on the 60 µg clinical trial data and non-supplement intakes of not more than 9 µg.

IADSA safety value for vitamin D	
ULS	60 µg

Comparison of safety values for Vitamin D	
FNB UL	50 µg
EC SCF UL	50 µg
UK EVM guidance level, supplemental	25 µg

Vitamin E

To simplify safety consideration of different forms of vitamin E and to reach appropriately cautious conclusions, the conversion of the IU to mg α-TE is recommended. Because most clinical trials have been conducted with synthetic dl-a-tocopheryl acetate (that is, *all rac*-a-tocopheryl acetate in the currently accepted scientific nomenclature) with dosages identified in IU, conversion of a ULS in IU to the corresponding vitamin E activity in mg α-TE will result in a more conservative UL. An OSL of 1,600 IU is identified from clinical trial data that showed no adverse effects at this level of intake. Correspondingly, the 1,600 IU OSL is also the ULS because of the very low level of uncertainty apparent through the absence of adverse effects at the higher intake of 3,200 IU. With the conversion to mg α-TE as performed by the UK EVM, the IADSA ULS of 1,600 IU is equivalent to 1,073 mg, a value we recommend rounding off to 1000 mg, which is the same value identified by the US FNB through extrapolation from animal data.

IADSA safety value for vitamin E	
ULS (OSL method)	1,000 mg (1,073 mg rounded off)

Comparison of safety values for Vitamin E	
FNB UL	1,000 mg
EC SCF UL	300 mg (rounded up from 270 mg)
UK EVM guidance level, supplemental	800 IU (540 mg)

Vitamin K

Vitamin K has an extremely low potential for toxicity, but the data are insufficient to establish just how low. The EVM decision to apply an uncertainty factor of 10 seems unnecessarily cautious in view of the absence of reports of adverse effects at intakes of 30 mg or more, although data to support that value are relatively sparse. Consequently, the ULS for vitamin K is identified as 10 mg/day. This value is based on the same clinical data identified by the UK EVM, but without the 10-fold uncertainty factor used by the EVM. Omission of the uncertainty factor (literally, using a factor of 1 instead of 10) is justified by the history of apparent absence of adverse effects at intakes of 30 mg or more. Dietary intakes and intestinal biosynthesis are trivial in comparison with the ULS of 10 mg.

Because of the strong interaction of vitamin K with anticoagulant drugs, the ULS does not apply to persons taking such medications.

IADSA safety value for vitamin K	
ULS (OSL method)	10 mg

Comparison of safety values for Vitamin K	
FNB UL	Reviewed but not set (no toxicological basis)
EC SCF UL	Reviewed but not set (no toxicological basis)
UK EVM guidance level, supplemental	1 mg (1,000 µg) (10 mg ÷ 10)

Water-Soluble Vitamins

Vitamin C

Vitamin C has an extremely low potential for toxicity. Despite decades of widespread use at multigram levels, the only established adverse effects are the gastrointestinal impacts such as irritation, bloating and diarrhea. These effects are usually mild, transient, and self-limiting through discontinuation at the adverse dosage.

Very high intakes of vitamin C can cause diarrhea and related gastrointestinal adverse effects, and these are a sufficient basis to set a ULS. The FNB identified a LOAEL of approximately 3,000 mg. Given the mild, transient, and self-correcting nature of the adverse effects, an uncertainty factor of 1.5, as identified by the US FNB is ample. The FNB and EVM set their UL in relation to total intake per day, but neither considered in detail whether the UL could be higher if the intake were quite evenly spread out over a day or whether it should be lower for a single dose. An IADSA ULS of 2,000 mg per day is identified, but limitation of any single dose to 1,000 mg is recommended to provide greater certainty of avoiding undesirable gastrointestinal effects.

IADSA safety value for vitamin C	
ULS	2,000 mg per day and 1,000 mg per single dose (doses separated by 4 or more hours)

Comparison of safety values for Vitamin C	
FNB UL	2,000 mg (per day)
EC UL	Not reviewed (October 2003)
UK EVM, Guidance Level, supplemental	1,000 mg (per day)

Vitamin B_1 (Thiamin)

Based on clinical trial data, an Observed Safe Level (OSL) is identified at 100 mg supplemental thiamin hydrochloride per day. The marketing of thiamin products at much higher levels, together with the clinical trial data strongly suggest that much higher levels of thiamin may be safe, but the data are compelling at 100 mg, and this value is selected as the ULS.

