Response to: "Discussion Paper on the setting of maximum and minimum amounts for vitamins and minerals in foodstuffs"

Elizabeth J. Johnson, Ph.D.
Research Scientist, Carotenoids & Health Laboratory
Jean Mayer USDA Human Nutrition Research Center on Aging
Assistant Professor
Friedman School of Nutrition Science and Policy
Tufts University, Boston, MA 02111 USA
Email: elizabeth.johnson@tufts.edu

Allen Taylor, Ph.D.
Director, Laboratory for Nutrition and Vision Research
USDA Jean Mayer Human Nutrition Research Canter on Aging
Tufts University, Boston, MA 02111 USA
Email: allen.taylor@tufts.edu

Norman I. Krinsky, Ph. D.
Scientist, Jean Mayer USDA HNRCA at
Tufts University
Boston, Ma 02111
Email: norman.krinsky@tufts.edu

John C. Lang, Ph.D.
Director, Consumer Products Research & Development
Alcon Research, Ltd.
Fort Worth, Texas 76134 USA
Email: john.lang@alconlabs.com

Overview

First, and most importantly, we applaud the efforts of the Directorate to enforce the use of sound analytical, scientific, and statistical methods for determining effective and safe levels of nutrients for a broad spectrum of EU, and probably world, populations. We endorse the Directorate's effort to harmonize these standards of nutrition. We also understand the difficulty of concluding such a comprehensive evaluation. Our concerns, and perspectives, are considerably narrower, as can be gathered by our affiliations. Our comments will concentrate on nutrition for the aging and aged, and in particular on preserving eye health in that segment of the population where clinical studies indicate improved nutrition may postpone progression of sight-threatening pathologies.

There are essentially four areas in which the Directorate has addressed questions (page numbers refer to the Discussion paper):

1. Setting of safe maximum levels of vitamins and minerals (p. 11)
2. Population-dependent values for intake levels of vitamins and minerals (p.12)
3. Selection of reference values (PRIs /RDAs and ULs / MSLs) of vitamins and minerals (p. 14)
4. Establishing minimum levels of vitamins and minerals in fortified foods and food supplements (p. 15)

We will address each of these areas separately in the next four sections. The segment of the population to which our responses are directed will be that fraction with ages 45-50 years and older. And even more narrowly, we are addressing the needs for those at particular risk of age-related eye disease, diseases such as macular degeneration, cataracts, and ocular complications of diabetes. It is well-known that the risk of each of these diseases increases significantly with age.

Finally, it should be clarified that we do not intend to provide the Directorate with new, profound, comprehensive information that their experts have not discovered or developed. On the contrary we wish to share concerns about how those data will be judged and interpreted.

In addition to these four areas for which we have provided responses, we also hazard to make recommendations related to the perspective presented in the text of the Discussion Paper itself. That will be the final section entitled:

5. Selective responses to the EC discussion paper

1. Setting of Safe Maximum Levels of Vitamins and Minerals

Let us begin by comparing current and proposed worldwide standards for the nutrients of greatest interest to the segment of the ophthalmic community interested in preserving eye sight by improving nutrition of the elderly.

Nutrient	Current EU PRI	Proposed MSL (Max Supp Level)	AREDS (daily)
Vitamin A Retinol Beta-Carotene	800 mcg	800-1000 mcg 4.8 – 7 mg	 15 mg
Vitamin C	60 mg	1.75 g	500 mg
Vitamin E	10 mg	270-970 mg	400 mg
Vitamin B1	1.4 mg	-	-
Vitamin B2	1.6 mg	-	-

Nutrient	Current EU PRI	Proposed MSL (Max Supp Level)	AREDS (daily)
Vitamin B3	18 mg	820 mg	-
Vitamin B5	6 mg	-	-
Vitamin B6	2 mg	18-93 mg	-
Vitamin B9	200 mcg	600 mcg	-
Vitamin B12	1 mcg	-	-
Zinc	15 mg	10-15 mg	80 mg
Copper	-	1-2 mg	2 mg
Manganese	-	2 mg	-
Selenium	-	200 mcg	-
Lutein			AREDS II
Zeaxanthin			AREDS II
DHA (docosahexaenoic acid)			AREDS II
EPA (eicosapentaenoic acid)			AREDS II

The AREDS column has been added because this widely publicized, ground-breaking, 10-year clinical study proved the benefit of the nutritional ingredients, antioxidants and zinc, on diminished rate of loss of visual acuity and rate of progression to advanced AMD.[1,2,3] That important study indicated that the rate of progression to advanced AMD was slowed by more than about 25% for those individuals who routinely consumed the daily AREDS regimen found in the last column of the table. The consequence is that vision was extended several years for those individuals simply compliant with the AREDS multivitamin mineral doses.

