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The following comments were submitted by John Hathcock, Ph.D., Vice President, Nutritional & Regulatory Affairs, Council for Responsible Nutrition in response to the Food and Nutrition Board's Workshop on Dietary Reference Intakes and Discretionary Fortification, held on November 21, 2002 in Washington, D.C.

## **1. UL – TOLERABLE UPPER INTAKE LEVEL: What it *IS*, and What it is *NOT***

FNB defines the UL 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.” The UL is calculated by identifying a No Observed Adverse Intake Level (NOAEL) (or the Lowest Observed Adverse Intakes, or LOAEL) and dividing by an uncertainty factor (UF), which is the numerical value assigned to uncertainty in the data.

Several aspects of the UL definition and method of calculation are subject to misinterpretation and thus deserve additional explanation:

- In the definition, the word “daily” means each day for the life of a healthy member of the general adult population. Hence, the UL, very appropriately, is likely to be much lower than the intakes that could be tolerated over a shorter period of time.
- In the definition, the term “no risk” does not mean that risk begins just above the UL, but, instead, the UL is the level confidently judged **not** to carry risk.
- The NOAEL is just that, a level at which **no** adverse effects have been observed. The NOAEL is **not** the threshold for adverse effects.
- If the UL is calculated from a LOAEL because a NOAEL could not be identified, a substantial UF is used. It is standard practice in toxicological extrapolations of animal data to use a factor of 3 for most data sets to convert the LOAEL to a likely NOAEL. Although the LOAEL is likely to be above the threshold for adverse effects, the UF is selected to provide a comfortable margin of safety. Note that the FNB has applied UF values larger than 3 to human LOAEL values for nutrients with potentially severe adverse effect (e.g., folic acid masking the hematological effects of vitamin B-12 deficiency while allowing the neurological effects to progress), but UF values smaller than 3 for human LOAEL values for nutrients with mild and transient effects (e.g., vitamin C osmotic diarrhea and nicotinic acid skin flushing).
- The UL is intended to apply to total intakes from all sources, unless specified otherwise. In some cases, intakes from conventional foods make trivial contributions in comparison with the UL (e.g., pyridoxine), but in others the amounts from conventional foods may make major contributions toward intakes that carry risk (e.g., retinol).
- The UL values for some nutrients have been based on effects that probably should not be deemed to be a “hazard” and thus qualify as the basis for the UL.

For example:

- Vitamin C: The “hazard” identified, and which served as the basis of the UL, is osmotic diarrhea and related gastrointestinal effects. The DRI report on vitamin C indicates that mild diarrhea may occur with intake of 3 to 4 grams. Any suggestion that all intakes above the UL are likely to prove “hazardous” is an exaggeration.
- Magnesium: In assessment of the uncertainty in the data on the “hazard” associated with excess magnesium intake, the DRI document notes the “...very mild, reversible nature of osmotic diarrhea caused by ingestion of magnesium salts...” Any suggestion that an intake above the UL is likely to

be so debilitating that the person would not consume the same amount the next day is an exaggeration of what the actual evidence shows.

- Niacin: The FNB has set the UL in relation to the flushing reaction to nicotinic acid. The LOAEL identified was 50 mg/day, but the discussion acknowledged that a recognizable amount of flushing can result from a 30 mg intake of nicotinic acid, but added that "...this reaction was not bothersome enough to change the dosing pattern." It is very dubious that the reaction at 50 mg is bothersome enough to be regarded as a "hazard" and thus qualify as the critical effect in a risk assessment under the UL or any other method.  
**The FNB further compounded this questionable endpoint selection by making a fundamental mistake in applying the nicotinic acid-derived UL to nicotinamide, a form of niacin that simply does not cause the flushing**
- For some other nutrients, the adverse effects certainly qualify as a "hazard" and their selection as the critical endpoint is fully justified. Any debate on the UL values for retinol, pyridoxine, selenium, and some others relates to the evaluation of their dose-response relationships and uncertainty in the datasets.

### **UL Summary**

- The UL is safe by a comfortable margin.
- The UL is not the threshold for adverse effects.
- The UL is not an intake that if exceeded by any amount will likely cause harm.
- The UL does not apply to temporarily elevated intakes.
- The UL does not apply to persons who have greater needs and tolerances than the average person (due to depleted status, poor absorption, or very large body size).
- The possible contribution of conventional foods and dietary supplements toward a UL level of intake varies greatly among nutrients.
- An intake that somewhat exceeds the UL is not necessarily unsafe.

