

## Executive Summary

Vitamins and minerals are essential for life and health, with supplements of these nutrients serving as helpful components of the total diet. To that end, supplemental intakes provide 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 such health benefits, several government institutions have developed—as part of a greater emphasis on health self-care—recommendations on tolerable upper intake levels for nutrients, in terms of both total dietary intake and supplementary amounts.

The U.S. Food and Nutrition Board (FNB) of the Institute of Medicine (IOM), a component of the National Academies; the European Commission Scientific Committee on Food (EC SCF); and the United Kingdom Expert Group on Vitamins and Minerals (UK EVM) have all 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 being considered by the governments of several countries as well as by the European Commission (EC) and the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU). The Codex guidelines would be recognized by the World Trade Organization (WTO) and would therefore have special implications for international trade.

Acting in a voluntary, self-regulatory capacity, the dietary supplement industry has taken leadership for many years in assessing the safety of vitamins and minerals used in supplements and in providing this information to all interested parties. These efforts have included the development and publication of *Essential Nutrients in Supplements*, by Derek Shrimpton, Ph.D., for the European Federation of Associations of Health Product Manufacturers (EHPM); *Vitamin and Mineral Safety*, by John Hathcock, Ph.D., for the Council for Responsible Nutrition (CRN); *Vitamins and Minerals—A Scientific Evaluation of the Safe Range of Intakes*, by Derek Shrimpton, Ph.D., for EHPM; *Risk Assessment of Vitamins and Minerals*, by the European Responsible Nutrition Alliance (ERNA); and *The Safety of Vitamins and Minerals: An Overview of the U.S. Institute of Medicine's Risk Assessment*, by ERNA.

## CRN Safety Methodology

Most approaches to safe upper levels are based on widely applicable risk assessment models similar to those used by FNB in its Dietary Reference Intakes documents, published from 1997 onward. The FNB method and reviews are a formalization and extension of the quantitative methods used earlier in risk assessment of other substances. Because of the systematic, comprehensive, and authoritative character of the FNB risk assessment method for nutrients, this

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approach has gathered widespread support and adoption by other organizations such as EC SCF and UK EVM, with some slight modifications. All current methodologies emphasize the concept of nutrient-appropriate quantitative risk assessment, but disparities in the selection and interpretation of available scientific literature on safety and the approach to handling uncertainty have led to differences, sometimes substantial, in the safety values for various nutrients as derived by FNB, EC SCF, and UK EVM. The safety evaluation method underlying this document utilizes the basic features from the methods of those organizations. CRN, however, emphasizes the direct evaluation of the safety of supplemental intakes of nutrients—rather than total intakes from all sources—wherever such data are available.

## **Nutrient-Appropriate Scientific Risk Assessment for Vitamins and Minerals**

The term “nutrient-appropriate,” when 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 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. Application of these factors leads to identification of “safety limits” that are below the recommended intakes of 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 (EPA) involve arbitrary uncertainty factors that calculate zinc safety limits below the Recommended Dietary Allowance (RDA) for some populations.

### **The UL method from FNB**

Because of its general validity and widespread acceptance, CRN’s safety evaluation approach closely resembles FNB’s Tolerable Upper Intake Level (UL) method and its adaptations by EC SCF and UK EVM. CRN’s approach additionally includes modifications that emphasize a preference for direct evaluation of supplement safety from data related to supplemental use of those nutrients, rather than total intake from all sources. Thus, **CRN has identified Upper Levels for Supplements (ULS), 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. Alternatively, 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 a UF appropriate to the conversion to a NOAEL. If the NOAEL or LOAEL are identified from animal data, appropriate UF are assigned to the extrapolation to UL values for humans.
- **Derive the UL:** Calculate the UL as follows:  $UL = NOAEL \div UF$  (or  $UL = LOAEL \div UF$ ).

### **EC SCF UL Values and EC Proposal for Setting Maximum Amounts of Vitamins and Minerals in Supplements**

The EC SCF has published UL values for several vitamins and minerals, using methodology similar to that developed by FNB. The EC's Food Supplements Directive requires the identification of maximum amounts for supplements, presumably through application of a *difference* method. 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 FNB.
- Consider intakes from other dietary sources.

## **Step 2**

When applying Step 1, also give “due account” to population reference intakes (presumably the RDA).

This proposal would seem 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. CRN suggests that the population reference intakes referred to in Step 2 could be used to assure that the risk assessment and identification of other intakes are not excessively conservative, thereby producing a UL and a supplement maximum below recommended intakes.

## **UK EVM Report—Risk Assessments**

The UK EVM report on vitamin and mineral safety is based on the UL method developed by FNB, but has assigned the term Safe Upper Level (SUL) to the values derived by this method. Although UK EVM applies the term SUL, these values use the same UL methodology developed by FNB and adopted by EC SCF. The UK EVM has stated that for most nutrients, the databases were not sufficient to set an SUL, and a Guidance Level (GL) was identified. Nonetheless, this GL was often derived and used for overall safety evaluation and discussion in the same manner as an SUL value. For a few nutrients, the UK EVM report takes an additional step toward risk management recommendations for supplements. A safety value based on supplemental intake effects could logically be used to identify maximum contents of products marketed and regulated as supplements. UK EVM assumes daily consumption throughout the adult lifetime (sixteen years to death), whereas FNB and EC SCF are not explicit on this issue. Additionally, the UK EVM approach includes identification of a presumably safe level for nutrients without any established *hazard*.