IADSA safety value for vitamin B_1 (thiamin)	
ULS (OSL method)	100 mg

Comparison of safety values for Vitamin B_1	
FNB UL, total intake	Reviewed but not set (no toxicological basis)
EC SCF UL, total intake	Reviewed but not set (no toxicological basis)
UK EVM, Guidance Level, supplemental	100 mg (103 mg total)

Vitamin B_2 (Riboflavin)

From clinical trial data, 400 mg/day vitamin B_2 is identified as a level that is reported to product a few scattered but not a significant pattern of adverse effects. The minor and inconsistent adverse effects reported with 400 mg supplemental intake suggests that the EVM uncertainty factor of 10 is unnecessarily restrictive. Hence, a ULS is identified from the 400 mg LOAEL using an uncertainty factor of 2, which is considered to be sufficient. This level of supplemental riboflavin is further judged to be safe based on a widespread market presence of such high potency supplements without reported adverse effects.

IADSA safety value for vitamin B_2 (riboflavin)	
ULS	200 mg

Comparison of safety values for vitamin B_2	
FNB UL, total intake	Reviewed but not set (no toxicological basis)
EC SCF UL, total intake	Reviewed but not set (no toxicological basis)
UK EVM, Guidance Level, supplemental	40 mg (43 mg total intake from all sources)

Vitamin B_6 (pyridoxine)

There is marginal evidence suggesting possible adverse effects at intakes of 200 mg but not at 100 or 150 mg. Consequently, a human supplemental intake NOAEL for pyridoxine at 100 mg is identified. The absence of adverse effects in most, but not all, studies at 200 mg intake, together with the absence of significant adverse effects of any type at 100 or 150 mg strongly reduces the uncertainty about the safety of pyridoxine at 100 mg supplemental intake. Intakes from conventional foods alone are generally below 3 mg, and thus this source does not contribute significantly to safety concerns.

The major uncertainties about the reliability of the data of Dalton and Dalton on intakes near 100 mg include lack of objective neurological measurements and lack of dose verification of the reported pathology by any means other than a telephone interview. Due to these large uncertainties, these data were not used by the FNB as the basis of its risk assessment on pyridoxine. These large uncertainties eliminate the Dalton and Dalton data from use in the evaluation of the safety of vitamin B_6.

The complete absence of adverse effects in well-designed (credible) studies at 100 and 150 mg indicates that 100 mg can be confidently concluded, with a low level of uncertainty, as producing no adverse effects over periods of several years. Intakes from conventional foods are almost always less than 4 mg per day. Thus, intake from conventional foods is minor compared with maximum safe level, and 100 mg is identified as the ULS for pyridoxine. Somewhat higher amounts may be safe for most people.

IADSA safety value for vitamin B_6 (pyridoxine)	
ULS (supplemental intake)	100 mg

Comparison of safety values for vitamin B_6 (pyridoxine)	
FNB UL, total intake	100 mg
EC SCF UL (supplemental intake)	25 mg (based on Dalton and Dalton data)
UK EVM SUL for chronic supplemental intake	10 mg (extrapolated from animal data)

Vitamin B_{12}

Lack of any adverse effects for vitamin B_{12}, as noted by the FNB, together with the context of extensive testing and use of oral vitamin B_{12} dosages up to 1,000 µg in pernicious anemia patients would suggest also that high dosages of vitamin B_{12} are safe in these persons. Vitamin B_{12} has no observable adverse effects at any level of recorded use, not even by parenteral administration at 1,000 µg (1 mg) twice weekly for up to three years, or intravenously at 1 mg per day for one year. Thus, there is no basis for a LOAEL for oral intake.

There is sufficient experience and clinical evidence with oral intakes of 3,000 µg (3 mg) per day to support the identification of this amount as the OSL, and higher intakes may also be safe. Thus, the ULS is set as the OSL at 3,000 µg of supplemental vitamin B_{12} per day.

IADSA safety value for vitamin B_{12}	
ULS (OSL method)	3,000 µg

Comparison of safety values for vitamin B_{12}	
FNB UL	Reviewed but not set (not toxicological basis)
EC SCF UL	Reviewed but not set (no toxicological basis)
UK EVM Guidance Level	2,000 µg

Folic Acid

A folic acid supplement of 4 mg per day (4,000 µg) was used without adverse effect in the seven-nation trial, involving a total of 1,817 women at 33 study centers A committee advising the FDA on folic acid and NTDs concluded that adverse effects are unlikely with intakes of 1,000 µg (1 mg) or less. The evidence that intakes of 1,000 µg (1 mg) of total folic acid plus food folates are without identifiable risk of any known adverse effects is sufficient to identify this level as the NOAEL. Some data suggest that the LOAEL might be 5,000 µg or higher.

