Expanded Approach to Tolerable Upper Intake Guidelines for Nutrients and Bioactive Substances1,2

John N. Hathcock* and Andrew Shao

Council for Responsible Nutrition, Washington, DC 20036

Abstract

The original tolerable upper intake level (UL)3 method greatly improved the application of risk assessment to the evaluation of nutrient safety for humans, but a UL is only set where the data establish a hazard resulting from high intakes. Absence of a UL for those nutrients with no established hazard has been misinterpreted by regulators and resulted in overly restrictive policies. To prevent such misinterpretation, the observed safe level (OSL) was developed and defined as “the highest intake with convincing evidence of safety, even if there are no established adverse effects at any level.” More recently, a FAO/WHO report gave a similar definition for the highest observed intake (HOI). Another disadvantage of the UL method is the application of arbitrary uncertainty factors (UF). An alternative to the traditional adjustment for uncertainty involves arranging the data in decreasing order of daily intake, followed by evaluation of each trial for quantity and quality of data. Studies are selected downward until no adverse effects are observed in a trial of sufficient quality to justify no further correction for uncertainty (i.e. selection of data that qualify for UF = 1). Thus, the no observed adverse effect level or OSL selected requires no further adjustment for uncertainty. For supplemental intakes of some vitamins, many bioactive substances, and most amino acids, no adverse effects that are clearly related to high intakes have been established, but where the dataset is sufficiently robust, application of the OSL-HOI technique can provide risk assessment values. J. Nutr. 138: 1992S–1995S, 2008.

Introduction

The tolerable upper intake level (UL)3 risk assessment method was specifically designed for application to “nutrients and food components” (1) and is broadly based on older risk assessment approaches for noncarcinogenic substances (2). An important aspect of the adaptation for nutrients was the derivation of uncertainty factors (UF) from each dataset, including fractional values where the UL is derived from human data. The UL method was a major improvement over previous methods for application to nutrients, principally because the UL method utilizes UF values derived from the dataset for each nutrient. Despite this advantage and wide acceptance of the UL method, it is less than ideal in 2 important respects: the absence of a UL for many nutrients and the seemingly arbitrary size of the UF. This article describes expansions of the UL method to provide safety guidance for nutrients or bioactive substances without evidence of toxicity and a more direct approach to accounting for uncertainty and provides examples of application.

Risk assessment methods

When evidence does not justify establishing a UL. For nutrients with known adverse effects, i.e., those for which a lowest observed adverse effect level (LOAEL) or no observed adverse effect level (NOAEL) can be identified, the UL method has become internationally accepted (3). The UL method involves a few simple steps: identification of the critical effect, dose-response assessment, evaluation of uncertainty, and calculation of the UL (1).

\[ \text{UL} = \frac{\text{NOAEL} \text{ or LOAEL}}{\text{UF}} \]

A common further step, often termed risk characterization, is to compare the UL to the range of intakes to determine whether some fraction of the population is at risk of adverse effects. In the reviews by the Institute of Medicine (IOM) and the European Commission Scientific Committee on Food (now European Food
Safety Authority), no data were found to identify any hazards related to high intakes of thiamin, riboflavin, vitamin B-12, biotin, and pantothenic acid (4). By definition, a UL cannot be set if a NOAEL or LOAEL cannot be identified (i.e. absence of established adverse effect or hazard). To serve the advisory and potentially the policy and regulatory functions of the UL, a similar but alternative concept has been developed and defined: the observed safe level (OSL) in the peer-reviewed literature (5) and the highest observed intake (HOI) in an authoritative report (3). Like the OSL, the HOI is defined as the highest level with adequate data to reasonably exclude adverse effects. Therefore, the OSL or HOI can be used to identify the highest intake with adequate evidence of safety, but neither term should be misinterpreted to mean that a given substance is safe at all possible intakes.

**New method for considering uncertainty.** The usual approach to uncertainty involves identifying the highest NOAEL supported by the data and judging the strengths and extent of the available data to select a numerical UF to be used in calculating the UL. The size of the UF depends on the robustness of the data used to identify the NOAEL, the severity and persistence of the critical effect, and the strengths and amount of supporting data. The factors that affect the UF are widely accepted, but there are no specific or universally accepted criteria used to derive the exact values. Indeed, the overall UF values that have been selected and applied by the IOM to the various nutrients range from 1 to 5 for human datasets and up to 300 for animal data, with each of these being the product of several independent factors for different data characteristics (Table 1).