## **The CRN 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.

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 consequence, such as liver toxicity.

Levels for supplements that are expected to be safe can be identified by either of two related but different methods. The direct method, which is 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 ULS may be determined directly from those data. 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 does not require any additional consideration of amounts contributed by consumption of conventional foods. That is:

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

The expected intake of most nutrients from conventional foods does not invalidate this approach for two primary reasons: either (1) intakes are small in comparison with the UL or ULS (e.g., for vitamin B<sub>2</sub>), or (2) the evidence for the safety of supplemental amounts was developed under conditions in which the amount of the nutrient consumed from conventional foods was well known (e.g., in the case of selenium). These considerations are taken into account in each section on the specific nutrients.

**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 EC, may be used.

The *difference* method involves:

- Determination of the UL for total intake from all sources
- Identification of the usual intake from conventional foods (ICF) from appropriate food intake surveys and food composition tables, taking consumption of fortified foods into account, and
- Calculation of the ULS as a difference:  $ULS = UL - ICF$

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

**Option 3—Observed Safe Level:** For some nutrients that have no established hazard at high intakes, the toxic potential is so low that there is no credible evidence of adverse effects in widespread consumption or in clinical trials. 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)

### **Characteristics of CRN's Safety Methodology**

The CRN approach as described above occasionally differs and goes beyond both the FNB UL method and the EC proposal. For some nutrients, the CRN and UK EVM methods are the same; for others, CRN and UK EVM use different approaches. CRN's principal points of departure from all three of these approaches are shown below. The CRN method:

- gives preference to data on effects of *supplemental* intake, rather than total intake, thereby eliminating any need to correct for intake from conventional foods;
- gives stronger preference to use of human data rather than animal data, thereby avoiding the uncertainties involved in extrapolation between species;
- gives stronger preference to clinical trial data from human studies, if available, rather than other types of human data, including epidemiological data;
- gives stronger preference to identifying NOAEL values, rather than LOAEL values, thereby eliminating the uncertainty related to extrapolation from the LOAEL;
- considers only effects that represent a true hazard (i.e., risk of impaired health), rather than nuisance effects;
- preferentially uses direct evidence of adverse effects, if available, rather than biochemical markers or other indirect indicators;
- utilizes history of use data, if necessary, to identify an OSL and a ULS when adverse effects in humans have not been identified for a nutrient. This approach relies on previous human experience when consistent with the scientific evidence that for some nutrients includes an indication of a high order of safety;
- conservatively selects human NOAEL values that justify selection of an uncertainty factor of 1.0; and
- recognizes that supplement use is an independent choice for the consumer and does not impose increased intake on anyone who does not select it; this contrasts with food fortification programs that require the consumer to scrutinize labels in an effort to obtain or avoid increased intake of nutrients.

## **RDA-Based Upper Limits Are Not Scientific or Appropriate**

While the use of the RDA to set upper limits for vitamins and minerals in supplement products has been seen by some governments as convenient, RDA-based limits have no scientific validity. Risk assessment is the only scientifically valid approach toward identifying supplement maximums.

The imposition of drug regulations on products with amounts of nutrients higher than the RDA serves no health purpose, and may in fact preclude certain benefits. Also, drug regulations on supplements with nutrient amounts above the RDA are disproportionate in comparison with regulations on conventional foods, some of which also contain many multiples of the RDA of certain vitamins.

RDA values are set on a very similar basis from one country to another, as they represent the consensus of scientific opinion on the nutrient quantities necessary to assure the performance of recognized and essential physiological functions.

### **RDA-based limits and drug regulations for higher amounts are not appropriate for several important reasons:**

- The RDA is not defined or identified to describe safety or represent a safety limit for total or supplemental intake.
- 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 appropriate to identify an RDA in each case. Risk assessment can be used to identify appropriate safety limits for these important nutrients, whether or not an RDA has been set.
- 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 the following:
  - Folic acid, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> help control plasma homocysteine concentrations. Homocysteine is becoming accepted as a recognized risk factor for heart disease, and there is an ever-increasing body of scientific evidence to support this finding. Supplementation with these three vitamins definitely lowers plasma concentrations of homocysteine, and may reduce the risk of heart disease.