Two relevant clinical application reports found no significant increase in risk of masking neurological effects with folic acid doses of 1.25 mg/day, whereas there is a small amount of evidence that masking of vitamin B_{12} deficiency could be a problem with intakes of 1.5 and 2.55 mg. On the basis of the absence of adverse effects at 1.0 mg and no significant effects up to 1.25 mg, the ULS for folic acid is 1,000 µg.

IADSA safety value for folic acid	
ULS	1,000 µg

Comparison of safety values for Folic Acid	
FNB UL	1,000 µg
EC SCF UL	1,000 µg
UK EVM guidance level, supplemental	1,000 µg

Biotin

A properly defined UL cannot be set because of the absence of known adverse effects at any observed level of intake, but an OSL can be identified as the highest level of intake for which there are sufficient data to support a conclusion of safety at that level of supplementation. In the USA, biotin supplements of 5 mg and 7.5 mg have been quite common for several years. FDA has never announced receipt of any reports of adverse effects associated with biotin at any level of intake. The absence of adverse effect reports in the presence of marketed products up to at least 7.5 mg and the absence of any adverse effects in a clinical trial at 9 mg per day suggests that biotin is likely to be safe at intakes of 5 mg or 7.5 mg.

Based on (1) the absence of adverse effects at 9 mg of supplemental biotin, but recognizing that the study size was small, and (2) the absence of any reported adverse effect reports for biotin, even though 5 mg products are quite common in the USA, 2.5 mg is identified as the ULS.

IADSA safety value for biotin	
ULS (OSL method)	2.5 mg

Comparison of safety values for biotin	
FNB UL	Reviewed but not set (no toxicological basis)
EC SCF UL	Reviewed but not set (no toxicological basis)
UK EVM guidance level, supplemental	900 µg

NIACIN - Nicotinic Acid and Nicotinamide

Nicotinic Acid

With its transient and non-pathological effects, the flushing reaction in response to supplemental nicotinic acid deserves to be characterized as a nuisance but not as a hazard. When high intakes result from supplementation, appropriate product labeling can alert the consumer of this nuisance effect. Thus, flushing does not qualify as a hazard for supplemental intakes of nicotinic acid.

There are only two anecdotal cases at intakes less than 1,000 mg per day and 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 compromises of liver function. For these reasons and for the principle of demonstration of causality, the clinical trial data of McKenney and co-workers (1994) are more appropriate to identify NOAEL and LOAEL values. From these data, a NOAEL of 500 mg per day and a LOAEL of 1,000 mg per day are identified for liver or gastrointestinal effects. It should be noted, however, that the adverse reactions to 1,000 mg of unmodified nicotinic acid were mainly gastrointestinal effects, which generally have less potential for serious outcomes, compared with the liver toxicity that results in some persons consuming 1,000 mg per day of slow-release nicotinic acid. Additionally, gastrointestinal effects seem much more likely to be self-limiting due to consumer awareness and likely self-correction. These differences warrant advising a smaller limit for slow-release nicotinic acid than for the unmodified form, and the two-fold decreases in NOAEL and LOAEL for slow-release nicotinic acid seem ample. Thus, for slow-release nicotinic acid the NOAEL is 250 mg and the LOAEL is 500 mg.

Therefore, the following values are identified for nicotinic acid supplements:

Considering the infrequent effects at the LOAEL levels of intake and the reversible nature of mild, short-term hepatotoxicity, the NOAEL values are identified as the ULS values, provided that immediate release formulations carry appropriate labeling about the flushing reaction. Thus, the ULS values for nicotinic acid supplements are:

Immediate-release nicotinic acid formulations	
LOAEL, based on hepatotoxicity	1,000 mg/day
NOAEL, based on hepatotoxicity	500 mg/day
Flushing threshold	>35 mg/day

Slow-release nicotinic acid formulations	
LOAEL	500 mg/day
NOAEL	250 mg/day
Flush label warning	None; not needed

Immediate release nicotinic acid supplements

IADSA ULS = 500 mg (contingent upon proper label statements about flushing)
= 35 mg when based on flushing reaction

Slow-release nicotinic acid supplements

IADSA ULS = 250 mg

Nicotinamide

Clinical trial results support a very confident NOAEL of 25 mg/kg/day. Because some of these trials were performed with younger subjects with lower than fully adult body weights, 60 kg is used to calculate a NOAEL of 1,500 mg/day. The absence of adverse effects in clinical trials that included nicotinamide dosages up to 3,000 mg/day distinctly reduces the uncertainty in this value. Nicotinamide does not produce the vasodialative flushing reaction that can be caused by nicotinic acid. Thus, the NOAEL of 1,500 mg is selected as the ULS for nicotinamide.

