

Part 1: Introduction

Objective

To identify the highest chronic daily supplemental intakes of vitamins and minerals that can be confidently asserted to pose no risk of adverse effects for nearly everyone in the healthy adult population.

Background

Consumers are taking increasing personal responsibility for their health, particularly in the areas of protection and maintenance. This trend is associated with increased use of dietary supplements, including those containing vitamins and minerals at levels above 100 percent of their Daily Values (which are based on Reference Dietary Intakes, or RDI, for vitamins and minerals). Vitamin and mineral supplements as well as fortified foods are commonly intended to decrease the risk of specific chronic diseases, but the levels at which such products are being consumed make careful evaluation of the scientific evidence related to safety issues crucial.

The U.S. Food and Nutrition Board (FNB) of the Institute of Medicine (IOM), part of the National Academies; the Codex Alimentarius Commission, created by the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO); the European Commission (EC), an institution of the European Union; and several individual countries, including Argentina, China, Japan, and the United Kingdom (UK), have developed or are considering regulatory policies to place maximum limits on vitamins and minerals in supplements and/or fortified foods. Various schemes are being considered for the identification of maximum limits. Some countries establish limits on the basis of simple, low multiples of the Recommended Dietary Allowance (RDA), whereas others base limits on safety considerations evaluated by risk assessment. The FNB has described the Tolerable Upper Intake Level (UL) method and has, with a few exceptions, applied it to *total* intake of micronutrients. The FNB addresses *supplemental* intake of only a few nutrients. The EC has adopted, but has not implemented, an approach that identifies the supplement maximum as the difference between the UL and the expected intake from conventional foods.

A safe upper intake level for every vitamin and mineral can be identified using a direct scientific evaluation of supplement safety data or, when necessary, from data related to total intake from all sources. The approach used in this document is a modification of those approaches employed by the Council for Responsible Nutrition (CRN) in its original 1997 edition of *Vitamin and Mineral Safety*, by FNB, beginning in 1997; and more recently by the European Commission Scientific Committee on Food (EC SCF), and the United Kingdom Expert Group on Vitamins and Minerals (UK EVM). The largest difference is that CRN now

emphasizes the direct evaluation of the safety of supplemental intake of nutrients from human supplemental intake data, where available.

This publication will demonstrate that:

- The safety of each vitamin and mineral is best determined by nutrient-appropriate risk assessment.
- The safety of vitamins and minerals in dietary supplements is best evaluated from data on supplemental uses of the nutrients, where such data are available, but can, when necessary, be evaluated indirectly from data related to total intake.
- Limits not based on safety (i.e., limits based on RDA or unnecessarily restrictive risk assessment) could restrict intake of several nutrients to levels below those that may reduce the risk of certain chronic diseases.

This introduction will describe the FNB UL method in some detail before outlining the CRN method and then comparing and contrasting the two. The EC's indirect method (the difference between the UL for total intake and the expected intake from conventional food) will also be compared with the CRN direct method. A *difference* method similar to that proposed by the EC, but utilizing CRN or FNB values, will be adopted by CRN when the data for a direct approach are not adequate. The similarities and differences in outcome when CRN, FNB, EC SCF, and UK EVM methods are applied will be described in each of the sections on specific nutrients.

Scientific Approach to Safety Evaluation

A safe intake of any substance is one that provides an adequate margin below the levels at which recognizable adverse effects occur (Hathcock 1993, 1996, 1997); therefore, the term "safety limit" may be defined as the largest intake providing an adequate margin of safety below the levels that carry a risk of adverse effects (Hathcock 1996, 1997).

The data used in these evaluations are never sufficient to ensure identification of a biological limit (theoretical maximum value) of the safe range of intake. Instead, the data are sufficient to give confidence that specific levels of intake are without adverse effects. These are identified as No Observed Adverse Effect Levels (NOAEL). When a NOAEL is identified with conservative procedures, uncertainty is reduced to a minimum, and no additional correction for uncertainty is needed. In other words, an implicit uncertainty factor (UF) of 1.0 is justified.