- Supplementation of 200 µg of selenium in addition to diets containing about 100 µg 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 good reason not to restrict selenium supplements to the current RDA.
- Supplementation of diets containing less than 40 µg chromium with an additional 200 to 400 µg helps maintain normal blood glucose levels and minimize the signs and symptoms of type II diabetes. Clinical trials have confirmed the safety of up to 1,000 µg of supplemental chromium.
- The imposition of RDA-based upper limits is a disproportionate restriction on supplement products, compared with the amounts found in conventional foods. Certain conventional foods contain many multiples of the RDA of some nutrients. For example, the natural amounts of vitamin B<sub>12</sub> in conventional foods such as liver and some shellfish can approach 100 µg per 100 g serving. The adult RDA for this vitamin is commonly set at approximately 2 to 2.5 µg. These ordinary, conventional foods, therefore, may contain upwards of 40 to 50 multiples of the RDA of vitamin B<sub>12</sub>. There is no known toxicity of oral vitamin B<sub>12</sub> in humans. This demonstrates that RDA-based UL are not rational, serve no useful purpose, and are a disproportionate response to any hypothetical safety concern about the vitamin.
- Labeling, not limits, can address proper usage by providing information on contents of packaging, by noting any benefits related to the RDA or any other measure of benefit, and by drawing attention to limits imposed on a safety basis, as identified by risk assessment.

## **Safety Summaries for Individual Vitamins and Minerals**

References are provided at the end of each chapter in the main text.

### **Fat-Soluble Vitamins**

#### **Summary of Vitamin A (as Retinol and Its Esters)**

CRN considers supplements of 3,000 µg (10,000 IU) of preformed retinol or its esters to be safe for most, but perhaps not all, consumers. For users of large amounts of fortified foods or foods naturally high in retinol, a ULS of 1,500 µg (5,000 IU) is appropriate. These values are identified on the following basis:

- The LOAEL for birth defects is at least 7,500 µg (25,000 IU) of retinol, and there are no credible data to suggest that it is likely to be lower than 6,510 µg (21,675 IU) of retinol.
- The FNB selected a retinol NOAEL of 4,500 µg (15,000 IU), but conservatively applied a UF of 1.5 to derive a 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 (3,330 IU).
- There is a long history of safe use of dietary supplements containing 1,500 µg, 2,400 µg, and 3,000 µg of retinol (5,000 IU, 8,000 IU, and 10,000 IU, respectively).
- The FNB NOAEL equivalent to 4,500 µg (15,000 IU) and the highest likely intake of 1,000 µg (3,330 IU) from sources other than supplements are compatible with ULS of 3,000 µg (10,000 IU).
- The possible effects of retinol on bone fragility are based on epidemiological evidence and remain speculative and unconfirmed.
- People with high dietary intakes of retinol—for example, those who regularly consume liver or other organ meats—should not consume supplements that contain preformed vitamin A, but may safely consume vitamin A activity as beta-carotene.
- A large number of companies are voluntarily decreasing the maximum amount of retinol in multivitamin products to 1,500 µg (5,000 IU) or less to avoid any potential concerns about bone fragility.
- 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 of less than 1,500 µg (5,000 IU) may need to be set.

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### **CRN supplement safety values for vitamin A (as retinol and its esters)**

ULS, Low users of retinol-rich foods	3,000 µg (10,000 IU)
ULS, High users of retinol-rich foods	1,500 µg (5,000 IU)

### **Comparison of safety values for vitamin A (as retinol and its esters)**

US FNB UL	3,000 µg
EC SCF UL	3,000 µg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	1,500 µg

## **Summary of Beta-carotene**

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

The only evidence of adverse effects of beta-carotene comes from the Alpha Tocopherol Beta Carotene (ATBC) and Carotene and Retinol Efficiency Trial (CARET) studies, which looked at long-term heavy smokers or asbestos workers. These data suggest a LOAEL of 20 mg per day for smokers or asbestos workers, but disparities between the ATBC and CARET results and other data prevent a confident identification of any LOAEL for beta-carotene. Smokers and asbestos workers should control those health risks.

### **CRN supplement safety value for beta-carotene**

ULS (OSL method)	25 mg for nonsmokers; no supplement for smokers
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### **Comparison of safety values for beta-carotene**

US FNB UL	Reviewed but not established; smokers should not use
EC SCF UL	Reviewed but not established; risk for smokers
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL, supplement	7 mg (LOAEL ÷ 3) smokers should not use

## **Summary of Vitamin D**

Recent data indicate that the NOAEL may be as high as 100 µg, making the LOAEL greater than 100 µg per day in relation to its hypercalcemic effects. Both FNB and UK EVM estimate vitamin D intake from all non-supplement sources to be in the range of 9 µg or less, whereas the majority of dietary supplements that include vitamin D contain 10 µg or less. There are no reports of adverse effects at this level of intake.

The CRN 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 a UF of 1.2. CRN considers the database for an intake of 100 µg to be highly supportive of a NOAEL at that level, but not yet replete enough to warrant setting the NOAEL that high. In any case, the data at 100 µg strongly reduce any uncertainty about the safety at a 60 µg intake. The EC 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.

With the confidence in the safety at the 60 µg intake level increased by the data related to 100 µg intake, CRN considers a UF of 1.0 to be appropriate. Thus, CRN sets its ULS at 60 µg, based on the 60 µg clinical trial data and the assumption that non-supplement intakes are not more than 9 µg.

