A Critical Assessment of the Upper Intake Levels for Infants and Children

Stanley Zlotkin

Departments of Paediatrics, Nutritional Sciences, and Public Health Sciences and Centre for International Health, University of Toronto, Toronto, Ontario, Canada and Division of Gastroenterology, Hepatology and Nutrition, and Programs in Metabolism, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada

ABSTRACT The dietary reference intake (DRI) committees of the Institute of Medicine (IOM) report, Dietary Reference Intakes (DRIs): Applications in Dietary Assessment, the tolerable upper intake level (UL) is typically derived to apply to the most sensitive members of the general population (1). For this reason, many members of the population may regularly consume nutrients at, or even somewhat above, the ULs for those nutrients without experiencing adverse effects. Because there is no way to establish which individuals are the most sensitive, however, it is necessary to interpret the ULs as applying to all individuals. From a public health perspective, this approach is consistent with, for example, the recommendations of the World Health Organization (WHO) for the prevention of anemia in children (2). WHO suggests that if the community prevalence of anemia is 40% or greater, there is justification for nontargeted programs. Thus, 60% of the population would not benefit from the intervention, but for the good of the community, the risk of overtreatment outweighs the benefits of undertreatment. Of note is the fact that this public health approach is applied only when a combination of epidemiologic data substantiating the degree of disease in the community and a proven intervention to treat or prevent the disease exists. The IOM approach to ULs does not meet either of these criteria for the majority of nutrients for infants and children. For most nutrients, there was no direct evidence of toxicity in infants and children and no proof that applying UL standards would result in a benefit. In fact, limiting intakes could lead to nutrient deficiencies.

The UL is based on a risk assessment model that includes 4 key components: 1) hazard identification, 2) dose-response assessment, 3) intake assessment, and 4) risk characterization (1). The risk assessment model contains no discussion of recommendations for reducing risk; these are the focus of risk management. A principal feature of the risk assessment process is the long-standing acceptance that no risk of adverse effects is expected unless a threshold dose (or intake) is exceeded. The model assumes that adverse effects that may be caused by a nutrient or food component almost certainly occur only when the threshold dose is exceeded (3,4). The model, which assumes no risk below the threshold, is taken from the toxicology literature; however, unlike carcinogens, adverse effects are more often observed with inadequate intakes (below a threshold) than excessive intakes. Nevertheless, the critical issue for the IOM committee was the method used to identify the approximate threshold of toxicity for a large and diverse human population, because thresholds vary among members of the general population (3). For any given adverse effect, if the...
distribution of thresholds in the population could be quantitatively identified, it would be possible to establish ULs by defining some point in the lower tail of the distribution of thresholds that would be protective for some specified fraction of the population. However, the data were not sufficient to allow identification of the distribution of thresholds for all but a few well-studied nutrients and compounds found in foods (e.g., for chemicals such as lead, for which the database from studies with humans is very large).

The method described for the identification of thresholds for the general population was designed to ensure that almost all members of the population would be protected, but it is not based on an analysis of the theoretical distribution of thresholds, because these values for all age and gender groups are simply not available. The IOM committee, however, relied on the proposition that the threshold, which became the UL, lies very near the low end of the theoretical distribution, which is the end that represents the values for the most sensitive members of the population. To ensure that the UL is at the low end, the model includes a practical examination of the lowest level of a nutrient that is not associated with any adverse effect (the no observed adverse effect level, or NOAEL) and the lowest level at which an adverse outcome is observed (the lowest observed adverse effect level, or LOAEL). In addition, in recognition of the uncertainty in the process and the lack of hard data, the threshold is modified by an uncertainty factor.

For a number of nutrients, especially for older infants and toddlers, the ULs are lower than the current mean intake of the nutrient. Juxtaposed to this is the observation that there is no evidence that current intake levels of these same nutrients are harmful to that population. Thus, when intakes exceed the UL, either the intakes are a problem or the application of a UL without adequate data are a problem. It should also be noted that the logic of the process of establishing ULs for children has not been universally accepted. For example, the ULs for folate and niacin for children and adolescents were based on no data [even the adult UL for niacin is based on data from a single study by Sebrell and Butler (6), published in 1938, that included 6 subjects]. The Food and Nutrition Board wrote about folate: “There are no data for other life stage groups that can be used to justify a NOAEL or LOAEL and derive a UL” (7). Therefore, the UL that was established for children, which was based on data for adults but which was adjusted on the basis of relative body weight, simply makes no sense. Similarly, for niacin, the adverse effect is flushing. Flushing is not seen in children (other than as a sign of embarrassment or after vigorous exercise) (7).