For some nutrients, the data are sufficient to indicate that certain levels of some nutrients can produce adverse effects, allowing possible identification of a Lowest Observed Adverse Effect Level (LOAEL).

For other nutrients, the toxic potential is so low that there is no evidence of adverse effects at any observed level of intake. In such cases, the maximum level with credible evidence of safety will be identified as an Observed Safe Level (OSL). For example, vitamin B₂ has no record of toxic effects at any dose, by any route of administration. Thus, no LOAEL can be identified, and no NOAEL, with its usual meaning of avoiding effects seen at higher levels, can be identified. The first edition of this document, *Vitamin and Mineral Safety*, did not distinguish between a NOAEL for nutrients that had LOAEL values and those that had no LOAEL. In this updated edition, an OSL rather than a NOAEL will be used for those nutrients without established adverse effects.

Definitions for intake-level values

- **LOAEL:** Lowest Observed Adverse Effect Level. This is the lowest level at which observed adverse effects can be credibly and confidently ascribed to the nutrient.
- **NOAEL:** No Observed Adverse Effect Level. For nutrients that show observed adverse effects and that have been assigned a LOAEL, this is the level at which the data can confidently indicate an absence of the adverse effects seen at higher levels.
- **OSL:** the highest Observed Safe Level of intake. This applies to nutrients without known adverse effects and for which there are sufficient scientific data or history of use to assert, with ample credibility, a safe level of intake. The OSL does not describe a “safety limit” but is instead the highest level for which there is adequate evidence of safety.

RDA-Based Limits: A Scientifically Invalid and Inappropriate Approach to Safety

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 for such a purpose. Risk assessment is the only scientifically valid approach to 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 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 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 to 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, or for many other important substances with nutritive value. These substances have beneficial effects, but the available evidence has not been judged appropriate to identify RDA. 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 B₆, and vitamin B₁₂ 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 such a finding. Supplementation with these three vitamins definitely helps to control plasma concentrations of homocysteine and may reduce the risk of heart disease.
 - Supplementation of 200 µg of selenium to diets already 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 no reason to restrict selenium supplements to the RDA.
 - Supplementation of diets containing less than 40 µg chromium with 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 B₁₂ 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, then, may contain upwards of 40 to 50 multiples of the RDA of vitamin B₁₂. There is no known toxicity of oral vitamin B₁₂ in humans. This demonstrates that RDA-based upper limits are not rational, serve no useful purpose, and are a disproportionate response to any hypothetical safety concern about the vitamin.

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- 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.

Food and Nutrition Board UL Method

The UL is defined as “the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population” (Food and Nutrition Board 1998). The UL method provides a quantitative risk assessment, and therefore shares many characteristics with quantitative toxicological methods that are used to determine safe exposures to other substances. The UL method is a general risk assessment method, originally developed to characterize the likelihood of harm resulting from agents in the environment, but adapted by FNB for application to nutrients and food components.

Comparison of the UL Method with Other Risk Assessment Methods

The process of establishing an Acceptable Daily Intake (ADI) is an older, related method that is not appropriate for nutrients but is widely used for food additives by the U.S. Food and Drug Administration (FDA) and for many food components by the WHO and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The U.S. Environmental Protection Agency (EPA) for pesticides and environmental contaminants uses the Reference Dose (RfD) in determining safety levels.

Like the ADI and RfD methods, the UL method defines safety as the absence of harm. All three identify intakes that are the highest observed to cause no harm (NOAEL) or the lowest shown to cause adverse effects (LOAEL), with needed adjustments made in relation to the uncertainties involved.

The UL differs from the ADI and the RfD in how these uncertainties are handled. The UL incorporates a UF that is fully derived from the specific database for each nutrient. The ADI method, which often uses animal data to calculate safe intakes of food additives and contaminants for humans, most often relies upon a UF that is a multiple of 10, such as 10, 100, or 1,000. The RfD method also uses default values for the composite UF; it considers five types of uncertainty and assigns a numerical value of 10, 3, or 1 to each, depending on the level of uncertainty on that issue within the database. The result is a final, composite UF used in the RfD method that can range from 1 to 100,000. A significant problem and limitation of the RfD method is that there are no uncertainty factor values between 1 and 3 or between 3 and 10.