### **CRN supplement safety value for vitamin D**

ULS	60 µg
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### **Comparison of safety values for vitamin D**

US FNB UL	50 µg
EC SCF UL	50 µg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	25 µg

## **Summary of Vitamin E**

To simplify safety consideration of different forms of vitamin E and to reach appropriately cautious conclusions, CRN recommends conversion of the international unit (IU) to mg α-tocopherol equivalents (α-TE). Because most clinical trials have been conducted with synthetic *dl*-α-tocopheryl acetate (that is, *all rac*-α-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. CRN identifies the OSL at 1,073 mg (1,600 IU) from clinical trial data that showed no adverse effects at this level of intake. Correspondingly, CRN considers this value

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as the ULS because of the very low level of uncertainty signified through the absence of adverse effects at the higher intake of 2,146 mg (3,200 IU). CRN recommends rounding off to 1,000 mg, which is the same value identified by FNB through extrapolation from animal data.

### **CRN supplement safety value for vitamin E**

ULS (OSL method)	1,000 mg (identified as 1,073 mg, but rounded off; 1600 IU)
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### **Comparison of safety values for vitamin E**

US FNB UL	1,000 mg
EC SCF UL	300 mg (rounded up from 270 mg)
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL, supplement	540 mg (800 IU)

## **Summary of Vitamin K**

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Vitamin K has an extremely low potential for toxicity, but the data are insufficient to establish just how low. The UK EVM decision to apply a UF of 10 seems unnecessarily cautious in view of the absence of reports of adverse effects at medically supervised intakes of 30 mg or more, although data to support that value are relatively sparse. Consequently, CRN identifies the ULS for vitamin K as 10 mg per day. This value is based on the same clinical data identified by UK EVM, but without the tenfold UF. Dietary intakes and intestinal biosynthesis are trivial in comparison with the ULS of 10 mg.

Because vitamin K interacts so strongly with certain anticoagulant drugs, the ULS does not apply to persons taking such medications.

### **CRN supplement safety value for vitamin K**

ULS (OSL method)	10 mg
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### **Comparison of safety values for vitamin K**

US FNB UL	Reviewed but not established (no toxicological basis)
EC SCF UL	Reviewed but not established (no toxicological basis)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	1 mg (1,000 µg) (10 mg ÷ 10)

## Water-Soluble Vitamins

### Summary of Vitamin C

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

The severe gastrointestinal distress that may accompany very high intakes of vitamin C, however, provides 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, CRN considers a UF of 1.5, as identified by FNB, to be ample. The FNB and UK EVM set their UL in relation to total intake per day, but neither consider in detail whether the UL could be higher if the intake were spread out over a day or whether it should be lower for a single dose. CRN identifies a ULS of 2,000 mg per day, but recommends limiting any single dose to 1,000 mg, to increase the certainty of avoiding undesirable gastrointestinal effects.

#### CRN supplement safety value for vitamin C

ULS	2,000 mg (1,000 mg per single dose—doses separated by four hours or more)
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#### Comparison of safety values for vitamin C

US FNB UL	2,000 mg
EFSA UL	Reviewed but not established (1,000 mg as guidance)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	1,000 mg

### Summary of Vitamin B<sub>1</sub> (Thiamin)

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CRN identifies an OSL of 100 mg supplemental thiamin hydrochloride per day. Thiamin products are commonly marketed at much higher levels, and available clinical trial data reinforce the suggestion that thiamin may be safe in dosages greater than 100 mg; but as the data are compelling at 100 mg, this value is selected as the OSL and, consequently, as the ULS.

#### CRN supplement safety value for vitamin B<sub>1</sub> (thiamin)

ULS (OSL method)	100 mg
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### **Comparison of safety values for vitamin B<sub>1</sub> (thiamin)**

US FNB UL	Reviewed but not established (no toxicological basis)
EC SCF UL	Reviewed but not established (no toxicological basis)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	100 mg (103 mg total)

### **Summary of Vitamin B<sub>2</sub> (Riboflavin)**

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CRN identifies, from clinical trial data, 400 mg per day of vitamin B<sub>2</sub> as a level that produces scattered side effects not consistent with any significant pattern. The minor effects reported with 400 mg supplemental intake suggest that the UK EVM UF of 10 is unnecessarily restrictive. Hence, CRN identifies a ULS from the 400 mg LOAEL and considers a UF of 2 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.

### **CRN supplement safety value for vitamin B<sub>2</sub> (riboflavin)**

ULS	200 mg
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### **Comparison of safety values for vitamin B<sub>2</sub> (riboflavin)**

US FNB UL	Reviewed but not established (no toxicological basis)
EC SCF UL	Reviewed but not established (no toxicological basis)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	40 mg (43 mg total)

### **Summary of Niacin (as Nicotinic Acid)**

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With its transient and non-pathological characteristics, the flushing reaction that occurs in response to supplemental nicotinic acid deserves to be characterized as a *nuisance*, but not a *hazard*. When high intake results from supplementation, appropriate product labeling can alert the consumer to 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 of less than 1,000 mg per day, and they contain many uncertainties about the accuracy of patient reports regarding the amount of nicotinic acid consumed, as well as 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 (McKenney et al. 1994) are more appropriate than these anecdotal cases for the identification of NOAEL and LOAEL values. From

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the McKenney data, a NOAEL of 500 mg per day and a LOAEL of 1,000 mg per day can be identified for liver or gastrointestinal effects. It should be noted, however, that most adverse reactions to 1,000 mg of unmodified nicotinic acid are gastrointestinal in nature, posing less potential for serious outcomes than the liver toxicity that results in some persons who consume 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; twofold decreases in the NOAEL and the 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.

