Methodology

Introduction

Vitamins and minerals are essential for life and health. Supplemental intakes of several nutrients provide clearly established benefits for many people, most obviously for those in specific age and gender groups. Dietary supplements are commonly used in pursuit of these benefits, as well as to provide “nutritional insurance” to those who do not know whether they are consuming recommended amounts of vitamins and minerals. For those consuming supplements for health benefits, it is important to have information about the upper levels of these nutrients that may be safely consumed.

Risk assessment is the accepted approach to evaluate the safety of any substance. The methodologies for risk assessment have been in development for decades and are accepted by the U.S.’s Institute of Medicine (IOM), the European Food Safety Authority (EFSA), and many other authoritative institutions and organizations as well as a large number of national governments.

The first step in risk assessment is to decide which type of data and what sources are relevant to the assessment. For vitamins and minerals, data from both animals and humans are available. In each of these datasets, the most reliable type of data is for overt clinical endpoints rather than for surrogate biochemical markers. Each data source has advantages and disadvantages. Animal data have the advantage of quite extensive and robust datasets and the disadvantage of requiring very uncertain and problematic extrapolation for application to humans. Human data are in many ways the exact opposite—the disadvantage is that types and amounts of human data are quite limited for many nutrients, but the advantage is that little or no extrapolation is needed for decisions that are relevant for humans.

In general, risk assessments for noncarcinogens can be separated into two main types: (1) those that depend on threshold dose-response concepts (the threshold approach) and (2) those that
construct probability estimates (the benchmark dose approach). Carcinogenicity is usually treated as a nonthreshold event and for the most part will not be further considered in this document. Risk assessments that use the no observed adverse effect level (NOAEL) or the lowest observed adverse effect level (LOAEL) identify intakes that are either below (NOAEL) or just above (LOAEL) the threshold for adverse effects. The quantitative methodology for risk assessment for unknown effects of nutrients with no observed adverse effects at any intake will be discussed later in this chapter.

Studies of vitamin and mineral safety based on animal data generally use the threshold approach. In contrast, studies of drug, pesticide, and environmental chemical safety often use the benchmark dose (BMD) approach to identify an intake that produces adverse effects in some specified percentage (often 10 percent) of a population. This method constructs a probability basis for evaluating the safety of the substance being tested, but it requires an extensive database that involves administration of (or exposure to) a range of levels of the test substance at least up to those that produce adverse effects in 10 percent of the population. Such data are almost never available for human subjects, and it would be unethical to perform the experiments to obtain such data.

This third edition of the Vitamin and Mineral Safety handbook is based almost exclusively on human data. This methodology is based on the premise, supported by observation, that no matter how robust and extensive an animal dataset may be, the extrapolation to humans carries a very large uncertainty. This document flows from that decision and relies almost entirely on studies using human data only.

During the last several decades, the tolerable upper intake level (UL) has become internationally accepted as the best approach for nutrient safety evaluations. To this end, several international organizations and numerous government agencies have developed or accepted recommendations on UL values. These UL values may be expressed in terms of total dietary intake, supplementary amounts, or both. The UL values have been accepted by the Codex Alimentarius Commission (a food standards organization jointly formed by the UN and the World Health Organization) venture as the only valid basis for regulatory maximum limits on the contents of vitamins and
minerals included in supplement products, and the adoption of this approach by Codex is leading many national governments to do likewise. The UL assumes a threshold for adverse effects and is calculated from either a NOAEL or LOAEL.

The Institute of Medicine (IOM), the European Commission’s Scientific Committee on Food (EC SCF) and its successor EFSA, the UK’s Expert Group on Vitamins and Minerals (EVM), industry groups, and peer-reviewed publications have all reviewed and published risk assessments for one or several of the vitamins and minerals (including trace elements). Regulatory strategies to specify maximums or other guidelines for vitamins and minerals in supplements have been or are being considered by the governments of several countries as well as by the EC, the Association of South East Asian Nations (ASEAN), and the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU). The Codex guidelines are recognized by the World Trade Organization (WTO) as being the most authoritative view on vitamin and mineral safety and therefore have special implications for international trade. The Codex guideline is a method, approved by the Codex Alimentarius Commission, but no quantitative values have yet been identified.