When applied to vitamins and minerals, the ADI can result in values for some nutrients that are well below the RDA for certain age and gender groups. The RfD, which is calculated on a body weight basis and involves default values for uncertainty, produces values that are inappropriately near the RDA for some nutrients. An example of this is zinc, for specific age gender groups. The UL method was developed to avoid these illogical outcomes.

UL Method—Basic Steps

The UL method is an example of nutrient-appropriate scientific risk assessment in that the UF selected are fully derived from the database for each nutrient. This method avoids arbitrary default values such as the multiples of 10 and 3 that are common in most risk assessment methods applied to food additives, pesticides, and environmental contaminants.

The UL method includes the following major steps:

1. *Hazard identification*—the evaluation of all pertinent information relative to the substance's potential to cause harm in humans. This step identifies the nature of the adverse effect, including its persistence and severity.
2. *Dose-response assessment*—a quantitative evaluation of the relationship between the nutrient and any adverse effects that result from excessive intakes. The NOAEL or the LOAEL are identified along with any attendant uncertainties.
3. *Derivation of the UL*—a simple arithmetic operation: $UL = NOAEL \div UF$ (or $UL = LOAEL \div UF$).

Step 1. Hazard Identification

The judgment to characterize or not characterize an effect as adverse is complex. A finding of *no adverse effect* is not equivalent to a finding of *no effect*. Changes in some enzyme activities or concentrations of certain important metabolites may not be adverse. Judgment based on evidence about the health consequences of a particular change must be used in determining whether the change should be considered adverse—that is, whether it constitutes a *hazard*. Certainly, not all adverse effects give equal cause for concern. Severe and/or permanent effects warrant greater concern than those of a transient or mild nature.

The process of hazard identification includes:

1. Summary of the evidence for adverse effects in humans, considering all types of studies but giving preference to data derived from human study.
2. Assessment of all types of data, including epidemiological data and adverse event reports (AERs), using the appropriate criteria for causality

(Food and Nutrition Board 1998) as incorporated into the UL method.
These criteria include:

- a. Strength of association
 - b. Consistency of association
 - c. Specificity of association
 - d. Dose-response relationship
 - e. Temporally correct relationship
 - f. Biological plausibility
 - g. Coherence
3. Judgment of the relevance of experimental data from controlled administration of the nutrient and appropriate measurements of the effects, where causality is easier to establish.
 4. Consideration of the mechanisms of toxic action.
 5. Assessment of the quality and completeness of the data set.
 6. Identification of distinct and highly sensitive subpopulations.

Step 2. Dose-Response Assessment

Data Selection

Selection of the most pertinent data includes the following considerations:

- Human data are preferable to other types.
- If animal data must be used, preference is given, if available, to that data derived from the species most like humans.
- If data from the most appropriate species are not available, data from the most sensitive species should be selected.
- Oral intake data are preferable.
- An acceptable data set must define a dose-response relationship, with adjustments made for bioavailability as needed.
- The data set documents the route and duration of exposure.

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- A preferable data set includes intakes that do not produce adverse effects (the NOAEL).

Identification of the NOAEL (or LOAEL) and Critical Endpoint

If the nutrient produces multiple adverse effects, the endpoint selected should be the one with the lowest NOAEL or LOAEL that genuinely qualifies as a hazard, occurring with significant severity and persistence. In calculation of the UL, the NOAEL is preferable to the LOAEL. If neither a NOAEL nor a LOAEL can be identified from the available evidence, strict application of the UL risk assessment model leads to the decision not to identify a UL, as exemplified by several decisions of FNB and EC SCF.