From our perspective the new guidelines for Maximum Supplement Levels (MSL's) goes a very long way toward allowing the AREDS formulation to be acceptable in a harmonized European setting. Few complications were observed, and those that were have been openly discussed in the literature describing the AREDS trial.[4,5] This large 4000 patient trial supports the perspective of the Directorate, that these levels of nutrients are indeed safe.

There remains one significant outlier; namely, zinc. The amount of zinc is roughly five to eight times the proposed MSL. But please note that the derivation of this limited amount assumes that the high level of zinc results in copper deficiency, which compromises the activity of superoxide dismutase. This points out both a specific and a general issue arising from the analysis, and plainly indicates the complexity of arriving at specifications for nutritional ingredients. Specifically, combinations of ingredients appear to alter the simple calculations of toxicity. That

gredients appear to alter the simple calculations of toxicity. That is, there may be no simple additive contribution of elements in these combinations.

In the specific case of zinc, it is well-known that the depletion of copper generated by excess zinc is readily reversed by complementary supplementation of copper. This was precisely one of the factors investigated in the AREDS trial.[6] And even at the 69-84 mg of zinc provided, no systematic increase in toxicity, either of gastrointestinal side effects or changes in serum lipids, was detected, and with only 2 mg of copper, no systemic effects of copper deficiency were observed.

And so the general recommendation is that the Directorate allow for some flexibility in the designation of the MSL's as a consequence of complementary effects expected from adjunctive ingredients. More specifically, in the case of appropriate results from controlled clinical trials, we urge the Directorate to allow the MSL's to be adjusted. Presumably in other circumstances one can imagine the converse happening, in that one ingredient potentiates the effect of another ingredient, and in so doing may require adjustment downwards of the collective MSL's.

We pursue one final point with regard to maximum levels important to ocular nutrition. Certainly, the designated safe levels of minerals such as manganese and selenium come a long way toward allowing appropriate ocular supplementation, providing antioxidant cofactors important to tissues undergoing rapid metabolism. On the other hand there is sufficient epidemiological data, pilot clinical data, and even theoretical data to support a very large clinical evaluation in the AREDS II trial of the effect of both ocular carotenoids, lutein and zeaxanthin, and omega-3 fatty acids on progression of AMD. All of these ingredients are GRAS (Generally Recognized As Safe, and their European equivalent) at the levels administered, and are essential nutrients, not available from human biosynthesis. From this perspective we encourage the Directorate to develop means of establishing categories of essential nutrients, other than vitamins and minerals, whose nutritional value once demonstrated in adequate trial(s) can be approved and harmonized, for the appropriate levels, throughout the EU.

2. Population-Dependent Levels of Vitamins and Minerals

While we applaud the direction that the Directorate's analysis has led and the very rational approaches and conclusions drawn from them, we want to encourage the Directorate to acknowledge that these analyses apply to populations of individuals, but not necessarily to each individual. That is, the variable requirements for individuals are affected by numerous additional factors that impact individual nutritional responses ranging from their individual physiology to how and when the nutrients are administered, to what nutrients are provided more or less concurrently, to the dosage form, excipients, or food or drug that are provided concurrently, to the individual's nutritional, medical and disease status, and so on. Ultimately, these are

guidelines that should be respected for what they are, approximate markers that, in the absence of a full nutritional analysis, can serve to guide the consumer in his or her selection of foods and supplements to provide for themself a full balanced diet. The rationalization on energy is sound, so that individuals appreciate the fraction of good nutrition they are receiving for the calories they must consume.

However, the Directorate is aware, as are the nutritional experts cited, that any individual's needs may depart significantly from the guidelines and are shaped by their own individual health and nutritional circumstances. The ultimate designation of a nutritional requirement is derived from the composite bioavailability of the essential nutrients required for optimal biofunction of the human organism.

