

Opportunity to Respond to Questions

This form provides the opportunity to respond to the questions posed in the Background Paper: Joint FAO/WHO Development of a Scientific Collaboration to Create a Framework for Risk Assessment of Nutrients and Related Substances.

Responses may be typed in to the form directly or appended as an 'attachment' to each question (use 'Upload file'). Fields with asterisks are required. Responses and your name/organization will be available for public viewing.

Name/Organization

Title

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First name *

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Name of Organization (Use 'None' if none) *

Council for Responsible Nutrition

Affiliation Category (click on bar to select a sector) *

Industry

Today's Date *

09/12/2004

Question 1

The Background Paper discusses the possibility that hazard identification and hazard characterization have global relevance, while exposure assessment and risk characterization are relevant to populations. If such a conceptual framework for the four steps is appropriate, then scientific principles could be organized and considered along these same lines.

Question 1a: Is the distinction between global relevance and population relevance for the four risk assessment steps a meaningful consideration for the purposes of developing an international nutrient risk assessment approach? (Please indicate why or why not)

(attachment)

Yes, the distinction between global and population relevance is appropriate and useful.

Global relevance: The discussion should recognize that the UL process is conservative and provides a comfortable margin of safety, thereby justifying a single UL value for each nutrient that applies to all healthy adults.

Population relevance:

The discussion should recognize that food intakes and consequently nutrients intakes vary for different reasons. Food habits and selection may cause wide variations in the intakes of specific nutrients, e.g., liver intake leading to high intakes of vitamin A in a few persons. Soil mineral composition, and consequently local food composition, may vary geographically, e.g., selenium content of soil in different geological/geographical areas can vary enough that selenium deficiency occurs in one area while selenium toxicity occurs in another.

Discussion: Consideration of both UL and usual intakes could be useful in risk assessment for vitamins and minerals in fortified foods and supplements in a context that could be used directly in risk management decisions on the maximum amounts of these nutrients permitted in products. The European Commission Food Supplements Directive (FSD) (Article 5) approaches this issue in the setting of maximums for supplements by identification of a difference, i.e., the UL for total intake from all sources less the expected intake from other dietary sources. The FSD also permits giving "due account" to population reference intakes. Some countries have attempted to interpret this "due account" as the authority to set limits directly based on population reference intakes, PRIs (also known in some countries as recommended dietary allowances, RDAs), but the European Court of Justice has struck down several attempts to take this action. More recently, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) has approved a vitamin and mineral supplement guideline that is similar to the EC FSD, except that the guideline states that "due account" to PRIs does not allow maximums to be based solely on these values.

Question 1b: If so, please provide specific suggestions about how best to further articulate and make good use of the differences in identifying the scientific principles for nutrient risk assessment.

(attachment)

Global and population based factors should be recognized and assessed separately. Final risk assessment inputs for use in risk management must involve integration of these two domains. This can be done through either of two approaches: (1) the difference between UL for total intake

and the expected dietary intake, or (2) a direct risk assessment on evidence relevant to supplemental intakes of the nutrients. The direct approach is described in some detail by Hathcock 2004 (cited by FAO/WHO under Other Information Identified). The direct approach is simpler, subject to less uncertainty, and logically valid when the intakes from foods were known for the subjects involved the experiment that provided the supplemental intake risk assessment (for example, the selenium trial by Clark et al., 1996), or when the intake from conventional foods is small in comparison with the UL (or guidance) value. Chromium is an excellent example of the latter.

Question 2

Hazard identification and characterization involve a number of decision points that require scientific judgment in order to derive a UL. Please provide input as to how guidelines for these judgments can be developed for the following decision points:

Question 2a: Criteria for the evaluation of the quality and utility of relevant scientific evidence.

(attachment)

Endpoint (“hazard”) selection

Identification of an effect that qualifies as a “hazard” is a critical part of the UL risk assessment procedure. Effects may be undesirable but not qualify as a hazard.