Uncertainty Assessment

Several types of uncertainty are considered in selection of the overall UF to be used in calculation of the UL. These include:

- Extrapolation from animals to humans
- Extrapolation from short-term to long-term exposures
- Scaling from higher to lower dose exposures
- Extrapolation from LOAEL to NOAEL
- Inherent variability in response
- Uncertainty in measurement of the effect

Characterization of the Estimate and Special Considerations

Certain subpopulations may be more sensitive to a specific nutrient than would be predicted from the variability of the response in the general population. This greater sensitivity may be based on body size or age (as in cases of children, infants, and the elderly), special physiological conditions (pregnancy, for example), genetics, or disease (such as compromised liver or kidney function). Increased sensitivity based on genetic differences cannot always be used to establish a UL. For example, a copper intake low enough to protect those with Wilson's disease would be deficient for the general population.

Step 3. Derivation of the UL

Once the NOAEL has been identified and uncertainty evaluated, the uncertainty is assigned a numerical value (the UF). The degree of uncertainty tolerated is increased if the adverse effect has low severity or persistence.

Finally, the UL is calculated as: $UL = NOAEL \div UF$.

The UL represents an intake that is expected to be safe for nearly everyone in the general population. Because the UL is derived from a NOAEL and a UF (or a LOAEL and a larger UF), it does not represent a threshold for toxicity. The UL is set to identify a highest intake that can be asserted to be safe for most of the healthy population, and it provides a margin of safety below the intakes at which adverse effects are expected. Thus, intakes somewhat above the UL would not be expected to be unsafe for most people.

European Commission Maximum Levels in Food Supplements

The EC has adopted a directive that implies that maximum levels of vitamins and minerals in food [dietary] supplements should be set by a *difference* method, as follows:

1. Maximum amounts of vitamins and minerals present in food supplement per daily portion of consumption as recommended by the manufacturer shall be set, taking the following into account.
 - (a) Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups;
 - (b) Intake of vitamins and minerals from other dietary sources.
2. When the maximum levels referred to in paragraph 1 are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

Paragraph 1(a) describes the UL risk assessment process adopted by EC SCF (Scientific Committee on Food 2001). This UL method is equivalent in concept, criteria, and procedure to that of FNB, although some differences in selection of data have led to distinct differences in the UL identified for some nutrients, such as vitamin B₆. Paragraph 1(b) requires consideration of the intake from other dietary sources, which is logical when the UL applies to total intake from all sources.

Although not characterized as such by EC, these steps logically constitute a *difference* method for setting maximums for vitamins and minerals in supplements. The method may be captured by the following equation:

MA = UL – IDS

where: **MA** is the maximum amount permitted in supplements,

UL is the number established by scientific risk assessment for a safe total intake from all sources, and

IDS is the intake from dietary sources.

Paragraph 2 of the EC directive permits giving “due account” to reference intakes (possibly the RDA, but possibly values estimated to reduce the risk of chronic disease), but only when setting maximums through the risk assessment method described in Paragraph 1. No description is provided for the process of taking “due account” of the reference intakes.

Whatever the original intent was for the meaning of taking “due account” of the population reference intakes when setting maximums based on risk assessment, the lack of an overt, specific definition or description may allow attempts to impose RDA-based limits. The only logical and science-based way to give due account to reference intakes in identification of maximums is to use them as a “floor.” That is, the reference intakes could be used to make certain that the risk assessment is not unnecessarily restrictive, but RDA-based limits cannot be the overt, predetermined objective of the risk assessment, or else it is not a risk assessment.

The risk assessment must, as specified in Paragraph 1(a) of the EC directive, be based on generally accepted scientific data and procedures. Meeting that requirement would dictate that giving due account to the reference intakes *cannot* be used as subterfuge to set RDA-based maximums. If the concept of scientific risk assessment is abused by using vague wording in the directive as a “back door” approach to RDA-based limits, such limits will not pass the test of being based on generally accepted scientific procedures.