The inclusion of epidemiologic data on food and nutrient consumption was specifically included in the description of the UL model. Yet, in the application of the model, a consideration of intake was omitted for some nutrients even though intake data were readily available. Two examples of this problem can be seen with the ULs for zinc and niacin. Typical intakes of both of these nutrients by young children are 50% greater than the ULs, but there has been absolutely no suggestion that intakes of these nutrients at these levels cause adverse outcomes.

The derivation of the UL using inadequate data (e.g., a lack of dose-response and confirmatory data) and on the basis of subjective judgment as to the uncertainty factor are inadequate criteria for the derivation of policy. It is a starting point, not an endpoint. In the sections below I provide further information on the misuse of the UL as a benchmark.

Zinc

The shortcomings of relying on ULs, and specifically on using the UL as a model to expose nutrient intake risk, is readily demonstrated by examining the UL for zinc (8). According to the DRI documents, the 4 factors that should be considered when the risk of adverse effects from high intakes (of zinc) are assessed include: 1) the accuracy of the intake data (the dose), 2) the percentage of the population consistently consuming the nutrient at intake levels in excess of the UL, 3) the seriousness of the adverse effect, and 4) the extent to which the adverse effect is reversible when intakes are reduced to levels less than the UL.

How does the assessment of zinc fit when these 4 factors are used? I will assume that the intake data are accurate. A high proportion of children (particularly young children) ingest zinc at levels greater than the UL from the 2001 DRI (9). The data

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Problems associated with the tolerable upper intake level (UL) as a benchmark</td>
</tr>
</tbody>
</table>

The UL is not based on evidence-based concepts
Inadequate data are available for individuals of all ages, especially for children, and for all nutrients
Epidemiologic data were not considered
The uncertainty factor is very uncertain
It does not provide a balanced risk assessment
from both United States National Health and Nutrition Examination Survey (NHANES III) [Centers for Disease Control and Prevention, National Center for Health Statistics] and the United States Department of Agriculture (USDA) Continuing Survey of Food Intakes by Individuals (CSFII) surveys are fairly consistent in identifying the population of children with intakes greater than the UL. The real issue, as I see it, is the critical lack of evidence, based on good science, that proves that a serious adverse effect occurs in healthy individuals who habitually consume an “excess” of zinc.

The DRI report states: “Although there are no data indicating adverse interactions between zinc and other nutrients when zinc is found in food, adverse nutrient interactions are present after feeding zinc in the form of dietary supplements” (8). The adverse effect of excess zinc on copper metabolism (i.e., reduced copper status) was chosen as the critical adverse effect on which to base a UL for total daily intake of zinc from food, water, and supplements in humans. This selection was based on the consistency of findings from studies that measured the interaction of zinc and copper, the sensitivity of erythrocyte superoxide dismutase (ESOD) activity as a marker for this effect, and the quality and completeness of the database for this endpoint.

As a general observation, although I did not participate on the UL panel, it is my understanding that there was no systematic review of the literature by an evidence-based approach (10). Evidence on each topic was certainly reviewed, but there is a significant methodological difference between recommendations based on evidence and a formal evidence-based approach according to established guidelines; an example of the latter are the Cochrane guidelines for systematic review of the literature (11). Without the use of systematic reviews, it is possible that important literature related to the topic was missed and that professional interpretation/expertise was given undue value versus an objective review of the literature.

Criticism of the derivation of the UL for zinc is based on the following observations: To the best of my knowledge, there is only 1 case report of an otherwise healthy infant who apparently developed copper deficiency while receiving a normal diet that was supplemented with zinc syrup (12). The supplement provided 16 mg/d of zinc for 6 mo and 24 mg of zinc/d for an additional month. Combined with the typical amount of zinc in the diet of a 1-yr-old child, the total amount of zinc would have been in the range of 18–26 mg/d. With the discontinuation of the zinc and with the provision of intravenous copper, the child fully recovered in 2–3 weeks. This may be the only case in the literature of an otherwise healthy child who inadvertently developed copper deficiency from excessive dietary zinc intake. On the basis of this single case, one could argue that the LOAEL should have been set at 18 mg/d.