The UL method as defined and implemented by the IOM is an extension of the earlier quantitative methods used in risk assessment for other substances, such as food additives and environmental chemicals. Because of the authoritative character of the IOM publications, the UL risk assessment method for nutrients has gathered widespread support and adoption by other organizations such as the EC SCF/EFSA and the EVM, with some slight modifications. All current UL methods 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 sometimes large differences in the values for various nutrients. The safety evaluation method used in this document utilizes the basic features of these methods but emphasizes the direct evaluation of supplemental intakes, rather than total intakes, when feasible.
Intake Level: Definitions and Applications

There are several types of intake levels used in the literature on vitamin and mineral safety. This section reviews the definitions and differences between two of the most common ones.

**Tolerable Upper Intake Level (UL)**

In its report on nutrient risk assessment, the IOM states the following:

> “The Tolerable Upper Intake Level (UL) is 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.”

For most nutrients, the UL is defined to apply to the total nutrient intake from all sources, including food, fortified foods, water, and supplements. For a few nutrients, the UL values identified apply only to supplemental sources. For example, the UL for magnesium is based on the amount needed to cause diarrhea or unacceptably loose bowels. This effect is most likely when the magnesium is consumed in a single bolus dose, and therefore the UL applies only to magnesium consumed as supplemental to the normal diet. In addition, bolus dose magnesium compounds are sometimes used as a nonprescription drug (laxative), and the UL could be used as an indicator of the dose likely needed to begin to achieve this effect.

The IOM’s interpretation of this definition led them to not establish UL values for nutrients with no established adverse effects, such as vitamin B₁, vitamin B₂, vitamin B₁₂, biotin, pantothenic acid, and trivalent chromium. This interpretation was based on the premise that risk communication would adequately explain why there was no UL value for some nutrients; therefore, in these examples, a UL value would not be useful. Similar decisions have been made by EC SCF/EFSA.

Without defining the procedure or giving it a name, the EVM established guidance levels (GLs) for nutrients without sufficient evidence of adverse effects to establish a safe upper level (SUL), their approximate equivalent to the UL. The EVM expressed less confidence in the numerical
values described as GLs compared with those characterized as SUL (equivalent to UL) values. Nonetheless, the interpretation and proposed use of the GL were the same as for the SUL (UL).

A major issue in setting an UL value is determining the size of the uncertainty factor (UF), or safety factor, to apply to the NOAEL or LOAEL. In some instances, credence is given to any hint whatsoever that a risk might occur at an intake below the recognized NOAEL. This point is illustrated in considerable detail in the 2010 IOM publication on vitamin D, as will be described in the Vitamin D chapter of this document.

**Highest Observed Intake (HOI) Level**

The highest observed intake (HOI) level was established by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) to supply guidelines for those nutrients for which there is no established UL by the IOM or SCF/EFSA. The FAO and WHO adopted the highest observed intake (HOI) under this guideline and definition:

> “The *Highest Observed Intake* is derived only when no adverse health effects have been identified. It is the highest level of intake observed or administered as reported within (a) study(ies) of acceptable quality.”

Under these guidelines, a complete risk assessment for nutrients will include the identification of UL values for those nutrients with observed adverse effects and HOI values for those with no known adverse effects. The procedures for UL and HOI are identical—both are risk assessments. If evaluation of the data shows risk, a UL can be set; if no risk is found in the data analysis, an HOI can be identified as the highest intake level with adequate data to establish that adverse effects do not occur at intakes up to that level.

In the previous edition of this document, a concept equivalent to the HOI was termed the observed safe level (OSL). This term was suggested to the FAO/WHO committee but they ultimately adopted the HOI terminology. The basic concepts of the HOI and OSL are identical.
Due to the sanction of the HOI term by the FAO/WHO and further adoption in the Codex guideline on nutrient risk analysis (Codex Alimentarius Commission 2010), CRN will use the HOI term in this document.