For nutrients such as vitamin B₆, that have a large margin of safety between the reference intake and adverse levels, the intake from dietary sources is small in comparison with the UL. Any supplement maximum set through EC’s procedure would be far above the current reference intake. Thus, giving due account to the reference intake should not impose any restriction on the maximum. For certain nutrients, this might not be true. If the margin of safety between the reference intake and the NOAEL is relatively small, and if the intake from dietary sources is relatively high, the supplement maximum identified might be near or even below the RDA. Possible examples might include selenium or vitamin A (as retinol or retinyl esters) in populations with high intakes of these nutrients from dietary sources.

UK Expert Group on Vitamins and Minerals

The UK EVM has adopted (Expert Group on Vitamins and Minerals 2003) a UL method very similar to that developed by FNB and adopted by EC SCF. The UK EVM approach differs in two major ways from the methods of FNB and EC SCF:

1. The UK EVM has set speculative, and generally quite restrictive, “guidance levels” (GL) for nutrients showing no clear evidence of toxicity. The FNB and EC SCF, by contrast, do not set UL values in such situations. The UK EVM does not clearly indicate any difference in the application of the UL value and the GL in establishing policy or regulations.
2. The UK EVM uses either direct or indirect methods to identify Safe Upper Level (SUL) or GL values for supplemental intake of nutrients, whereas the FNB and EC SCF have generally identified UL for total intake from all sources. The EC food supplements directive outlines a *difference* method for identifying maximum amounts of vitamins and minerals in supplement products from the UL for total intake. The EC has not indicated whether or how it will set product maximums when no UL was established by EC SCF.

CRN’s Safety Approach

Methods for Upper Supplement Levels

Option 1: Direct Supplemental Data Method If appropriate clinical data on *supplemental* intake of a specific vitamin or mineral are available, an upper level that can confidently be characterized as safe is identified as an Upper Level for Supplements (ULS). This finding, which represents a conservatively selected NOAEL, is determined directly from the relevant data on supplements, with no correction for regular dietary intake. In situations where no toxicologically relevant data are available—despite extensive clinical research and clinical databases (as is the case with vitamin B₁₂)—the ULS may be set as equivalent to the OSL. This means that the upper safe level for supplementation is the highest intake for which there is a reliable database that supports safety.

Rationale: With this direct method of identifying a ULS, there is no need to correct for dietary consideration because the data being used are sufficient, sound, and directly related to supplemental intake. For example, the CRN supplement-use NOAEL of 200 µg selenium (Hathcock 1997) was determined from a well-designed and conducted randomized, double-blind, placebo-controlled clinical trial (Clark et al. 1996). The study, which lasted seven to ten years for each subject, involved a sufficient cohort (more than 1,300 persons) and multiple objective endpoints that were appropriate to determine a lack of adverse effects with a high level of confidence. The data obtained supported a confident

conclusion that 200 µg was a safe level for *supplemental* selenium intake. Therefore, using the direct supplemental data method, CRN identified a selenium ULS of 200 µg. The dietary selenium intake was approximately 100 µg per day, resulting in a total intake of approximately 300 µg per day.

In contrast, FNB used Chinese epidemiological data to identify a selenium NOAEL of 800 µg, and assigned a UF of 2 to calculate that selenium is safe at a *total* intake level of 400 µg (Food and Nutrition Board 2000). The EC SCF evaluated the same epidemiological data, concluded that the NOAEL is 900 µg, and assigned a UF of 3 to calculate a safe total selenium intake of 300 µg (Scientific Committee on Food 2000). With both the FNB and the EC SCF UL values, determination of an upper level for supplemental intake of selenium must take into account the usual intake from conventional foods. This approach, described in Option 2, depends on the food intake and composition values selected for the calculation. With the 100 µg dietary intakes in the clinical trial mentioned above, the direct method and the *difference* method using the EC SCF UL give the same 200 µg ULS. Use of the FNB UL of 400 µg gives an even higher ULS of 300 µg. Selection of survey values for dietary intake brings in additional uncertainties. With fewer uncertainties included, Option 1 will provide a higher level of confidence than Option 2.