## **2. RDA – RECOMMENDED DIETARY ALLOWANCE: What it *IS*, and What it is *NOT***

A theoretical risk from intakes near or above the UL is likely to be overemphasized if the risk of inadequacy with intakes near the RDA are not recognized. Consider the following scenario that clearly demonstrates that the RDA is not an ideal intake or an appropriate nutrient intake target for all individuals in a population:

**If the mean requirement is known with certainty (by including all members of the population), and the statistical distribution around that mean is exactly Gaussian, thus providing exact quantification of the variance (standard deviation), the RDA identifies an intake that would be sufficient for 97.5 percent of the population—but also insufficient for 2.5 percent of the population. If every member of the population put complete confidence in the sufficiency of the RDA and consumed a diet that provided exactly the RDA level of intake, 2.5 percent of the population would have nutrient intakes that were, by definition, inadequate. A health policy that would result in 2.5 percent of the population having**

**inadequate intakes cannot be justified as a goal—thus the RDA is not an appropriate target intake for the population.**

An ideal target intake for a population would be one that is a safe and convenient intermediate between the RDA and the UL. Such an intermediate level of intake could simultaneously provide safety from adverse effects of excess intakes and from risk of inadequacy resulting from insufficient intakes. For example, in contrast to the 2.5 percent inadequacy rate expected for intakes equal to the currently defined RDA, the mean requirement plus four standard deviations would identify intakes that protect all individuals but 1 in 13,000. (Note: a risk of 0.0001 would occur an intake 3.88 SD above the EAR.) It should be recognized, however, that there is no number of SD above the mean that would provide *certainty* of covering everyone in a population with a true Gaussian distribution.

For adult males, the following would apply:

Nutrient*	EAR	RDA based on + 2SD (as rounded by FNB)	“RDA” based on +4SD (with rounding)	UL
Folate (_g DFE)	320	400	500	1000
Vitamin A (as _g RE)	625	900	1150	3000
Vitamin B-6 (mg)	1.4	1.7	2	100
Vitamin C (mg)	75	90	105	2000
Vitamin E (mg TE)	12	15	18	1000
Selenium (_g)	45	55	65	400
Zinc (mg)	9.4	11	13	40

\* For the nutrients listed, the FNB assumed a 10 % CV, except retinol with a 20% CV.

This scenario comparing the RDA and a value 4 SD above the EAR does not address the issue of whether the endpoints selected by the FNB to serve as the basis of the RDA are the most appropriate ones. If endpoints related to risk of chronic disease (e.g., increased folic acid intake lowering homocysteine levels and the related risk of heart disease, or increased selenium intake decreasing the risk of certain cancers) had been selected as the basis of the RDA (regardless of the 2 SD vs 4 SD issue) the separations of the RDA and the UL would be considerably different. In such a circumstance, these relationships would need to be reexamined.

Under the scenario described, an intake at the EAR + 4 SD would occur at the location shown in the graph provided at the end of this document.

### **RDA Summary**

- The RDA applies to well established endpoints, but not to other effects with much supporting evidence, which may also be critical to the public health.
- The RDA is a useful guide to assist individuals in understanding their risk of inadequacy in relation to the endpoints used in setting the RDA.

- The RDA is not an appropriate target intake for a population because if the data are reliable and all assumptions are correct **and** every member of the population consumed exactly the RDA amount of a nutrient, 2.5 percent of the population would have inadequate intakes.
- An RDA defined as the EAR + 4 SD would provide much better protection of a much higher proportion of the population without generating intakes anywhere near the UL, as shown with the examples given in the table above and the graph at the end of this document.

### 3. CRN'S RECOMMENDATIONS

- The degree (both probability and severity) of risk of intakes at or somewhat above the UL should not be exaggerated.
- The RDA should not be used as the target intake for a population.
- The RDA may be used as a guide to inform individuals of the risk of inadequacy they would encounter at that intake.
- The UL may be used to assure individuals that there is little or no risk at that intake or lower.
- The FNB Panel on Use of Dietary Reference Intakes in Nutrition Labeling should take overt actions to recognize and utilize the principles listed above.

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#### **Graph of nutrient intake vs risk of deficiency and toxicity**

If the RDA were defined as the EAR + 4 SD, the RDA line would be approximately at the first "e" of the word Observed, on the x-axis. Note that the x-axis scale is not known to be proportional for any specific nutrient. On a linear scale, the overall U-shaped curve could be narrower for some nutrients but is much wider for others, such as pyridoxine.