**Sources of Nutrients**

To assess the safety of a nutrient, all significant sources of intake must be considered, but this is more important for some nutrients than for others. The relative importance of each source depends on several factors, including the difference between the UL value and either the recommended intake, such as the recommended dietary allowance (RDA), or the typical intakes from commonly consumed foods, as well as the chronic or acute nature of the adverse effect that is the basis of the UL.

For example, an intake equal to the UL for calcium is difficult but can be reached with consistent consumption of multiple servings (but not a single serving) of dairy foods. Moreover, excessive intakes of calcium for short periods do not lead to any acute toxicity, and acute high intakes are not known to lead to chronic adverse effects. Therefore, intakes of calcium that temporarily exceed the UL probably do no harm. In addition, calcium is a macro-mineral needed in relatively large amounts (approximately 1 g per day), and therefore a supplement that exceeded the UL (2,000 mg) would be noticeably large (bulky). In safety evaluations of dietary calcium, all sources should be considered: foods, fortified foods, and dietary supplements. In addition, the consumer should be aware that some nonprescription antacids have calcium carbonate as their active ingredient, but these are not known to cause any harm with short-term use.

In contrast to calcium, the UL for vitamin A (preformed vitamin A as retinol or one of its esters) can be exceeded by consistent intakes of liver or other organ meats. Furthermore, retinol is a micro-nutrient and the UL is only 3 mg; thus, an excessive intake could be contained in a physically small tablet or capsule. An additional factor is that adverse effects of vitamin A can be chronic (e.g., birth defects after a pregnant woman consumes far too much at a critical early stage). In safety evaluations of vitamin A, all sources of retinol must be considered, but vitamin
A activity from high intakes of carotenes seems not to produce adverse levels of vitamin A. The safety of beta-carotene itself will be discussed separately from vitamin A.

Vitamin B₁₂ has no known adverse effects, and the RDA and intakes from foods are in the low microgram range. In contrast, the proposed HOI is 2,000 µg. The HOI value could be considered to apply to supplements only, with food supplying amounts that are trivial in a safety evaluation.

**Methodologies for Determining Safety Levels: A Comparison**

The methodology described in this document and the quantitative values identified are intended to assist in interpreting reports of adverse effects, making a quantitative approach to nutrient safety issues, and establishing policies that will help ensure consumer safety without inappropriate and unneeded restrictions based on current concepts of “nutrient need” or the composition of the most common foods. These scientific concepts and analyses are valid in any country or population with a few adjustments, such as those for nutrient intake levels related to specific local or national dietary composition and patterns. The quantitative values identified for most nutrients have sufficient margins of safety that few adjustments should be necessary. Specifically, the UL definition includes the phrase “almost all individuals in the general population” and therefore it should be valid to apply the UL values to populations with large differences in average body weight.

Some governments and agencies base their safety recommendations on the RDA of the vitamins and minerals under consideration. The sections below review the limitations of using RDA for supplements and the appropriateness of the risk assessment approach.

**The Limitations of RDA-Based Methods**

Recently some governments have used the RDA to set upper limits for vitamins and minerals in supplement products and have applied drug regulations on products with amounts of nutrients higher than the RDA. Although the RDA may appear to be a convenient marker, there are several problems with using the RDA in this way.
First, RDA-based limits have no scientific validity for identifying supplement safety. The RDA is not defined or identified to describe safety or represent a safety limit for either total or supplemental intake. Risk assessment is the only scientifically valid approach toward identifying supplement maximums. The Codex Alimentarius Commission, for example, has declared that maximums for nutrients in foods offered into international trade must be based primarily on risk assessment.

Second, the application of RDA-based limits to supplements leads to inconsistency in allowable ULs among products. Some countries have applied drug regulations on products with amounts of nutrients higher than the RDA. These regulations are much more stringent than regulations on conventional foods, some of which also contain many multiples of the RDA of certain vitamins. For example, the natural amounts of vitamin B$_{12}$ 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. Thus, these ordinary, conventional foods may contain upward of 40 to 50 multiples of the RDA of vitamin B$_{12}$. Since there is no known toxicity of oral vitamin B$_{12}$ in humans, RDA-based upper limits serve no useful purpose.