To avoid the seemingly arbitrary aspects of UF derivation, an alternative approach to select a NOAEL or OSL-HOI value that justifies use of a UF of 1.0 has been developed for application to human clinical trial datasets (6). Regardless of the approach, with either the usual treatment of uncertainty or this alternative approach, qualitative scientific judgment is required. However, the alternative avoids the quantitative judgment required to select a specific numerical value for the UF. The new approach involves arrangement of the clinical trial dataset in decreasing order of intake of a substance, identification of those trials that produced no adverse effects (provisional NOAEL values), and selection downward until the dataset is judged strong enough to justify application of UF = 1.0, with the consequence that the selected NOAEL (or OSL-HOI) equals the UL (i.e. NOAEL + 1).

**Examples**

**In the absence of a UL: OSL or HOI.** For vitamin B-12, the absence of a UL has led to the misinterpretation that there is insufficient data to evaluate the safety. This misinterpretation has occurred despite the accumulation of large amounts of human clinical data demonstrating a lack of adverse effects of oral vitamin B-12 at doses hundreds or thousands of times higher than the nutritional requirement or recommended intakes (7). Nonetheless, the absence of a UL for this vitamin has led to the proposal or implementation of unjustifiably and unnecessarily restrictive policies for maximum amounts that may be incorporated into products. For example, Germany proposed a regulatory limit of 9 μg for vitamin B-12 (8) and France implemented a limit of 3 μg in supplement products (9) even though the amounts in unfortified conventional foods can range upward of 100 μg/serving of beef liver (10). There is no apparent public health purpose of such restrictions and the regulatory actions taken by France and considered by Germany seem disproportionate and are in violation of the European Commission’s guidelines in its document on the precautionary principle (11).

The OSL or HOI method allows for the examination of data and the possible conclusion that adverse effects are unlikely up to the specified intake. This approach has been used in a series of published risk assessments for several nonessential nutrients, i.e. bioactive food components, including carnitine, chondroitin sulfate, coenzyme Q10, creatine monohydrate, glucosamine, lutein, and lycopene (12–16). None of these substances have any established adverse effects, although most of them have been tested at a range of intakes in human clinical trials and some have extensive supporting animal data. This same approach has also been applied in risk assessments of taurine, L-glutamine, and L-arginine, amino acids without known specific toxic effects. The OSL risk assessment method indicates the evidence for the absence of adverse effects is strong for taurine at supplemental intakes up to 3 g/d, L-glutamine at intakes up to 14 g/d, and L-arginine at intakes up to 20 g/d (17).

Although the UK Expert Group on Vitamins and Minerals did not name the procedure, it applied the term guidance level in 2 ways, 1 of which is analogous to the OSL or HOI definitions, e.g. their 2000-μg guidance level for vitamin B-12 (7).

**New approach to accounting for uncertainty.** Assessing and accounting for uncertainty in the data considered in a risk assessment inevitably include qualitative scientific judgment. The UL method, as developed and applied by the IOM, also includes quantitative judgment. Consequently, the UF values chosen by the IOM for the nutrients with UL values range from 1 to 300, depending on the type of adverse effect (basis of the NOAEL), age-gender group represented, species tested, strength of study design, and replication of the results by other researchers (1,4,18–21). Values selected by the IOM for application to human adult data include, 1.0 for fluoride and manganese, 1.2 for vitamin D, 1.5 for zinc, 2.0 for pyridoxine, and 5.0 for folic acid (Table 1).

The new approach, feasible when the dataset includes clinical trials at a variety of nutrient dosage levels, is intended to avoid the seemingly arbitrary process of assigning a specific numerical value to the uncertainty. Applying this method to vitamin D (6),

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**TABLE 1** Various UF values selected by the IOM

<table>
<thead>
<tr>
<th>UF</th>
<th>Nutrient</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>Fluoride</td>
<td>Epidemiologic NOAEL</td>
</tr>
<tr>
<td>1.2</td>
<td>Manganese</td>
<td>Epidemiologic NOAEL and clinical trial</td>
</tr>
<tr>
<td>1.5</td>
<td>Vitamin A</td>
<td>Moderate data to support NOAEL for women of child-bearing age</td>
</tr>
<tr>
<td>2.0</td>
<td>Vitamin B-6</td>
<td>Clinical trial NOAEL</td>
</tr>
<tr>
<td>5.0</td>
<td>Folic acid</td>
<td>Epidemiologic NOAEL</td>
</tr>
<tr>
<td>36</td>
<td>Vitamin E</td>
<td>Animal data LOAEL</td>
</tr>
<tr>
<td>300</td>
<td>Nickel</td>
<td>Animal data LOAEL</td>
</tr>
<tr>
<td>500</td>
<td>Vanadium</td>
<td>Animal data LOAEL</td>
</tr>
</tbody>
</table>

1 UF applied to NOAEL or LOAEL to derive adult UL; obtained from individual IOM DRI reports (4,18–20).
no credible evidence of adverse effects were reported in separate clinical trials with orally administered cholecalciferol at daily supplemental intakes of 2500 μg (22, 23), 1250 μg (24), 1000 μg (25), 450 μg (26), 321 μg (27), and 250 μg (24, 28), as well as in a large number of trials at lower levels (29–40) (Table 2). The designs of these trials involving daily doses >250 μg left considerable uncertainty and if the levels used were selected as the NOAEL, each would have required application of a UF >1.0 in the calculation of the UL. The 2 trials at 250 μg were of stronger design, thereby decreasing the uncertainty, and the absence of adverse effects in other trials from 321 to 2500 μg further decreased uncertainty sufficiently to justify the selection of UF = 1.0 for application to the 250 μg NOAEL that was selected, thus yielding the recommended UL of 250 μg.