Safety values for Niacin - Nicotinic acid and Nicotinamide

Nicotinic acid

IADSA safety value	
ULS	500 mg, based on liver toxicity
Threshold for flushing warning on label	35 mg

Comparison of safety values	
FNB UL, total intake	35 mg*, based on flushing effects
EC SCF UL, total intake	10 mg, based on flushing effects
UK EVM, Guidance Level, supplemental	17 mg, based on flushing effects

Nicotinamide

IADSA safety value	
ULS	1,500 mg

Comparison of safety values	
FNB UL, total intake	35 mg*
EC SCF UL, total intake	900 mg
UK EVM, Guidance Level, supplemental	500 mg (560 mg for total nicotinamide)

*This UL for nicotinic acid is applied to the total of all forms of niacin.

Pantothenic Acid

There are no reports of toxicity from oral administration on which a LOAEL value could be based. The clinical trial data identified by the EVM provide evidence that supplemental intakes of 2,000 mg do not produce adverse effects. The amount of available information is much smaller than desirable, but with the absence of adverse effects with daily intakes as high as 10 g, and systematic clinical experience with oral intakes up to 1,000 mg per day 1,000 mg per day is selected as the ULS value.

IADSA safety value for pantothenic acid	
ULS (OSL method)	1,000 mg

Summary of safety values for pantothenic acid	
FNB UL	Reviewed but not set (no toxicological basis)
EC SCF UL	Reviewed but not set (no toxicological basis)
UK EVM guidance level, supplemental	200 mg

Minerals

Calcium

The widely observed safe use of calcium at intakes up to 1,500 mg or slightly more per day justifies this value as the NOAEL for supplemental calcium. This conclusion is supported by the data from clinical trials that showed no adverse effects with calcium supplements containing 1,200 mg and 1,600 mg. From these data, 1,600 mg is identified as the supplemental calcium NOAEL, but agrees with the prudence of the EVM 1,500 mg guidance level, principally because of the potential for substantial other sources for intake of calcium, especially from fortified foods and dairy products. Thus, the ULS for calcium is set at 1,500 mg per day for adults.

IADSA safety value	
ULS	1,500 mg

Comparison of safety values for calcium	
FNB UL, total intake	2,500 mg
EC SCF UL, total intake	2,500 mg
UK EVM Guidance level, supplemental	1,500 mg

Phosphorus

In adults with normal kidney function, phosphorus is readily excreted and no imbalance in calcium metabolism occurs except at extreme intakes. The gastrointestinal effects of phosphorus are greatly influenced by the specific chemical form consumed, and other dietary ingredients, especially calcium. There are no data appropriate for identifying direct adverse effects of dietary phosphorus, and therefore no LOAEL can be identified. Similarly, no specific intake level qualifies as the NOAEL or OSL level. The very high NOAEL value identified by the FNB is perhaps too hypothetical. Similarly, the very low NOAEL identified by the EVM was based on a speculative, worst-case interpretation of a very few reports that could have had other causes. There is a need for an appropriate ratio of calcium-to-phosphorus intake within a broad range of acceptable ratios, and therefore, in the absence of more specific evidence, a ULS value identical to that for supplemental calcium is considered most appropriate.

IADSA safety value for phosphorus	
ULS	1,500 mg

Comparison of safety values for phosphorus	
FNB UL, total intakes	4,000 mg
EC SCF	Not reviewed (April 2004)
UK EVM guidance levels	250 mg supplement; 2,400 mg total

Magnesium

The only severe adverse effects reliably attributed to oral consumption of magnesium relate to prolonged use in multiple-gram quantities as an antacid or cathartic. Mild to moderate but easily reversible diarrhea can result from nonfood magnesium intakes at levels above 400 mg per day. The infrequent, mild, reversible diarrhea found at lower levels do not justify selection of those levels as a LOAEL, characteristics that also justify selection of a UF of 1.0 for use in deriving a ULS. The mild diarrhea effects are a nuisance rather than a hazard. Thus, the ULS for supplemental magnesium is 400 mg per day for healthy adults. Persons consuming such supplements should be aware that some antacids and laxatives also contain substantial quantities of magnesium.