To set the NOAEL, data from a single study by Walraven and Hambridge (13) were used. They fed 68 healthy full-term infants either a formula containing 1.8 mg of zinc/L or a zinc-fortified formula containing 5.8 mg of zinc/L for 6 mo. No adverse effects were identified in either group. By using a zinc concentration of 5.8 mg/L and estimating the typical volume intake of breastfed infants in the first 6 mo of life at 0.78 L/d, the NOAEL was set at 4.5 mg/d (0.78 × 5.8). For older age groups, this value (which was rounded down to 4 mg/d) was extrapolated upwards on the basis of reference weights for the different age groups. There are, in my opinion, 2 serious flaws with this method: 1) the values were extrapolated from a value that was rounded down, and 2) no physiological justification or rationale for the use of an extrapolation based on weight was provided. As indicated in Table 3, the NOAEL would have been 1–2 mg higher for the youngest age group if it were based on the actual value instead of a value that was rounded down.

The sensitivity of ESOD as a marker of copper status is very questionable. The DRI report on micronutrients provides a comment on the use of ESOD activity: “ESOD, although not as specific as serum copper or ceruloplasmin, may be a reliable indicator of copper status” However, it goes on, “methods of analysis are not standardized, and normal ranges for ESOD activity are not available.”Despite these limitations (which I would identify as significant), the report states that “sufficient data are available to include it as an indicator of change in copper status when it is measured in controlled studies at different levels of dietary copper intake” (8).

Is it appropriate to accept ESOD as a single marker of copper status? My reading of the literature suggests that ESOD does respond in time to elevated zinc intakes but that the change in ESOD activity is not related to serum copper or ceruloplasmin levels (14). There is no evidence that ESOD is a marker of functional copper deficiency. For one to conclude that it is a marker, one would have to demonstrate that high levels of zinc intake first lead to depressed ESOD activity, and then copper (or ceruloplasmin) levels would fall. That has never been demonstrated.

The UL-DRI committee did not, as far as I can tell, use any of the available epidemiologic data (e.g., from the USDA CSFII database) to justify its choice of a NOAEL. My understanding of the modeling process for the development of the UL is that it should take into consideration current population intakes and the adverse effects (if any) associated with current intakes. As discussed earlier in this paper, the current mean intake of zinc is above the UL for ages 1–8 y. Because the report does not state that 50% of children aged 1–8 y are suffering from copper deficiency (or are even at a risk of copper deficiency), one can only conclude that the UL for this age range is considerably too low.

A final major issue is the derivation of the UL for older children when data are not available. As stated in the DRI report, “Due to a dearth of information, the UL for young infants was adjusted for older infants, children and adolescents

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Based on a NOAEL</th>
<th>Based on a rounded-down NOAEL</th>
<th>Actual UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 mo</td>
<td>7</td>
<td>5.8</td>
<td>5.1</td>
<td>4</td>
</tr>
<tr>
<td>7–11 mo</td>
<td>9</td>
<td>8.4</td>
<td>7.4</td>
<td>7</td>
</tr>
<tr>
<td>1–3 yr</td>
<td>13</td>
<td>14.1</td>
<td>12.6</td>
<td>12</td>
</tr>
<tr>
<td>4–8 yr</td>
<td>22</td>
<td>25.7</td>
<td>22.9</td>
<td>23</td>
</tr>
<tr>
<td>9–13 yr</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
on the basis of relative body weight as described in Chapter 3 using reference weights from Chapter 1 (8). The rationale for this decision is not apparent. There is likely an intake of zinc above which metallothionein begins to be formed in the enterocytes of the gastrointestinal tract. At a certain point, homeostasis is disturbed (i.e., more copper is lost from the gastrointestinal tract than is ingested). The homeostasis is complex, however, and depends on zinc and copper intakes and excretion, growth rates, etc. It is simplistic and unsubstantiated to assume that one can simply adjust the UL on the basis of differential weights. It assumes that there is a true cutoff between a no-effect level and an effect level. That is simply not likely to be true. Although I do not have an answer based on good science, I believe that identifying a range between a true NOAEL and a LOAEL would be a much more reasonable approach. At the very least, the UL must take into consideration current dietary intake.