This approach was also applied to coenzyme Q10, with rejection of potential NOAEL values as high as 3000 mg/d and selection downward to a NOAEL of 1200 mg/d, which was judged to warrant a UF of 1.0 (12). Similar data treatments were applied to the clinical trial dataset for carnitine (13), creatine (16), lutein, lycopene (15), and amino acids (17).

The choice to completely rely on the human studies involving oral administration is not based on the absence of data from animal studies as invalid or unreliable with regard to impacts on the test species. However, animal data, no matter how extensive and robust, will always carry major uncertainties to the extrapolation of a quantitative dosage limit for humans and risk assessment outcomes and these uncertainties are likely to be larger than those related to even a very modest human dataset (e.g. nickel and vanadium) (20). In some authoritative risk assessments based on animal data, the composite UF were selected in a manner that seems intended to make the outcome of a quantitative dosage limit for humans and risk assessment outcomes and these uncertainties are likely to be larger than those related to even a very modest human dataset (e.g. nickel and vanadium) (20). In some authoritative risk assessments based on animal data, the composite UF were selected in a manner that seems intended to make the outcome

<table>
<thead>
<tr>
<th>Dose, μg/d (ref)</th>
<th>Details</th>
<th>Comments</th>
<th>UF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2500; 2 trials (22,23)</td>
<td>Adults and children; 4-d duration; 2nd trial in elderly adults treated once every 4 mo for 5 y</td>
<td>No adverse effects but duration so short that extrapolation to chronic use is very uncertain; treatment of adults was not daily</td>
<td>&gt;1</td>
</tr>
<tr>
<td>1250 (24)</td>
<td>Healthy men treated for 8 wk increased 25-hydroxycholecalciferol but not serum calcium</td>
<td>Possible NOAEL, but with some uncertainty</td>
<td>&gt;1</td>
</tr>
<tr>
<td>1000 (25)</td>
<td>Men with multiple sclerosis, treated for 28 wk, but without a control group</td>
<td>No adverse effects, but lack of control group precludes use as NOAEL</td>
<td>&gt;1</td>
</tr>
<tr>
<td>450 (26)</td>
<td>Adults with osteoporosis for 5 y but combined with high-dose fluoride</td>
<td>No adverse effects, but osteoporosis may tolerate more calcium; confounded by fluoride</td>
<td>&gt;1</td>
</tr>
<tr>
<td>321 (27)</td>
<td>Patients with various diagnoses treated for 6 mo; combined with high-dose fluoride</td>
<td>No adverse effects; confounded by fluoride</td>
<td>&gt;1</td>
</tr>
<tr>
<td>250 (24,28)</td>
<td>One arm of 1250 μg/d trial listed above; a 2nd trial for 20 wk</td>
<td>No adverse effects in either trial; duration, replication, and statistical power provide confidence; supported by higher dose trials with similar results</td>
<td>Sufficient confidence for UF = 1 and therefore a NOAEL of 250 μg/d is the recommended UL</td>
</tr>
<tr>
<td>Multiple trials at ≤190 μg/d (28–40)</td>
<td>Various ages, durations, etc.</td>
<td>Only 1 trial in 1984 found adverse effects at 95 μg/d (34), but that result is contradicted by longer, larger, better trials</td>
<td>No credible and confirmed adverse effects in the dosage range tabulated</td>
</tr>
</tbody>
</table>

1 Adapted from (8).

Summary and conclusions

The current UL method for risk assessment is broadly accepted but suffers from 2 serious limitations. No UL is set without established toxicity and the absence of a UL has led to overly restrictive policies on regulatory limits for some nutrients. The newer OSL or HOI approach to nutrient risk assessment allows for the identification of an upper limit for nutrients for which there are ample data demonstrating safety but an absence of established toxicity at any dose. The newer method for uncertainty takes a more conservative approach to identifying possible NOAEL (or OSL) values, but, in doing so, eliminates the apparent quantitative arbitrariness of the original UL method for uncertainty.

Other articles in this supplement include references (41–51).

Literature Cited


Expanded upper level method and applications 1995S