So that for any particular consumer, any symptoms linked to a suspected nutritional deficiency needs to be explored with the individual's physician. As the populace ages, and a larger fraction is consuming different sorts of medications, which can be expected to influence nutritional status, then one can expect significant departures may occur for the nutritional needs of the consumer / patient. One simple example, among an enormous number, is the need of individuals taking statins in order to control cholesterol levels to increase intake of other essential nutritional ingredients such as calcium. Another example is the dependence of the amount of required nutrient on the primary reason for its administration. More particularly, if essential omega-3 fatty acids are being provided to reduce symptoms of inflammation, the levels may be quite different from those provided to assist in the reduction of cholesterol. If vitamin A or vitamin E is being provided concurrently with large doses of omega-3 fatty acids, the demand for these vitamins may deviate from the guidelines being proposed.

We conclude that indeed some guidance should be provided to the different population subgroups in order that the inherent variability of the guidelines can be appreciated. The individuals in these subgroups should come to understand how they may need to adjust their nutritional requirements relative to the broad guidelines in order to match their personal nutritional status. Ultimately, we imagine genetic testing and blood screening could be done to provide optimized and individualized instruction of an individual's nutritional requirements. When such procedures become commonplace, it would be simple to eliminate unintentional duplication of nutrient effects. While we have not reached this status currently, we believe we should provide some guidelines to significant groups or subgroups having different nutritional requirements. And, furthermore, we believe these guidelines should be derived from nutritional studies and the conclusions of nutritional scientists, and not simply for the convenience of the manufacturer.

3. Selection of Reference Values (PRIs /RDAs and ULs / MSLs) of Vitamins and Minerals

The Directorate has in fact emphasized the importance of the tolerable upper level, UL, of Maximum Supplement Level (MSL). We presume that the UL is determined either as it is in the Dietary Reference Intakes description of the IOM (U.S.)[7] or an analogous manner. In either event, the reference standard is based on either the NOAEL, the LOAEL, the UL or the MSL wherein all are dependent on the lowest toxic concentration of the nutrient. We endorse this approach and encourage its adoption. These reference levels make clear how to define the maximum level an individual may consume on a chronic basis. Except for any population-dependent variability (discussed above) any reference to the PRI's or RDA's does not seem germane to setting upper levels.

This is not to suggest, however, that there is no need for PRI's or RDA's. The populace needs not only to avoid excessive amounts of nutrients, but also to achieve quite routinely the minimum recommended amounts. And these probably are assessed most thoroughly when there are preclinical data as well as a history of human consumption. Perhaps the most intricate and delicate question in a European context is to determine the boundary between a nutritional and a medicinal effect for essential nutrients. From our perspective, it would appear that this boundary has been set somewhat arbitrarily in some jurisdictions and results in a skewing of the nutrition available without a prescription. Evidently the Directorate in part is sympathetic to this position in that the level of vitamin E recommended as the MSL is more than twenty-five times the current RDA for some EU countries. We endorse this position of the Directorate since there appears to be so little risk in raising this boundary between a dietary level and a prescription level, permitting OTC purchase rather than requiring physician intervention.

Similarly, there are a few other nutrients for which harmonization of this type will assist in providing the populace with appropriate levels of essential nutrients without the need to seek a prescription from a physician.

We offer one further recommendation to those establishing these recommended (minimal chronic daily supplement) requirements. The suggestion is that the variability in human requirements for these essential nutrients be included in the assessment of the RDA's. Whether explicitly or implicitly, it is clear there are numerous sources of human variability, including age, weight, common medications, disease states, and even geographic distribution of a population. Some allowance and provision in the recommended levels of essential nutrients should be offered in guidance to significant fractions of the population for which some adjustment would be expected. It is in this context that perhaps it makes good nutritional sense to include on labeling not only the RDA's (see next section) but also the MSL or UL, so that the consumer can monitor that his or her consumption remains in a safe range.

4. Establishing Minimum Levels of Vitamins and Minerals in Fortified Foods and Food Supplements

Our consensus is that the standard minimum amount to be provided in the daily serving of either a fortified food or a supplement should be the PRI/RDA. It would seem unnecessarily burdensome for the consumer to be required to take 6 to 7 supplement doses to reach the RDA. In our view addition of a significant amount defined as about 15% of the RDA is unnecessarily small, would be misleading to the consumer, and lead to inadequate supplementation.

In some circumstances it may be appropriate to adjust the RDA in light of the PRI's, especially where it may be justifiably expected that a particular population could have different nutritional requirements than another. The recommendation would be to leave open the possibility of broadening tolerances in response to observations of increased confidence intervals, such as those that may result from divergent values found for disparate populations. For example Nordic stock may require different supplementation patterns than Mediterranean populations, perhaps for genetic reasons but equally possibly because of different environmental stresses. Or a segment of the population may have divergent needs because of age, sex, disease state, genetic requirement, and the like. One could imagine the possibility of a two-tiered RDA, with the recommendations dependent on the characteristic driving divergent results.