IADSA safety value for magnesium	
ULS	400 mg

Comparison of safety values for magnesium	
FNB UL, nonfood sources	350 mg
EC SCF, nonfood sources	250 mg
UK EVM guidance level, supplements	400 mg

Potassium

The clinical trial data on potassium chloride, together with the epidemiology supporting the safety of larger amounts of potassium from fruits and vegetables, indicates that this nutrient has a wide margin of safety. The clinical trials collectively, with the potassium from foods being unspecified, show no pattern of adverse effects for supplemental potassium of 1,500 mg. Larger quantities of potassium as potassium chloride can produce gastrointestinal effects, and these seem more if taken at one time, especially with an empty stomach. The EVM established guidance indicating that 3,700 mg of potassium is safe, but did not specify the amounts for foods and supplements. The evidence, however, related to supplemental potassium. Considering clinical trial evidence and the apparent safety of potassium intakes as high as 8 to 11 g/day from fruits and vegetables, the ULS for potassium is 1,500 mg/day, with the provision that it should be divided into doses no larger than 500 mg each. There is no discernable scientific justification for the US FDA threshold of 100 mg of potassium for regulation of the products as drugs.

IADSA safety value for potassium	
ULS	1,500 mg/day (as 500 mg, 3-times a day)

Comparison of safety values for potassium	
FNB UL	Reviewed but not set
EC SCF	Not reviewed (April 2004)
UK EVM guidance level, supplemental	3,700 mg/day, with minor adverse effects

Trace Elements

Boron

A clinical trial with an intake of 3 mg per day produced no adverse effect. Other studies confirm this observation and this intake may be considered as a clinical trial OSL for supplemental intake. Intakes from conventional foods are almost always less than 3 mg/day. All toxicity data relate to acute poisonings from very large amounts of borates, or experimental animal data.

The FNB UL, UK EVM UL and US EPA RfD apply to total intakes from all sources. In the face of these uncertainties, a ULS of 6 mg per day is reasonable, based on the adequately conservative EVM UL of 9.6 mg, and the fact that food intakes do not exceed 3 mg. The 6 mg ULS is further supported by the definite OSL character of 3 mg across several studies, together with the fact that food intakes are almost always less than 3 mg per day.

IADSA safety value for boron	
ULS	6 mg

Comparison of safety values for boron	
FNB UL, total intake	20 mg
EC SCF UL	Not reviewed (April 2004)
UK EVM SUL, total intake	9.6 mg

Chromium

The available clinical trial data are sufficient to indicate safety for chromium supplements at levels up to 1,000 micrograms of chromium per day for adults. The in vitro and insect studies on chromium picolinate are not appropriate for the safety evaluation of this form or any form of chromium for use in foods or supplements. On the basis of the large number of clinical trials summarized in this FNB review and the other official reviews of the evidence on other forms of chromium (III), the ULS is 1,000 µg per day, including the picolinate form. The toxicity of highly oxidized chromium (VI) is not relevant to food or supplement safety and is not in use.

IADSA safety value for chromium	
ULS	1,000 µg (any chemical form of chromium III)

Comparison of safety values for chromium	
FNB UL, total intake	Reviewed but not set (no toxicological basis)
EC SCF UL	Reviewed but not set (no toxicological basis)
UK EVM guidance level, total	10 mg (10,000 µg), but not including the picolinate

Copper

The NOAEL of 10 mg per day identified by the FNB and SCF is derived from a clinical trial of supplemental copper in subjects with unspecified copper intake. This value is appropriate as a supplemental NOAEL for copper. Considering the absence of adverse effects at intakes in the range of 10 to 12 mg per day and the mean copper being approximately 1.4 mg and the 97.5 percentile being 3 mg, the ULS for supplemental copper is identified as 9 mg.

IADSA safety value for copper	
ULS	9 mg

Comparison of safety values for copper	
FNB UL	10 mg
EC SCF	5 mg
UK EVM SUL, total	10 mg

Fluoride

High intakes of fluoride can have adverse effects on the kidneys and the immune, gastrointestinal, genitourinary and respiratory systems. All these effects occur at intakes higher than those that cause skeletal fluorosis and possibly increase bone fracture risk. Thus, none of these is the critical effect for identifying a UL. Instead, in agreement with the FNB, skeletal fluorosis is identified as the critical effect in the evaluation of fluoride safety for adults.