CRN identifies the following values for nicotinic acid supplements:

**Immediate-release nicotinic acid formulations**

LOAEL, based on hepatotoxicity	1,000 mg
NOAEL, based on hepatotoxicity	500 mg
Flush label warning	greater than 35 mg

**Slow-release nicotinic acid formulations**

LOAEL	500 mg
NOAEL	250 mg
Flush label warning	None; not needed

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

**Immediate-release nicotinic acid supplements**

CRN ULS	500 mg, contingent upon proper label statements about flushing
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**Slow-release nicotinic acid supplements**

CRN ULS	250 mg
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### **Comparison of safety values for nicotinic acid**

CRN ULS, immediate-release	500 mg, based on liver effects
CRN ULS, slow-release	250 mg, based on liver effects
US FNB UL	35 mg*, based on flushing effects
EC SCF UL	10 mg, based on flushing effects
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	17 mg, based on flushing effects

### **Summary of Niacin (as Nicotinamide)**

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

### **CRN safety value for nicotinamide**

ULS	1,500 mg
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### **Comparison of safety values for nicotinamide**

US FNB UL, total intake	35 mg*
EC SCF UL, total intake	900 mg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	500 mg (560 mg total)

### **Summary of Vitamin B<sub>6</sub> (Pyridoxine)**

There is marginal evidence suggesting possible adverse effects at intakes of 200 mg, but not at 100 or 150 mg. Consequently, CRN identifies the human supplemental intake NOAEL for pyridoxine at 100 mg. The absence of adverse effects in most, but not all, studies at 200 mg intake, combined 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 therefore do not contribute significantly to safety concerns.

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

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The major uncertainties about the reliability of some data (Dalton and Dalton 1987) 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. Because of these significant uncertainties, the Dalton and Dalton data were not used by FNB as a basis of its risk assessment on pyridoxine. For the same reasons, CRN has also eliminated the Dalton and Dalton data from use in the evaluation of the safety of vitamin B<sub>6</sub>.

The complete absence of adverse effects in credible, well-designed studies at 100 and 150 mg leads to the conclusion that 100 mg of vitamin B<sub>6</sub>, with a very low level of uncertainty, produces no adverse effects over a period of several years. Intakes from conventional foods are almost always less than 4 mg per day, and as this level is minor compared with any maximum safe level, CRN is able to identify 100 mg as the ULS for pyridoxine. Somewhat higher amounts may be safe for most people.

#### **CRN supplement safety value for vitamin B<sub>6</sub> (pyridoxine)**

ULS	100 mg
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#### **Comparison of safety values for vitamin B<sub>6</sub> (pyridoxine)**

US FNB UL	100 mg
EC SCF UL, supplement	25 mg (based on Dalton and Dalton data)
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL, chronic supplement intake	10 mg (extrapolated from animal data)

### **Summary of Folic Acid**

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A folic acid supplement of 4 mg per day (4,000 µg) was used without adverse effect in a seven-nation trial that involved 1,817 women at thirty-three study centers. A committee advising FDA on folic acid and neural tube defects (NTD) concluded that adverse effects are unlikely with intakes of 1,000 µg (1 mg) or less. The evidence that this amount of folic acid, plus food folates, poses no identifiable risk is sufficient to identify 1,000 µg (1 mg) as the NOAEL. Most data suggest that the LOAEL might be 5,000 µg or higher.

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

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### **CRN supplement safety value for folic acid**

ULS	1,000 µg
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### **Comparison of safety values for folic acid**

US FNB UL	1,000 µg
EC SCF UL	1,000 µg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	1,000 µg

### **Summary of Vitamin B<sub>12</sub>**

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Extensive testing and clinical use of oral vitamin B<sub>12</sub> dosages of up to 1,000 µg in pernicious anemia patients suggest that high dosages of vitamin B<sub>12</sub> are safe for those persons. Vitamin B<sub>12</sub> has no observed 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 that amount as the OSL, and higher intakes may also be safe. The CRN ULS is therefore set as the OSL at 3,000 µg of supplemental vitamin B<sub>12</sub> per day.

### **CRN supplement safety value for vitamin B<sub>12</sub>**

ULS (OSL method)	3,000 µg
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### **Comparison of safety values for vitamin B<sub>12</sub>**

US FNB UL	Reviewed but not established (no toxicological basis)
EC SCF UL	Reviewed but not established (no toxicological basis)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	2,000 µg

### **Summary of Biotin**

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A properly defined UL cannot be set for biotin because of the absence of known adverse effects at any observed level of intake. An OSL, however, can be identified as the highest level of intake for which there are sufficient data to support a conclusion of safety. In the U.S., biotin supplements of up to 5 mg and 7.5 mg have been standard for several years. Such evidence (or lack thereof) in the presence of marketed products containing up to at least 7.5 mg of biotin, as well as the absence of 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.

