Trans-Atlantic Business Dialogue
Dietary Supplement Expert Group

METHODS FOR SETTING TOLERABLE UPPER INTAKE LEVELS OF *SUPPLEMENTAL* VITAMINS AND MINERALS

Alternative approaches

Recommendation

1) Scientific Approach 1: If appropriate data on supplemental intakes of a specific vitamin or mineral are available, the tolerable upper intake level from supplements (ULS) may be determined directly from those data.

OR

2) Scientific Approach 2: If appropriate data on supplemental intakes of a vitamin or mineral are not available, a three-step procedure may be used as follows:
   a) Determine the tolerable upper intake level (UL) for total intake from all sources[1,2],
   b) Identify the usual intakes from conventional foods (ICF) from appropriate food intake surveys and standard food composition tables, taking consumption of fortified foods into account, and
   c) Calculate the tolerable upper intake from supplements (ULS) as the difference, that is, UL – ICF = ULS.

OR

3) Scientific Approach 3: If a significant scientific database identifies no need for a UL or a basis for identifying the value, no ULS should be set. Some nutrients, such as vitamins B_1, B_2 and B_{12} have been subjected to extensive testing and use at high levels without evidence of adverse effects. For such nutrients, no ULS should be set.

Rationale for Scientific Approach 1

For vitamins and minerals with appropriate data, the ULS may be identified directly. For example, the CRN supplement-use NOAEL of 200 µg selenium[3] was determined from a well-designed and conducted randomized, double-blind, placebo-controlled clinical trial[4]. This clinical trial of 7 to 10 years duration for each subject involved a sufficient cohort (more than 1300 persons) and multiple objective endpoints that are appropriate to determine a lack of adverse effects with a high level of confidence. These data supports a confident conclusion that 200 µg is a safe level for *supplemental* selenium intake, and thus, through the direct method of Scientific Approach 1, CRN concluded that 200 µg is a

safe level for selenium supplementation. The dietary selenium intake by the subjects was approximately 100 µg per day, and thus the supplement added double this amount for a total intake of approximately 300 µg per day.

The Food and Nutrition Board (FNB) concluded from Chinese epidemiological data that the selenium NOAEL is 800 µg, and assigned an uncertainty factor (UF) of 2 to calculate that selenium is safe at a *total* intake level of 400 µg[5]. The European Commission's Scientific Committee on Food (SCF) evaluated the same epidemiological data and concluded that the NOAEL is 900 µg and assigned an uncertainty factor of 3 to calculate a safe total selenium intake of 300 µg[6]. With either the FNB or SCF UL values, determination of an upper level for supplemental intake of selenium must take into account the usual intakes from conventional foods. This approach, described in Scientific Approach 2, depends on the food intake and composition values selected for the calculation. With the 100 µg intakes in the clinical trial mentioned above, the direct method and the difference method using the 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 intakes brings in additional uncertainties. With fewer uncertainties, Scientific Approach 1 will provide a higher level of confidence than Scientific Approach 2.

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

Rationale for Scientific Approach 2

If appropriate data related to supplemental use at a high intake level are not available, the ULS cannot be identified through Scientific Approach 1 and therefore must be determined indirectly. The ULS can be calculated as the difference between the Tolerable Upper Intake Level (UL), which by definition applies to total intakes from all sources, and usual intake from conventional foods (ICF). That is, the ULS = UL – ICF.

The EC's Amended Proposed Directive outlines such an approach, but details were not provided[7]. The UL values published by the FNB or SCF provide the starting point for Scientific Approach 2, but intake survey and food composition data must be selected to allow completion of this indirect method. However, the selection of the food intake and composition data brings additional questions. Because dietary patterns vary so much between nations and regions, calculations of usual nutrient intakes should be done nationally or regionally. UL values are designed (as are Recommended Dietary Allowances) to apply to almost all healthy adults. Thus in Scientific Approach 2, the median or mean nutrient intake (ICF) values most appropriate for use in calculation of the ULS from the UL when the difference method is the only recourse.

Rationale for Scientific Approach 3

Some nutrients, including vitamins B-1, B-2 and B-12, 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, the FNB declined to set UL values. There would be no practical value for ULS values and none should be set for such nutrients.

Overall Discussion

For several nutrients carrying the potential for adverse effects, data are available to allow the use of Scientific Approach 1. For other nutrients, Scientific Approach 1 is not possible and Scientific Approach 2 is the only recourse. For either nutrient, no adverse effects are known and neither of the first two approaches is appropriate or needed.

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

- For nutrients of very low or no known toxic potential, such as vitamin B-12, no UL or ULS can be set. For such nutrients, the contribution of conventional foods is not significant in comparison to the highest levels known to be safe.

- For some nutrients with definite toxicity profiles, such as vitamin B-6, the margin of safety is large and therefore the contribution of conventional foods toward the UL value is small. In the United States where many foods are fortified, the average intake of vitamin B-6 from food by adults is less than 2 mg per day[8]. This 2-mg value is only 2 percent of the FNB UL of 100 mg[8] and only 8 percent of the SCF UL[9], which is based on questionable toxicity data[3,8,10]. In comparison to the UL of 100 mg, taking into account the intake from conventional foods make a very small (perhaps trivial) difference in the ULS. Moreover, for vitamin B-6, the UL values by both FNB and SCF was set on the basis of *supplemental* intake data, without consideration of food intakes. Therefore, the UL values actually represent FNB and SCF views of values that correspond to the ULS as defined in this paper.

- For other nutrients with definite toxicity profiles with relatively narrow margins of safety, such as vitamin A, the potential contribution of conventional foods, with or without fortification, can range from trivial to overwhelming[3]. Many diets are marginal to deficient in vitamin A, but it is possible to select conventional sufficient intakes of conventional, unfortified food items (such as liver and eggs) to produce intakes that exceed the UL and possibly the LOAEL without any supplemental intake. Clearly, for such nutrients, the assumptions made about intakes from conventional foods must be based on adequate food intake 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 2400 µg, based on the FNB UL of 3000 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 the ULS calculated by the difference method varies greatly from one nutrient to another. If direct supplement use data are available, the use of Scientific Approach 1 to determine the ULS directly avoids this complication and the accompanying uncertainties. The selenium example given under Scientific Approach 1 illustrates this advantage.

References

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