Assuming a daily intake of 1.5 L of drinking water, these data suggest that increased risk of fractures related to skeletal fluorosis and fluoride from drinking water might occur with intakes of 6 mg/day or more from this source. Thus, if the fluoride intake from foods and nonfluoridated water is approximately 1 mg/day, and the intake from fluoridated toothpaste is approximately 1 mg/day, the addition of these quantities to the 6 mg/day for high-fluoride water suggests that a total intake of 8 mg/day increases the risk of bone fracture in persons drinking water with low calcium concentrations, thereby representing the adult LOAEL. This contrasts with the adult NOAEL of 10 mg/day identified by the IOM. Because of the conservative assumptions made, a UF of 1.3 may be adequate to calculate a ULS from this 8 mg LOAEL. Thus, the calculated UL would be 6 mg. The UF of 1.3 for application to a conservative LOAEL of 8 mg seems reasonable in face of the NAS's identification of 10 mg as the NOAEL and their selection of a UF of 1.0 that leads to a calculated UL of 10 mg.

Children are more susceptible than adults to dental fluorosis because their dental enamel is immature, and therefore the ULS value does not apply to children. The US FNB has derived lower UL values for fluoride to protect against dental fluorosis in children.

IADSA safety value for fluoride	
ULS	Reviewed but not set

Comparison of safety values for fluoride	
FNB UL	10 mg
EC SCF	Planned but not published (April 2004)
UK EVM SUL	Not reviewed by EVM

Iodine

The NOAEL values for iodine are identified as 500 µg per day for supplements and 1,000 µg for total intakes. These values are based on the absence of adverse effects in healthy adults given 500 µg of supplement, although the experimental subjects consumed diets of unknown composition. The dietary intake almost certainly did not exceed 500 µg. The supplemental iodine NOAEL is justified as the ULS because adverse effects occur only at 1,700 µg or higher total intake and because dietary intakes almost certainly will not exceed 500 µg. The SCF applied an arbitrary and excessive uncertainty factor to derive a low UL.

IADSA safety value for iodine	
ULS	500 µg

Comparison of safety values for iodine	
FNB UL, total intake	1,100 µg
EC SCF, total intake	600 µg
UK EVM guidance level	500 µg supplemental, 930 µg total

Iron

A large amount of experience supports a NOAEL value for longer-term iron supplementation of 18 to 65 mg per day (with little data on intermediate values). Clinical trial data indicate a low frequency of mild gastrointestinal effects that are not pathological and are self-limiting due to consumer awareness. This frequency of mild effects represents a nuisance rather than a hazard, and 60 mg of iron qualifies as a supplemental NOAEL if the product label makes the consumer aware of the potential effects. The large database supporting this conclusion and the complete absence of similar effects at lower supplemental levels, at least when the iron is not taken on an empty stomach, make it reasonable to apply a UF of 1.0. Thus, the ULS for iron is 60 mg per day.

There is no credible evidence that high intake of iron is the sole cause, in healthy adults, of increased in risk of cardiovascular disease or cancer. If reliable evidence continues to accumulate and becomes accepted that dietary iron contributes to chronic disease in genetically normal adults, the ULS would need to be reevaluated. Persons with hemochromatosis or alcohol injured intestines may be subject to adverse effects of iron at intakes well tolerated by healthy adults. A low frequency of adverse gastrointestinal effects (constipation and irritation) may occur after administration of ferrous fumarate, a soluble iron salt, in amounts of 60 mg or more supplemental iron, but the effects are more of a nuisance than a hazard.

IADSA safety value for iron	
ULS	60 mg

Comparison of safety values for iron	
FNB UL, total intake	45 mg
EC SCF, total intake	Not reviewed (April 2004)
UK EVM guidance level, supplemental	17 mg

Manganese

Several types of data show that oral manganese intakes up to 10 mg per day do not cause adverse effects in adults. The epidemiological data related to manganese intakes from well water in certain locations in Greece do not provide any reliable estimate that contradicts this conclusion. The potentially great variability of manganese intake from food and water, as well as factors that may limit manganese absorption, make it difficult to set a ULS, that is, identify a maximum safe level for supplemental manganese. The variability in the manganese intakes from foods would argue for caution on supplemental amounts but the absence of clinical signs of adverse effects, in contrast to biochemical markers, up to intakes of 20 mg argues that great caution is not needed for supplemental amounts. Considering the low efficiency of manganese absorption and the absence of any credible reports of adverse effects, although supplements of 50 mg or more are commonly used in short-term applications, it seems reasonable to set a ULS for chronically used supplements at 10 mg/day. This assumes a mean intake from conventional foods to be 4.9 mg and higher intake likely to come from beverages with components that would limit manganese absorption (tea, which contains high levels of manganese, also contains tannins that inhibit absorption). For shorter-term use, amounts above the ULS may be safe.