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Based on both the absence of adverse effects at 9 mg of supplemental biotin (recognizing that the study size was small) and the absence of any reported adverse effect for biotin despite the prevalence of 5 mg products in the U.S., CRN identifies 2.5 mg (2,500 µg) as its ULS.

#### **CRN supplement safety value for biotin**

ULS (OSL method)	2,500 µg (2.5 mg)
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#### **Comparison of safety values for biotin**

US FNB UL	Reviewed but not established (no toxicological basis)
EC SCF UL	Reviewed but not established (no toxicological basis)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	900 µg

### **Summary of Pantothenic Acid**

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There are no reports of toxicity from oral administration on which a LOAEL value could be based. The clinical trial data identified by UK 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 given the absence of adverse effects at daily intakes as high as 10 g, and systematic clinical experience with oral intakes of up to 1,000 mg per day, a level of 1,000 mg per day is selected as the CRN ULS value.

#### **CRN supplement safety value for pantothenic acid**

ULS (OSL method)	1,000 mg
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#### **Comparison of safety values for pantothenic acid**

US FNB UL	Reviewed but not established (no toxicological basis)
EC SCF UL	Reviewed but not established (no toxicological basis)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	200 mg

## Minerals

### Summary of Calcium

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

#### CRN supplement safety value for calcium

ULS	1,500 mg
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#### Comparison of safety values for calcium

US FNB UL	2,500 mg
EC SCF UL	2,500 mg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	1,500 mg

### Summary of Phosphorus

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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, as well as by 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; likewise, no specific intake level qualifies as the NOAEL or OSL level. The very high NOAEL value identified by FNB is perhaps too hypothetical, and the very low NOAEL identified by UK EVM was based on a speculative, worst-case interpretation of a small number of reports. 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 equivalent to that for supplemental calcium is considered most appropriate.

#### CRN supplement safety value for phosphorus

ULS	1,500 mg
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### **Comparison of safety values for phosphorus**

US FNB UL	4,000 mg
EC SCF UL	Not reviewed (as of May 2004)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	250 mg supplement; 2,400 mg total

### **Summary of Magnesium**

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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 nature of the diarrhea found at lower levels does not justify selection of those levels as a LOAEL, but does allow selection of a UF of 1.0 for use in deriving a ULS. These mild diarrhea effects qualify as a nuisance rather than a hazard. Thus, the CRN 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.

### **CRN supplement safety value for magnesium**

ULS	400 mg
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### **Comparison of safety values for magnesium**

US FNB UL, nonfood sources	350 mg
EC SCF UL, nonfood sources	250 mg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	400 mg

### **Summary of Potassium**

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The clinical trial data on potassium chloride, together with the epidemiology supporting the safety of larger amounts of potassium from fruits and vegetables, indicate that this nutrient has a wide margin of safety. Collective clinical trials (in which potassium from foods was 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, which seem greater if such amounts are taken at once, especially on an empty stomach. The UK EVM established guidance indicating that 3,700 mg of potassium was safe. Considering clinical trial evidence and the apparent safety of potassium intakes as high as 8 to 11 g per day from fruits and vegetables, the CRN ULS for potassium is set at 1,500 mg per 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 FDA threshold of 100 mg of potassium for regulation of the products as drugs.

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### **CRN supplement safety value for potassium**

ULS	1,500 mg (no more than 500 mg per dose)
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### **Comparison of safety values for potassium**

US FNB UL	Reviewed but not established
EC SCF UL	Not reviewed (as of May 2004)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	3,700 mg, with minor adverse effects

## Trace Elements

### **Summary of Boron**

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A clinical trial with a supplemental intake level of 3 mg per day produced no adverse effects. Other studies confirm this observation, making this amount of boron worthy of consideration as an OSL for supplemental intake. (Intakes from conventional foods are almost always less than 3 mg per day.) All available toxicity data are derived from acute poisonings caused by ingestion of very large amounts of borate, or from experiments conducted on animals.

The FNB UL, UK EVM UL, and EPA RfD for boron apply to total intakes from all sources. In the face of these uncertainties, CRN believes that the ULS should be 6 mg per day, based on the adequately conservative UK EVM UL of 9.6 mg and the fact that food intakes rarely exceed 3 mg. A 6 mg ULS is further supported by the definite OSL character of 3 mg across several studies.

### **CRN supplement safety value for boron**

ULS	6 mg
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### **Comparison of safety values for boron**

US FNB UL	20 mg
EC SCF UL	Not reviewed (as of May 2004)
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL	9.6 mg

### **Summary of Chromium**

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The available clinical trial data are sufficient to indicate safety for chromium supplements at levels of up to 1,000 µg 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 used in foods or supplements. On the basis of

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the large number of clinical trials summarized in the FNB review and other official reviews of chromium evidence, the CRN ULS for chromium III is set at 1,000 µg per day, for all forms including the picolinate form. Highly oxidized chromium (chromium VI) is recognized as toxic and is not used in food or supplements.