An undesirable effect may in be only a nuisance when it is expected, but may be considered a hazard if it occurs unexpectedly. Niacin (as nicotinic acid) provides an excellent example:

1. The vasodilative flushing reaction is undesirable but does not cause any known pathology. The EC SCF set its UL on the hypothetical possibility that vasodilation might cause positional hypotension and risk of falls, but did not cite any case in example. Notably, CRN (Hathcock 2004) has used to the flushing effect to require a warning label at the level equal to the FNB UL.
2. The data used by the FNB, SCF and EVM to derive UL values are of questionable relevance to foods or supplements. Those data were produced by giving bolus doses on free nicotinic acid to subjects with empty stomachs, thus maximizing the vasodilative potency of the nicotinic acid. The UL values derived from such data are apt to be unduly restrictive.
3. At much higher intakes than those that clearly cause flushing, nicotinic acid can cause liver and/or gastrointestinal pathology. Clinical trial data indicate a LOAEL of 1,000 mg and a NOAEL of 500 mg for these effects. These effects obviously would qualify as hazards and therefore be appropriate endpoints for nicotinic acid risk assessment.
4. The flushing effect may be the appropriate basis for a UL for products without a warning label (such as conventional foods and most manufactured foods). On the other hand, products, such as supplements, that can carry a flush warning label could have a UL based on the liver/gastrointestinal effects.

Considerable caution is routinely applied in selection of the adverse effects that serve as the critical effect “hazard” in the UL risk assessment procedure. For example, the FNB UL for zinc is based on a small clinical trial in adult women that showed somewhat decreased activity of copper-dependent superoxide dismutase, even though no pathology was associated with this biochemical change. The amount of reserve functional capacity in this enzyme system in humans is not known, and therefore selection of this endpoint as the basis of the UL is appropriate but cautious.

Some biochemical changes, however, are protective reactions that do not in any way represent potential hazard. For example, zinc induces metallothionein in the intestinal mucosa cells, and this induction has not and should not be identified as the critical effect in zinc risk assessment.

These examples are sufficient indication that selection of the effect to be considered the “hazard” in the risk assessment requires scientific judgment that must be exercised on a case-by-case basis.

Data quality and evaluation

Human data usually are of lower scientific quality than the analogous animal data. Ethical, legal, and practical considerations limit the types of human data that may be collected. Animal data may be more complete in terms of the types of tests performed and of higher statistical quality (replication and variability), but animal data have one major limitation—the necessity to extrapolate across species in order to evaluate the implications for humans. Quantitative extrapolation is most difficult, always resulting in considerable uncertainty in the human UL calculated, even if the data are of high quality.

The differences in data selection and the uncertainties of extrapolation are well illustrated in the FNC, SCF and EVM risk assessment on pyridoxine (vitamin B-6). All risk assessments agreed that excessive intakes of pyridoxine can cause a sensory neuropathy that only slowly or perhaps incompletely recovers. The differences in evaluation of pyridoxine data are summarized below:

- FNB considered the long-term uses of high-dose pyridoxine in subjects who were monitored by physical neurology methods to be sufficient and most appropriate for the setting of the pyridoxine UL. In contrast, the FNB considered the survey data on Dalton and Dalton (1986) to be of such low scientific quality as to not be an appropriate basis for the UL.
- SCF recognized the limitation of the Dalton and Dalton data but nonetheless used it as the basis of the UL. The UL was calculated from the median adverse effect level and an uncertainty factor of 4.0.
- EVM considered all the human data to be of insufficient quality and therefore identified a UL (SUL in EVM terminology) from animal (dog) data through application of a composite uncertainty factor of 300 to the NOAEL.

For pyridoxine, the EVM considered the high quality of the animal data and poor quality of the human data to warrant acceptance of the uncertainty of extrapolation between species. Even though an extrapolation from animals to humans was needed, the EVM considered the outcome to be a SUL rather than the comparatively uncertain “guidance level” it set in lieu of a SUL for most nutrients.

Question 2b: Extrapolation to various age/gender groups.

(attachment)

Extrapolation

Any extrapolation always involved uncertainty and requires assumptions to be made. The assumptions should be explicitly identified. The extrapolations that require assumptions and involve uncertainty involve at least the following:

- Diseased populations to the healthy population, or the reverse.
- Men to women, or the reverse.
- Adults to children (because most data relevant to safety applies to adults)
- Body size differences (often in combination with one or more of the other factors).

- Animals to humans.

The FNB has extrapolated from adult data to set UL values for children based on body size or metabolic body size. Many have criticized this process with its obvious assumptions and uncertainties, but a superior system has yet to be identified.

In the absence of a superior system, it is appropriate to use the FNB extrapolations from adults to children.