IADSA safety value for manganese	
ULS	10 mg

Summary of safety values for Manganese	
FNB UL, total intake	11 mg
EC SCF, total intake	Reviewed but not set (inappropriate data)
UK EVM guidance level	4 mg (0.5 mg for older people) supplemental, 12.2 mg total

Molybdenum

Although abnormal plasma uric acid levels are associated with that intake, there is little corroboration of the finding and the clinical impact is not clear. Although the data are not sufficient for a confident identification of a LOAEL value, this risk assessment relies upon human rather than animal data . Considering the large amount of uncertainty but relatively small intakes from foods (109 µg in the USA), the Reference Dose calculation by EPA is sufficiently conservative, and 350 µg is identified as the ULS. This conclusion is more restrictive than would have been necessary if IADSA based its values on the higher values from animal research, as done by the FNB and SCF.

IADSA safety value for molybdenum	
ULS	350 µg

Comparisons of safety values for molybdenum	
FNB UL, total intakes	2,000 µg
EC SCF, total intakes	600 µg
UK EVM guidance level	230 µg for food, no guidance for supplements

Selenium

The exact forms of selenium consumed by the Chinese population in the epidemiological studies relied upon by the FNB, SCF and EVM are not known, but it seems likely that much of it would have been selenomethionine, as in the clinical trial by Clark and co-workers. Considering the variability of dietary intakes, a supplemental selenium NOAEL is identified from the clinical trial data. Based on the absence of adverse effects at this supplemental level, and on the substantial margin of safety it provides below levels associated with adverse effects, a UF of 1.0 is sufficient, and the ULS for selenium is 200 µg per day. Except with unusually high selenium intakes in seleniferous areas, the 200 µg ULS would provide an ample margin of safety.

When dietary selenium is 100 µg per day, the ULS identified by this direct method for selenium supplementation safety is exactly equivalent to the difference between the SCF UL and the dietary intake.

IADSA safety value for selenium	
ULS	200 µg per day

Comparison of safety values for Selenium	
FNB UL	400 µg
EC SCF	300 µg
UK EVM SUL	(200 µg supplements) 300 µg total

Zinc

There are no known adverse effects of supplemental zinc at intakes of 30 mg per day, and this level provides a substantial margin of safety below the levels associated with adverse effects, i.e., the LOAEL of at least 50 mg of supplemental zinc. Therefore, 30 mg per day is identified as the ULS. Assuming a dietary zinc intake of 10 mg, the ULS is exactly compatible to the 40 mg FNB UL for total intake. This value is only slightly above the 25 mg supplemental UL by the EVM.

IADSA safety value for zinc	
ULS	30 mg

Comparison of safety values for zinc	
FNB UL, total intake	40 mg
EC SCF	25 mg
UK EVM SUL, supplement	25 mg

Table: IADSA ULS and Values from US FNB, EC SCF, and UK EVM

Part 1. Vitamins

Vitamins	FNB UL (total intake except as specified)	SCF UL (total intake except as specified)	EVM SUL or Guidance Level (total intake or supplemental as specified in text)	Japan, 1999 (total intake)	IADSA ULS 2004 (supplemental intake only)
Vitamin A, µg	Total 3,000	3,000 (not post-menopausal women)	1,500 bone effects (GL[a])	1,500	[b]3,000 low food retinol, 1,500 high food retinol
Beta-carotene, mg	25, smokers	20, smokers	7 (SUL[a])	Not set	[c]25, non-smokers
Vitamin D, µg	50	50	25 (GL)	50	[d]60
Vitamin E, mg	1,000	300 (270 rounded up)	540 = 800 IU (SUL)	600	1,000 (based on data at 1,600 IU = 1,070 mg)
Vitamin K, mg	-	-	1 (GL)	30	[e]10
Vitamin C, mg	2,000	-	1,000 GL)	Not set	2,000
Vitamin B_1, mg	-	-	100 (GL)	Not set	100
Vitamin B_2, mg	-	-	40 (GL)	Not set	200
Vitamin B_6, mg	100	25	10 (SUL)	100	100
Folic acid, µg	1,000	1,000	1,000 (GL)	1,000	1,000
Vitamin B_{12}, µg	-	-	2,000 (GL)	Not set	3,000
Biotin, µg	-	-	900 (GL)	Not set	[f]2,500
Nicotinic acid, mg	[g]35	10	17 suppl. (GL)	30	[h]35 based on flushing, 500/250 SR
Nicotinamide, mg	[g]35	900	500 suppl. (GL)	Not set	1,500
Pantothenic acid, mg	-	-	200 suppl. (GL)	Not set	1,000