Third, RDA values, or equivalent values such as the population reference intake (PRI), 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. Thus, the RDA values are geared toward avoiding classical nutrient deficiency signs and symptoms or meeting some nutrient storage level deemed acceptable. Although this approach may be appropriate for helping undernourished populations identify and reach minimum levels, the data and methodology used to establish RDAs or their equivalents is not applicable to establishing safe upper levels.

Fourth, 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 the RDA. Again, risk assessment is the appropriate methodology to identify safety limits for these important nutrients.

Fifth, drug-based regulations are not appropriate for food items for which Codex Alimentarius has established a standard or guideline. Codex is recognized by the WTO as presumptive international authority on food issues, and WTO agreements require that applied regulatory measures be no more restrictive than necessary to protect the health of consumers. The existence of a Codex guideline is direct evidence that drug-based regulations would be more restrictive than necessary.

Finally, arbitrary limits at or near the RDA may preclude certain benefits of some nutrients. There are currently many documented benefits of nutrient quantities above the RDA. For example, in 2010 the IOM updated the vitamin D RDA, which was based entirely on the skeletal effects. Although there is strong evidence to support several other beneficial effects of this vitamin, the IOM judged the evidence insufficient to serve as the basis for an RDA value. Several of the other functions, such as neuromuscular activities, require greater amounts of vitamin D than needed for the skeletal effects. Therefore, an upper limit based on the RDA might preclude these additional potential benefits. Likewise folic acid, vitamin B₆, and vitamin B₁₂ are known to help control plasma homocysteine concentrations. Homocysteine is not yet accepted as a recognized risk factor for heart disease, but there is an ever-increasing body of scientific evidence to support this conclusion. Supplementation with these three vitamins helps to control plasma concentrations of homocysteine and is likely to prove to reduce the risk of heart disease.

All of these facts point to the inappropriateness of using RDA-based limits for supplements. Labeling, not limits, can address proper usage by providing information on contents in the package, noting any benefits related to the RDA or any other measure of benefit and drawing attention to limits imposed on a safety basis, as identified by risk assessment.
The Risk Assessment Method

As indicated earlier, risk assessment is the accepted approach to evaluate the safety of substances. The methodologies for risk assessment are well established and are accepted by the IOM, EFSA, and many other authoritative institutions and organizations. The sections below address some of the recent developments and variations in risk assessment methodologies.

Nutrient Appropriateness. An important refinement of the risk assessment method is the concept of nutrient-appropriate methods. Before the advent and widespread adoption of the UL, the term nutrient-appropriate was used to describe risk assessment for vitamins and minerals. This terminology indicated that not all risk assessment methods are appropriate for the task. Certain risk assessment methods use default UF (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 can lead 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 UF's that calculate zinc safety limits below the RDA for some populations. The benchmark dose is a probability estimate that has not been shown to be useful for human data on vitamins and minerals.

Hazard Identification. Hazard identification identifies a hazard related to excess consumption of a vitamin or mineral, using the guidelines and procedures described in the UL method. Hazard is preferably determined from human data, but animal data can be used when necessary. Biochemical or other indirect indicators should be judged to represent a hazard only if they are surrogate markers for pathological conditions. If no hazard can be identified, the additional steps in the UL method can be used to identify an HOI value. The criteria for causality should be applied, including the strength of the association, consistency of the association, specificity of the association, dose-response relationship, temporal relationship, biological plausibility, and overall coherence. If a nutrient has more than a single adverse effect, the hazard occurring at the lowest intake is the critical effect for this risk assessment to set a UL through the following steps.
If no critical effect can be identified, the following steps allow identification of a HOI value. The Codex Alimentarius Commission uses the term *hazard* to refer to a chemical or physical agent even though the scientific publications they reference use the term *hazard* to mean an unacceptably adverse effect that is used as the basis of a policy standard or guideline. This difference in definitions should not cause a problem if it is recognized and taken into account.