My conclusion, therefore, is that the UL is set too low for zinc and, indeed, Table 4 shows that the recommended daily allowances (RDAs) and the UL for zinc are very close. When zinc requirements and toxicity are clearly established on the basis of strong science (basic and epidemiologic studies), a narrow range between an adequate intake and a toxic intake would be appropriate. This is simply not the case for zinc.

Vitamin A

The general features of hypervitaminosis A that define the critical adverse effects include anorexia, hyperirritability, occipital edema, pronounced craniotabes, bulging fontanels, increased intracranial pressure, skin lesions, and skin desquamation (8). The LOAEL (6460 µg/d) was identified by averaging the lowest doses from the 4 case reports that described toxicity (15). The average value was then rounded down to 6000 µg/d. An uncertainty factor of 10 was chosen to account for the uncertainty of extrapolating a LOAEL to a NOAEL for a nonsevere and reversible effect (bulging fontanel) and the interindividual variability in sensitivity. The same report identified a child whose chronic intake of vitamin A was 755 µg/d, with no signs of toxicity (15).

The concept of the uncertainty factor is based on a risk assessment for chemical exposures. For the UL process, the determination of the uncertainty factor was taken directly from the 1994 National Research Council (NRC) report entitled "Sciences and Judgment in Risk Assessment" (3). The NRC report states that small uncertainty factors (those close to 1) are used to represent adverse effects with little variability in the population and that large uncertainty factors (those close to 10) are used to represent those for which the variability is great. Because the critical adverse effect of bulging fontanel is virtually always observed with true vitamin A toxicity in infants and young children, with little variability in its presentation, one would expect that the UL committee would have chosen an uncertainty factor of 1, or at least a very low number (16). Instead, the committee chose an uncertainty factor of 10. With similar justification (or lack of justification), the committee could have chosen an uncertainty factor of 9, 8, 7, 6, 5, or even 1. The impact of the lower uncertainty factor and rounding down is shown in Table 5. The point of this exercise is to demonstrate the arbitrary nature of the process and the actual uncertainty of the final product (i.e., a UL of 600 µg/d).

It is also important to highlight that observed levels of chronic intake were not taken into consideration in setting the ULs. According to tables in the DRI report, the mean intake of vitamin A for children ages 1–3 y was 593 µg of retained activity equivalents (RAE)/d (95th percentile, 1259 µg of RAE/d) (8). Thus, about 25–30% of young children have, by definition, intakes above the UL.

It must be pointed out that vitamin A intakes based on CSFII data do not represent chronic intakes, but were determined from two 24-h recalls obtained on nonconsecutive days (3–10 d apart) (9). If >30% of young children have intakes greater than the UL, one would expect to see some evidence of vitamin A toxicity, most likely craniotabes, bulging fontanels (in the youngest children), skin changes consistent with hypervitaminosis A, or significant anorexia. That simply is not the case. Children in Canada and the United States routinely visit their physicians (family doctor or pediatrician) 4–5 times in the first year of life and at least biannually after that. There is absolutely no possibility that craniotabes or bulging fontanel would be consistently missed during routine physical examinations. It is therefore inappropriate, on the basis of science and common sense, that the UL of vitamin A for children in this age range be set at a level that places 30% of healthy infants in an at-risk category with absolutely no substantiation of the negative effects of vitamin A toxicity.

Folic acid

Hazard Identification: Excessive folate intake may obscure or mask and potentially delay the diagnosis of vitamin B-12 deficiency. A delayed diagnosis may result in an increased risk of progressive, unrecognized neurological damage. Folic acid and vitamin B-12 metabolism are closely linked; thus, it is important to ask whether children in Canada or the United States are at risk of B12 deficiency. The answer is clearly no. Vitamin B-12 deficiency has not been described in otherwise healthy children in Canada or the United States. Tables 9–4 of an IOM DRI report lists the conditions that may result from vitamin B-12 deficiency (7). These include dietary deficiency, lack of intrinsic factor (because of gastrectomy), atrophic gastritis, bacterial overgrowth of the small intestine, infection with Diphyllobothrium latum, terminal ileal disease, or resection or pancreatic insufficiency. All but the first are pathological conditions that would be identified by a health-care provider. In terms of dietary deficiency of vitamin B-12, the RDA is