### **CRN supplement safety value for chromium**

ULS 1,000 µg (any form of chromium III)

### **Comparison of safety values for chromium**

US FNB UL	Reviewed but not established (no toxicological basis)
EC SCF UL	Reviewed but not established (no toxicological basis)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	10 mg (10,000 µg), but not including the picolinate form

## **Summary of Copper**

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The NOAEL of 10 mg per day identified by FNB and EC SCF is derived from a clinical trial of supplemental copper in subjects with unspecified dietary copper intake. CRN agrees with this value as a supplemental copper NOAEL. Considering the absence of adverse effects at intakes in the range of 10 to 12 mg per day, and given that the usual amount of copper present in diets is less than 2 mg, CRN identifies 9 mg as the ULS for supplemental copper.

### **CRN supplement safety value for copper**

ULS 9 mg

### **Comparison of safety values for copper**

US FNB UL	10 mg
EC SCF UL	5 mg
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL	10 mg

## **Summary of Fluoride**

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High intakes of fluoride can have adverse effects on the kidneys and the immune, gastrointestinal, genitourinary, and respiratory systems. All of these effects occur at intakes higher than those causing skeletal fluorosis and possibly increasing bone fracture risk. Thus, none of these effects provides a critical basis for identifying a UL. Instead, CRN, in agreement with FNB, identifies skeletal fluorosis as the most significant effect in the evaluation of fluoride safety for adults.

Assuming a daily intake of 1.5 liters of fluoridated drinking water, an increased risk of fracture related to skeletal fluorosis might occur with intakes of 6 mg per day or more from this source. Thus, if the fluoride intake from foods and nonfluoridated water is approximately 1 mg per day, and the intake from fluoridated toothpaste is approximately 1 mg per day, the addition of these quantities to the 6 mg per day for high-fluoride water suggests that a total intake of 8 mg per day or more may increase the risk of bone fracture in persons whose drinking water contains low calcium concentrations. Eight mg per day thereby represents the adult LOAEL, which contrasts with an adult NOAEL of 10 mg per day identified by FNB. Because of the conservative assumptions made, a UF of 1.3 may be adequate to calculate CRN's UL of 6 mg from the 8 mg LOAEL. This UF seems reasonable in face of FNB's identification of 10 mg as the NOAEL and its selection of a UF of 1.0, leading to its calculated UL of 10 mg.

CRN identifies 6 mg as the UL but does not identify a ULS.

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

#### **CRN safety value for fluoride**

UL (not a ULS)	6 mg
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#### **Comparison of safety values for fluoride**

US FNB UL	10 mg
EC SCF UL	Not reviewed (as of May 2004)
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL	Not to be reviewed

### **Summary of Iodine**

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CRN identifies the NOAEL for iodine as 500 µg per day for supplements and 1,000 µg for total intake. These values are based on the absence of adverse effects in healthy adults given 500 µg of supplement; and although the subjects participating in the relevant experiments consumed diets of unknown composition, their 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 EC SCF applied an arbitrary and excessive uncertainty factor to derive a UL that CRN considers unjustifiably low.

#### **CRN supplement safety value for iodine**

ULS	500 µg
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### **Comparison of safety values for iodine**

US FNB UL	1,100 µg
EC SCF UL	600 µg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	500 µg supplement; 930 µg total

### **Summary of Iron**

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A large body of evidence supports a NOAEL value for long-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 CRN ULS for iron is 60 mg per day.

There is no credible evidence that high intake of iron is a significant cause, in healthy adults, of increased risk of cardiovascular disease or cancer. Persons with hemochromatosis or alcohol-injured intestines may be subject to adverse effects of iron at intakes comfortably tolerated by healthy adults. There is low frequency of adverse gastrointestinal effects (constipation and irritation) 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.

### **CRN supplement safety value for iron**

ULS	60 mg (full stomach)
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### **Comparison of safety values for iron**

US FNB UL	45 mg (empty stomach)
EC SCF UL	Not reviewed (as of May 2004)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	17 mg

### **Summary of Manganese**

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Several types of data show that oral manganese intakes of up to 10 mg per day do not cause adverse effects in adults, and the epidemiological data related to manganese intakes from well water in Greece do not provide any reliable estimate to contradict this conclusion. Unfortunately, the potentially great variability of

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manganese intake levels from food and water, in addition to factors that may limit manganese absorption, makes it difficult to set a ULS for supplemental manganese. The absence of clinical signs of adverse effects with intakes up to 20 mg combined with the low efficiency of manganese absorption permits establishment of a ULS for chronically used supplements at 10 mg per day. Considering the low efficiency of manganese absorption, it seems reasonable to set a ULS for chronically used supplements at 10 mg per day. For shorter-term use, larger amounts of manganese may be safe.