**Dose-Response Assessment.** This process identifies a NOAEL, from human data if possible. Alternately, if the data are appropriate but do not support a NOAEL, a LOAEL may be established. Animal data are used only if appropriate human data are not available and also to guide the search for a hazard that might be identified in the human data. The uncertainties in the data are assessed and a numerical UF is assigned. It applies to the overall database and the specific data used to establish the NOAEL or LOAEL. Reasonable judgment must be applied to avoid a choice of UF that represents a worst possible but exceedingly unlikely case. If a LOAEL is used, the UF must be greater than unity (1.0) and should be appropriate for the conversion to a NOAEL. If the NOAEL or LOAEL is identified from animal data, an appropriate UF is assigned to the extrapolation to UL values for humans. If no adverse effects are known, these procedures can be used to identify an HOI.

**Deriving the UL through Risk Assessment.** The UL of a vitamin or mineral may be calculated through risk assessment in the following way:

\[
UL = \text{NOAEL} \div \text{UF} \quad \text{(or) } \quad UL = \text{LOAEL} \div \text{UF}.
\]

If the HOI is based on sparse data, a similar procedure may be used to adjust for uncertainty in that value; however, if the total dataset is extensive (e.g., vitamin B\textsubscript{12}), the absence of any adverse effect at any intake supports the argument that no correction for uncertainty is needed (i.e., the UF should be 1.0). For all nutrients with large datasets that include multiple clinical trials involving administration of a range of doses, the uncertainties may be addressed by arranging the data in decreasing order of intake and then selecting downward until confidence in the data is sufficient to justify the selection of a NOAEL or HOI with a UF of 1.0. The vitamin D chapter provides such an example.
**European Commission Methodology**

The Scientific Committee on Food (SCF) was established in 1974 to provide the European Commission with scientific advice on food safety. In 2002, this mandate was transferred to the newly created European Food Safety Authority (EFSA). EFSA provides independent scientific advice and communication on existing and emerging risks.

The SCF/EFSA has published UL values for several vitamins and minerals, using a methodology similar to that developed by the IOM and first published in 1997. The EC’s Food Supplements Directive requires the identification of maximum amounts for supplements from risk assessments that at least nominally are derived from total intakes from all sources. No method for deriving the supplement maximums had been published by the EC as of the writing of this book. However, the approach specified in the directive would include the following steps.

**Step 1.** Step 1 comprises (1) use of the SCF/EFSA UL values identified through a UL method almost identical to the one developed by the IOM and (2) consideration of intakes from other dietary sources.

**Step 2.** Step 2 takes into “due account” population reference intakes (presumably the RDA or equivalent). However, no method for identifying or applying this due account had been published by the EC as of the writing of this book. Two industry associations have proposed that the RDA could be used along with the ULs and intakes from food sources to calculate a population safety index that separates the nutrients into three categories that demand different levels of regulation and monitoring.

CRN suggests that the population reference intakes referred to in step 2 could also be used to ensure that the risk assessment and identification of other intakes are not excessively conservative, thereby producing a UL and a supplement maximum below the RDA.

The EC proposal would seem to need to identify maximums for supplements plus fortified foods as the differences between the UL and the intakes from other sources. That is, the supplement maximum would be the UL minus the expected intake from conventional foods. The EC has not
yet proposed how it will allot the difference between the UL and unfortified intakes into fractions for supplementation and increased fortification, or for the variations in expected intake from one country to another or from one dietary pattern to another. It has been reported that the EC is working on establishing dietary “supplement maximums” by using risk assessments done by EFSA, but has not done so for any of the nutrients. These values with corresponding analysis will be added in future editions when this information becomes available.

**EVM Methodology**

The risk assessments in the EVM report on vitamin and mineral safety are based on the UL method developed by the IOM, but they assigned the term *safe upper level* (SUL) to the values derived by this method. The EVM stated that for most nutrients, the databases were not sufficient to set an SUL; therefore, a guidance level (GL) was identified. Nonetheless, this GL was often derived and used for overall safety evaluation and discussion of policy options in the same manner as a SUL value. In contrast to CRN’s views, the EVM used animal data to identify some SUL values entirely on the basis of high-quality animal data, despite the great uncertainty inherent in quantitative extrapolation from animals to humans.