### Table 4

<table>
<thead>
<tr>
<th>Age</th>
<th>RDA</th>
<th>UL</th>
<th>95th percentile intakes (NHANES III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7–12 mo</td>
<td>3</td>
<td>5</td>
<td>10.1</td>
</tr>
<tr>
<td>1–3 yr</td>
<td>3</td>
<td>7</td>
<td>12.9</td>
</tr>
<tr>
<td>4–8 years</td>
<td>5</td>
<td>12</td>
<td>14.2</td>
</tr>
</tbody>
</table>

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### Table 5

Effects of varying uncertainty factors and rounding down on the tolerable upper intake level (UL) of vitamin A for infants

<table>
<thead>
<tr>
<th>Uncertainty Factor</th>
<th>UL µg/d rounded at LOAEL 6000 µg/d</th>
<th>UL (µg/d) unrounded at LOAEL 6460 µg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5000</td>
<td>6000</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
<td>1200</td>
</tr>
<tr>
<td>3</td>
<td>500</td>
<td>600</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>500</td>
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<td>5</td>
<td>300</td>
<td>400</td>
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<tr>
<td>6</td>
<td>250</td>
<td>300</td>
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<tr>
<td>7</td>
<td>200</td>
<td>250</td>
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<tr>
<td>8</td>
<td>175</td>
<td>200</td>
</tr>
<tr>
<td>9</td>
<td>150</td>
<td>175</td>
</tr>
<tr>
<td>10</td>
<td>125</td>
<td>150</td>
</tr>
</tbody>
</table>

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Sciences and Judgment in Risk Assessment (3). The NRC report states that small uncertainty factors (those close to 1) are used to represent adverse effects with little variability in the population and that large uncertainty factors (those close to 10) are used to represent those for which the variability is great.
achieved except in vegans (those taking no animal-based foods or beverages) even at the 5th percentile of intake. Thus, the only children at risk of dietary B-12 deficiency are those who follow a vegan diet or those who have a gastrointestinal pathology. Indeed, in the medical literature I could find no cases of vitamin B-12 deficiency other than in infants exclusively breastfed from vegan mothers or those with a gastrointestinal pathology (17).

The discussion about vitamin B-12 deficiency is important because identification of the hazard of excess folate intake is based on the fact that folate masks vitamin B-12 deficiency. Therefore, if there is no vitamin B-12 deficiency among individuals in the age group in question, then the risk of a hazard from excess folate is virtually nonexistent and the process of extrapolating the folate UL for children from the folate UL for adults on the basis of relative body weight makes no sense. One can only conclude that the UL is set too low.

Since 1998, at least 3 governments and the WHO have published different recommendations for ULs for children (2,8). Table 6 shows the recommendations for zinc. There are many possible reasons why the recommendations are different, including different reviewers, different assessments of similar literature, different decision-making mechanisms, different outcomes measures, and competing interests. Clearly, the process of setting ULs is very complex and highlights the lack of sensitivity in the methods used to set ULs, especially for children.

In closing, I suggest that, as a basic principle, public health nutrition recommendations be based on good, sound evidence. The impacts of recommendations that are based on faulty science include public mistrust and cynicism, and a lack of confidence in all nutrition recommendations, not just the ULs. Whenever possible recommendations should be based on information gained by use of the principles of a formal, evidenced-based process. To summarize the major points, 1) When intakes exceed the UL, the significant uncertainty surrounding the UL allows me to conclude that intake is likely not the problem, but that the application of a UL with inadequate data is the problem. 2) For some nutrients, the narrow range between the RDA and the UL is unjustified when one considers the lack of demonstrated toxicity at current intakes above the UL. 3) Although the UL process was based on evidence, it did not use an “evidence-based” approach.

Although individual members of a community may be less at risk from uninformed policy making than they are from medicine that ignores the available evidence, the dangers to the community as a whole are substantial. The communication of public health policy carries an even greater responsibility than does the development of policy that is used for individual patients.

LITERATURE CITED