#### **CRN supplement safety value for manganese**

ULS	10 mg
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#### **Comparison of safety values for manganese**

US FNB UL	11 mg
EC SCF UL	Reviewed but not established (inadequate data)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	4 mg supplement; 12.2 mg total

### **Summary of Molybdenum**

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Although abnormal plasma uric acid levels are associated with high intakes of molybdenum, there is little corroboration of that finding, and the clinical impact is not clear. The available data are not sufficient for a confident identification of a LOAEL value; and while FNB and EC SCF have determined UL values using animal data, CRN prefers to rely upon human data. The CRN ULS is more restrictive than would have been necessary if CRN had based its conclusion on data used by FNB and EC SCF.

#### **CRN supplement safety value for molybdenum**

ULS	350 µg
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#### **Comparison of safety values for molybdenum**

US FNB UL	2,000 µg
EC SCF UL	600 µg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	230 µg for food, no guidance for supplements

## **Summary of Selenium**

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The FNB, EC SCF, and UK EVM rely largely on epidemiological studies of the Chinese population to formulate their safety levels for selenium. The exact forms of selenium consumed in those studies are not known, but it seems likely that the predominant form would have been selenomethionine, as was the case in the clinical trial conducted by Clark and coworkers. Considering the variability of dietary intake, CRN's supplemental selenium NOAEL is derived from this latter clinical intervention trial. No adverse effects are found at the supplemental level of 200 µg, and a substantial margin of safety is found below levels associated with adverse effects, making a UF of 1.0 sufficient to establish a CRN ULS for selenium at 200 µg per day. Unusually high selenium intakes in seleniferous areas may require different standards.

When dietary selenium is 100 µg per day, the CRN ULS of 200 µg identified by the direct method for the safety of selenium supplementation is exactly equivalent to the difference between the EC SCF UL and this dietary intake.

### **CRN supplement safety value for selenium**

ULS	200 µg
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### **Comparison of safety values for selenium**

US FNB UL	400 µg
EC SCF UL	300 µg
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL	350 µg supplement; 450 µg total

## **Summary of Zinc**

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

### **CRN supplement safety value for zinc**

ULS	30 mg
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### **Comparison of safety values for zinc**

US FNB UL	40 mg
EC SCF UL	25 mg
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL, supplement	25 mg

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## CRN Upper Levels for Supplements (ULS) Compared with FNB UL Values<sup>1</sup>

Nutrient	CRN ULS <sup>2</sup> 2004	FNB UL <sup>3</sup>
Vitamin A (retinol and its esters)	3,000 µg <sup>4</sup> (10,000 IU) 1,500 µg <sup>5</sup> (5,000 IU)	3,000 µg
Beta-carotene	25 mg nonsmokers (Smokers should not use.)	Not established. (Smokers should not use.)
Vitamin D	60 µg (2,400 IU)	50 µg
Vitamin E	1,000 mg (1,600 IU)	1,000 mg
Vitamin K	10 mg	Not established
Vitamin C	2,000 mg	2,000 mg
Vitamin B <sub>1</sub>	100 mg	Not established
Vitamin B <sub>2</sub>	200 mg	Not established
Nicotinic acid	500 mg <sup>6</sup> and 250 mg SR <sup>7</sup>	35 mg <sup>8,9</sup>
Nicotinamide	1,500 mg	35 mg <sup>8</sup>
Vitamin B <sub>6</sub>	100 mg	100 mg
Folic acid	1,000 µg	1,000 µg
Vitamin B <sub>12</sub>	3,000 µg	Not established
Biotin	2,500 µg	Not established
Pantothenic acid	1,000 mg	Not established
Calcium	1,500 mg	2,500 mg
Phosphorus	1,500 mg	4,000 mg
Magnesium	400 mg	350 mg (nonfood sources)
Potassium	1,500 mg (3 x 500)	Not established
Boron	6 mg	20 mg
Chromium	1,000 µg (any form of Cr III)	Not established
Copper	9 mg	10 mg
Fluoride	No ULS (UL= 6 mg)	10 mg
Iodine	500 µg	1,100 µg
Iron	60 mg (full stomach)	45 mg (empty stomach)
Manganese	10 mg	11 mg
Molybdenum	350 µg	2,000 µg
Selenium	200 µg	400 µg
Zinc	30 mg	40 mg

<sup>1</sup>See Appendix for Table of Comparison of CRN ULS, USFNB UL, EC SCF UL, UK EVM SUL or GL, and Japan UL

<sup>2</sup>ULS = CRN's Upper Level for Supplements (specific for supplements)

<sup>3</sup>UL = Tolerable Upper Intake Level (applies to total intake unless specified otherwise)

<sup>4</sup>Retinol ULS for persons with average levels of dietary retinol

<sup>5</sup>Retinol ULS for persons consuming liver or foods fortified with retinol

<sup>6</sup>Based on liver and gastrointestinal toxicity

<sup>7</sup>SR = slow-release (time-release) formulations of nicotinic acid

<sup>8</sup>UL for niacin applies to both nicotinic acid and nicotinamide

<sup>9</sup>Based on vasodilative flushing reaction