For a few nutrients, the EVM report takes an additional step toward risk management recommendations for supplements. A safety value based on supplemental intake effects could be logically used to identify maximum contents of products marketed and regulated as supplements. Indeed, most of the SUL and GL values identified by EVM were based on supplemental intakes. In these cases, the EVM uses data on typical intakes from foods along with the supplemental SUL or GL to calculate these values for total intakes. In addition, the EVM explicitly states that it assumes daily consumption throughout the adult lifetime (age 16 years to death), whereas the IOM and SCF/EFSA are not explicit on this issue for all nutrients.

**Methodologies for Determining Supplement Safety: A Summary**

The premise of this handbook is that the safety evaluation for dietary supplements is best determined on a case-by-case basis through nutrient-appropriate risk assessment, and not as
arbitrary multiples of the RDA. Scientific assessments used to identify adequate intake levels (RDAs or their equivalents) are not well suited to identifying hazards. Nutrient-appropriate risk assessment incorporates internationally recognized methodology and is grounded in sound toxicological principles.

Nutrient-appropriate risk assessment requires the safety evaluation to depend on identification of a hazard causally 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 also 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 the risk of a serious consequence, such as liver toxicity. Similarly, the dermal “flushing” that can be produced by nicotinic acid is a definite nuisance but does not produce any known pathology. Nonetheless, the IOM, EC SCF/EFSA, and EVM used flushing as the critical effect to establish UL or equivalent values. (For more details, see the Niacin chapter.)

**Direct Safety Evaluation of Supplemental Intakes**

If appropriate data on supplemental intakes of a specific vitamin or mineral are available, the safety may be determined by risk assessment directly on those data, as illustrated by the EVM report. 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). For some nutrients, the NOAEL or HOI data are related to the use of *supplemental amounts* of the vitamin or mineral, above and beyond the amounts contributed by the diet; therefore, such data do not require any additional consideration of amounts contributed by consumption of conventional foods.
The expected intakes of most nutrients from conventional foods do not invalidate this approach for two primary reasons: either (1) intakes are small in comparison with the UL or HOI (e.g., for vitamin B₁₂) 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.

**Indirect or Difference Method for Supplement Safety**

If appropriate data on supplemental intakes of a vitamin or mineral are not available, a *difference* procedure, similar to that identified by the EC, may be used. The difference method involves the following:

- Determination of the UL or HOI for total intake from all sources.
- Identification of the usual intakes from conventional foods from appropriate food intake surveys and food composition tables, taking consumption of fortified foods into account. There is considerable controversy about the selection and management of the intake data. Which source of data is appropriate? What percentile of intake should be considered?
- Calculation of the UL for supplements as a difference. This method still leaves an unresolved dispute about how to allocate this difference between supplementation and fortification and how to account for differences in dietary patterns and composition.

**Characteristics of CRN’s Safety Methodology**

The CRN approach as described above includes the basic elements of both the IOM and FAO/WHO methods. For some nutrients, the CRN and EVM methods are the same; for others, CRN and the EVM use different approaches. CRN’s principal points of departure from all three of these approaches include the following:

- CRN gives preference to data on effects of *supplemental* intakes, rather than total intakes, thereby eliminating any need to correct for intakes from conventional foods.
• CRN gives stronger preference to use of human data over animal data, thereby avoiding the uncertainties involved in extrapolation between species.

• CRN gives stronger preference to clinical trial data from human studies, if available, but also uses epidemiologic data.

• CRN gives stronger preference to identifying NOAEL values than to LOAEL values, thereby eliminating the uncertainty related to extrapolation downward from the LOAEL.

• CRN considers only effects that represent a true hazard (i.e., risk of impaired health) rather than nuisance effects.

• CRN preferentially uses direct evidence of adverse effects, if available, rather than biochemical markers or other indirect indicators.

• CRN utilizes history of use data, if necessary, to identify an HOI and UL 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.

• CRN conservatively selects human NOAEL values that justify selection of an UF of 1.0, thereby eliminating the need to select a specific numerical value.

• CRN 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 carefully scrutinize labels in an effort to obtain or avoid increased intake of nutrients.

References