Another precaution we would recommend during the setting of these minimal guidelines is, given our observation that serum responses of placebo groups appear to diminish gradually over the course of a study, to be cautious about individual's assessments of their intake. It would seem, on using antioxidants as an example that either subjects may not recall all of the ingredients contributing to their antioxidant status, or that there are synergies not appreciated currently. The inference is that subjects may have higher baselines of particular ingredients than expected from either dietary recall or measurements, and so the RDA may actually be higher than these other assessments might suggest. Again, some assessment of the variability in the determinations, or the confidence intervals around them, might well be included in the RDA's.

5. Selective Responses to the EC Discussion Paper

For ease is identifying the location to which the comments are directed, these will be put in tabular form

p./#/l.	Citation	Comment / Query
6/6/2	"free circulation"	To what jurisdiction(s) is this to apply? The entire EU?
6/7/4	"labeling"	Request further labeling requirements, for inclusion of "other ingredients" and more information, when appropriate re. to sources
8/17/1	"significant amounts" …"by	This should not be set by manufacturers, with chance for unsubstantiated

	the manufacturer"	variability. This should be the EU RDA for each nutrient, eliminating inconsistencies. This should be the "significant amount". We do not believe "discretion" should play any role here. The RDAs / PRIs are scientifically determined, and it is these quantities to which industry should adhere.
11/Q1/1	in absence of scientific data …	Our recommendation is to use the Adequate Intake values from various populations. There is concern about the abuse by consumers of the UTL in these instances.
11/Q2/3	"maximum levels" for low risk	Yes, maximum levels should still be designated (based on sound scientific evaluation). At high enough levels risk of any nutrient will increase, and that should be designated.
11/Q3/2	"separately for food supplements and fortified foods"	The maximum level should make clear the cumulative combined limit from all sources. Nonetheless, the information from surveys should identify the amount from each source.
11/31/1	"household"	Our strong preference is to seek data from individuals (for whom an outcome is being investigated) not from a composite derived from a house-hold.
12/Q2/1	"Member States …"	The UTLs should be relatively independent of State of origin, though this should be confirmed for those nutrients for which the data are available.
14/Q1/2	"PRIs/RDAs …"	Since the goal of the PRIs / RDAs is to achieve health optimization, if there are segments of the population for which health optimization can be improved relative to PRIs / RDAs, then this information ought to be communicated.
22/ILSI	"at the 95th centile"	Use of an energy criterion may not always be appropriate. For nutrients, like lutein supplementation, in which the amount needed is affected by energy consumption / level of adipose tissue other criteria may more appropriate. Furthermore, the level from which benefit maybe derived may be in excess of the average amount consumed by a particular population.
25/Stage 2	"UTLs"	Based on ophthalmologic/nutritional/epidemiologic studies published to date (for current review see. Chiu and Taylor, 2006, *Exp Eye Res*. 2006 Jul 28), there is little contradiction between the levels recommended for eye health and those recommended by the EC and included in this discussion paper, with the single exception of zinc. Given both the differences in toxicity and health impact of the different salts of zinc as well as the significant benefit for one population (AMD patients), [1] at levels at an appreciable multiple of the RDA, we recommend the MSL for zinc be reassessed. This may be a good example of a nutrient for which the MSL is significantly population dependent, and should be based on a benefit to risk analysis.

[1] The Age-Related Eye Disease Study Research Group, *Controlled Clinical Trials* **20**:573-600 (1999).
[2] Age-Related Eye Disease Study Research Group, *Archives of Ophthalmology* **119**:1417-1436 (2001).
[3] Age-Related Eye Disease Study Research Group, *Archives of Ophthalmology* **119**:1439-1452 (2001).
[4] Age-Related Eye Disease Study Research Group, *Neurology* **63**:1705-1707 (2004).
[5] AREDS Research Group, *Archives of Ophthalmology* **122**:716-726 (2004).
[6] The Age-Related Eye Disease Study Research Group, *J. Nutr.* **132**:697-702 (2002).
[7] *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and* Carotenoids, Panel on Dietary Antioxidants and Related Compounds, Food and Nutrition Board, Institute of Medicine, National Academy Press (2000). See especially Chapters 4 and 6.