a. GL = Guidance Level, SUL = Safe Upper Limit
b. If the data on bone fragility become stronger and generally accepted, the safety evaluation of retinol will need to be based on these effects, and the supplement maximum might need to be less than 1,500 µg.
c. If certain behavioral and/or environmental factors are present, such as smoking and exposure to asbestos, the permissible level of beta-carotene supplementation would be much lower.
d. The 60 ug value is taken directly from the same clinical trial data that the FNB used to identify a NOAEL that was adjusted to a 50 µg UL by application of a 1.2 uncertainty factor. IADSA has confidence in 60 µg value because of newer data showing no adverse effect at 100 µg, which the SCF identified as a NOAEL, and adjusted those data to a 50 µg UL by application of a 2.0 uncertainty factor.
e. Based on the same clinical trial data at 10 mg identified by the EVM, but omitting the EVM's 10 uncertainty factor. A substantial history of safe clinical use at 30 mg justifies the confidence in 10 mg as the ULS. The FNB and SCF found no toxicological basis for any UL.
f. The 2,500 µg ULS is justified by the absence of adverse effects in a clinical trial at 9 mg, which was used by the EVM, along with an uncertainty factor of 10, to calculate a GL of 900 µg. The value of 2,500 µg was selected on the basis of safe clinical use and the absence of adverse effect at an intake of 9 mg. The FNB and SCF found no toxicological basis for any UL.
g. FNB set UL of 35 mg for total niacin (nicotinic acid plus nicotinamide).
h. IADSA characterizes the flushing effect as a nuisance and recommends appropriate labeling above 35 mg. IADSA identifies ULS values of 500 mg and 250 mg for conventional and time release formulations, respectively.

Part 2. Minerals

Minerals	FNB UL (total intake except as specified)	SCF UL (total intake except as specified)	EVM SUL or Guidance Level (total intake or supplemental as specified in text)	Japan, 1999 (total intake)	IADSA ULS 2004 (supplemental intake only)
Calcium, mg	2,500 total	2,500 total	1,500 suppl. (GL)	2,500	1,500 suppl.
Potassium, mg	-	-	3,700 suppl. w/ minor adverse effects (GL)	2,000	1,500 suppl. (3 x 500)
Phosphorus, mg	4,000	-	250 suppl. (GL)	4,000	1,500 suppl.
Magnesium, mg	350 free forms	250 free forms	400 suppl. (GL)	650-700	400 suppl.
Boron, mg	20	-	9.6 (SUL)	Not set	6.2
Chromium, µg	-	-	10,000 (not picolinate) (GL)	250	1,000 (any salt of Cr^{3+})
Copper, mg	10	5	10 (SUL)	9	[a]9
Fluoride, mg	10	-	Not set	Not set	Not set
Iodine, µg	1,100	600	940 total, 500 suppl. (GL)	3,000	500 suppl.
Iron, mg	45 (empty stomach)	-	17 (GL)	40	[b]60 (full stomach)
Manganese, mg	11	-	12.2 total, 4 suppl. (GL) (0.5 for older people)	10	[c]10
Molybdenum, µg	2,000	600	230 diet, 0 suppl. (GL)	250	350 suppl.
Selenium, µg	400 total	300 total	300 total, 200 suppl. (SUL)	250	200 suppl.
Zinc, mg	40 total	25	25 suppl. (SUL)	30	30 suppl.

a. Assuming intake from conventional foods is the median or mean, as specified in the section on this nutrient.
b. If certain genetic, physiological, or dietary factors are present to enhance iron uptake and retention, the ULS may need to be much lower.
c .Assuming intake from conventional foods is the median or mean, as specified in the section on this nutrient.

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