Comparison of the 200 µg direct-method ULS with a ULS calculated from either the FNB UL or the EC SCF UL shows the appropriateness and conservative nature of this direct ULS approach used by CRN.

Option 2: Difference Method If adverse effects are established at some level of total intake and a UL can be identified for total intake, but no appropriate safety data related to *supplemental intake* are available, a three-step procedure similar to that of EC may be used to establish a ULS by difference, as follows:

- 1) Determine the UL for total intake from all sources,
- 2) Identify the usual intake from dietary sources (IDS) from appropriate food intake surveys and standard food composition tables, taking consumption of fortified foods into account, and,
- 3) Calculate the ULS as the difference; that is, $UL - IDS = ULS$.

Rationale: If appropriate evidence of adverse effects and data related to supplemental use at a high intake level are not available, the ULS cannot be identified through Option 1 and therefore must be determined indirectly. The ULS can be calculated as the difference between the UL (which by definition usually applies to total intake from all sources) and the common intake of the nutrient from dietary sources.

The EC's Food Supplements Directive outlines such an approach, but details have not been provided (European Commission 2002). The UL values published by FNB and EC SCF provide the starting point for Option 2, but intake survey and food composition data must be selected to allow completion of this indirect method. The selection of the food intake and composition data brings additional uncertainties. Because dietary patterns vary so much between nations and regions, calculations of usual nutrient intake should be done nationally or regionally. UL values are designed (as are RDA values) to apply to almost all healthy adults. Thus in Option 2 the median or mean nutrient IDS values are the most appropriate for use in calculation of the ULS from the UL when the *difference* method is the only recourse.

Option 3: ULS as the Observed Safe Level If a significant scientific database identifies no basis for a NOAEL or a LOAEL, a ULS cannot be identified by the UL risk assessment procedures. Some nutrients have been subjected to extensive testing and use at high levels without evidence of adverse effects. For such nutrients, there is no apparent basis for a LOAEL or a NOAEL, but an OSL may be identified and used in a similar manner—as the highest supplemental intake that has been shown to be safe. The OSL may be used to establish the ULS, recognizing that higher levels have not been shown to cause harm. For this reason, the NOAEL and OSL values are identified separately, and used as the basis of the CRN ULS when Option 1 is not supported by the available data. Notably, UK EVM has utilized this approach, albeit without the OSL name, for certain nutrients, e.g., vitamin B₁₂.

Rationale: For some nutrients, including vitamins B₁, B₂ and B₁₂, there are significant experimental, clinical, and practical-use databases that show no credible evidence of adverse effects within the wide range of intakes with which one has experience. For these nutrients, FNB declined to set UL values. If extensive human and animal data have not revealed any effect that warrants the descriptor “hazard,” a LOAEL is impossible, and a conventional NOAEL does not apply.

Comparison of CRN ULS with FNB UL, EC UL, and UK EVM SUL and GL

The CRN method conservatively selects human NOAEL values for vitamins and minerals, characterizing these as ULS values without formal correction for uncertainty. The CRN data selection is sufficiently conservative to warrant use of a UF of 1.0 in the usual UL method. Thus, the CRN human NOAEL is equivalent to using the UL method with conservative data selection to justify a UF of 1.0 in each case.

Advantages of the CRN Method

The direct human NOAEL and OSL approaches used by FNB, EC SCF, and UK EVM differ from CRN's UL method in some ways. Specifically, the CRN method:

- Gives stronger preference to evidence related to supplemental intake, rather than total intake (e.g., for selenium)
- Gives stronger preference to identifying human NOAEL values, rather than LOAEL values (e.g., for folic acid)
- Considers only effects that represent a true hazard—risk of impaired health—rather than nuisance effects (e.g., the skin-flushing effect of niacin)
- Gives stronger preference to clinical trial data from human studies, if available, rather than other types (e.g., for vitamin E)
- Uses only direct evidence of adverse effects, if available, rather than biochemical or other indirect indicators or markers (e.g., for calcium)
- Conservatively selects human NOAEL values that justify not using any additional correction for uncertainty by use of a UF greater than 1.0
- Selects an OSL value where there is substantial evidence to support safety, and no data that establish adverse effects of relevance to oral intake by humans

Contribution of Conventional Foods

The contribution that conventional foods might make toward the UL or ULS level of intake varies from one nutrient to another, as follows:

- For nutrients of very low or no known toxic potential, such as vitamin B₁₂, no UL can be set. In these cases, the contribution of conventional foods is not significant in comparison to the highest levels known to be safe (the OSL).
- For some nutrients with potential toxicity, such as vitamin B₆, the margin of safety is large compared with the RDA, and the contribution of conventional foods toward the UL value is small. In the U.S., where many foods are fortified, the average intake of vitamin B₆ from food by adults is less than 2 mg per day. This 2 mg value is only 2 percent of the FNB UL of 100 mg and only 8 percent of the EC SCF UL. Compared with the UL of 100 mg, the intake from conventional foods makes a very small (perhaps trivial) contribution toward a ULS level of intake. Moreover, for vitamin B₆, the UL values established by both FNB and EC SCF were actually set on the basis of *supplemental* intake data, without consideration of food intake. Therefore, the UL values actually represent FNB and EC SCF views of values that

correspond to the ULS as defined in this paper, although not recognized as such by these authorities.

- For other nutrients with potential toxicity and relatively narrow margins of safety, such as vitamin A in the form of retinol, the potential contribution of conventional foods, with or without fortification, can range from trivial to overwhelming. Many diets are marginal to deficient in vitamin A, but it is possible to select sufficient intake of conventional, unfortified food items (such as liver and eggs) to produce nutrient intake that exceeds the UL and possibly the LOAEL without any supplemental intake. Clearly, for such nutrients, the assumptions made about intake from conventional foods must be based on adequate food intake survey and composition data. If the usual food intake of vitamin A (as retinol and its esters, not carotenes) is 600 µg, the calculated ULS calculated by the *difference* method would be 2,400 µg, based on the FNB UL of 3,000 µg.

In summary, the contribution of conventional foods toward the tolerable upper intake levels (either UL or ULS) varies greatly. Thus, the degree to which conventional food intake would impact a ULS calculated by the *difference* method also varies greatly from one nutrient to another. If direct supplement- use data are available, the use of Option 1 to determine the ULS avoids this complication and the accompanying uncertainties. The selenium example given under Option 1 illustrates this advantage.

Detailed comparisons of the CRN ULS with the values established by FNB, EC SCF, and UK EVM will be made in the sections on individual nutrients.

References

Clark LC, Coombs GF, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Leshner JL, Park HK, Sanders BB, Smith CL, Taylor JR. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. JAMA 1996; 276:1957-1963.

European Commission. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Official Journal 2002; L183:0051-0057.

Expert Group on Vitamins and Minerals. Safe upper levels for vitamins and minerals, Food Standards Agency, United Kingdom, 2003.

Food and Nutrition Board. Dietary reference intakes: A risk assessment model for establishing upper intake levels for nutrients. Washington, DC: National Academy Press, 1998.

Food and Nutrition Board. Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids. Washington, DC: National Academy Press, 2000.

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Hathcock JN. Safety limits for nutrient intakes: Concepts and data requirements. *Nutr Rev* 1993;
51:278-285.

Hathcock JN. Safety limits for nutrients. *J Nutr* 1996; 126:2386S-2389S.

Hathcock JN. Vitamin and mineral safety. Washington, DC: Council for Responsible Nutrition,
1997.

Scientific Committee on Food. Guidelines of the Scientific Committee on Food for the
Development of Tolerable Upper Intake Levels for Vitamins and Minerals. European
Commission, SCF/CS/NUT/UPPLEV/11 Final, Brussels, 2001.

Scientific Committee on Food. Opinion of the Scientific Committee on Food on the Tolerable
Upper Intake Level of Selenium. European Commission, SCF/CS/NUT/UPPLEV/25 Final,
Brussels, 2000.