Age extrapolation: While there are problems with any system, that based on body sized used by the FNB is the best available at this time.

Gender considerations: No extrapolation is necessary if the UL is based on the most sensitive gender (e.g., vitamin A by the FNB and SCF).

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Question 2c: Determination and use of uncertainty factors.

(attachment)

The great advantage of the UL method for risk assessment is that it employs continuously variable uncertainty factors derived from each nutrient specific database, without use of any default uncertainty values. In this way, the UL method is far more appropriate for nutrient risk assessment than any other procedure. A disadvantage of the UL system is that identification of the uncertainty factors requires scientific judgment, but an overriding advantage is that identification of the UF from each dataset avoids the nonsensical answers of ULs sometime below recommended intakes. Because the UF values are limited to 1, 3, 10 or multiples of these values, the ADI and US Environmental Protection Agency's Reference Dose (RfD) sometimes identify "safety limits" below the recommended intakes or simply far lower than needed to achieve safety. The ADI and RfD were designed to calculate safe levels of substances such as pesticides and heavy metal contaminants that are not desirable at any intake level, but are simply unavoidable at some level. Large margins of safety are appropriate for such substances, but the same margins for nutrients would lead to safety limits below the recommended intakes.

Question 2d: Other

(attachment)

Sensitive subpopulations

Specific sensitive subpopulations are of concern, but reasonable judgments based on objective criteria must be applied. The UL procedure, as identified by the FNB (1998) includes consideration of "sensitive subpopulations." Therefore a properly identified UL includes consideration of sensitive groups, and this does not need to be done as a separate step after in risk management.

Careful and practical judgment needs to be applied in determination of which sensitive subpopulations should be considered in order to prevent the setting of nonsensical UL values.

Worst-case scenarios clearly must be avoided. For example, a UL for copper that would be protective of those with the copper-accumulation genetic disorder known as Wilson's disease would have to be so low that the general population would be copper deficient if intakes were limited enough to protect this most sensitive subpopulation. An analogous situation arises with phenylalanine and the subpopulation with phenylketonuria (PKU).

Similarly, certain extrapolation for essential nutritional benefits may not be extrapolated to genetically unusual groups. For example, the nutritional benefits of zinc intakes in normal individuals cannot be extrapolated to those with acrodermitis enteropathica, a genetic defect in zinc absorption that renders the usual intakes of zinc completely inadequate by one or two orders of magnitude.

Question 3

The conduct of exposure assessment and risk characterization also requires sound scientific principles that can be applied to the various decision points, including but not limited to compilation and collection of intake data and decision-making for summarizing the potential for harm.

Question 3a: Please provide input on general scientific principles relevant to the process of determining exposure for a nutrient or related substance.

(attachment)

Exposure assessment must be put into context of the size of the UL in relation to ordinary or usual intake (both mean and range) and the recommended intake. For example, the UL for vitamin E is far higher than ordinary dietary intake (mean and range). Thus, an intake that exceeds the recommendation does not carry the same risk that an excessive intake of vitamin A (as retinol) carries.

Exposure assessment from supplements (or fortified foods) should be judged against the variability of intakes from unfortified conventional foods. For example, retinol intakes from unfortified conventional foods can vary from deficient to toxic, and data from the UK indicate that the primary risk of exceeding the UL comes from consumption of liver, not supplement. Selenium provides an excellent example of high intakes coming from locally grown foods in certain geographical areas because of the high selenium content of those soils.

Question 3b: Please provide input on general scientific principles for the characterization of the severity and the degree to which intakes exceed the UL or other aspects of risk characterization.

(attachment)

Risk characterization should be influenced by the severity and persistence of the adverse effect. That is, to serve as the basis of the UL, the effect should qualify as a hazard, rather than a nuisance. For example, the choice of the vasodilative flushing reaction as the "hazard" resulting from excessive intake of nicotinic acid is not justified by either its severity or persistence.

Instead, basing the UL on this effect has led to a large fraction of many populations consuming without any known harm intakes above the UL. The flushing effect is a nuisance but it could be managed by appropriate labeling of products with added nicotinic acid.

Question 4

The Background Paper reflects a 'thought process' and is intended to inform a longer process for the development of a technical expert workshop. Clearly the process will benefit from additional input.

Question 4a: Please provide comments on other general factors or considerations that could be taken into account during the process of identifying principles for nutrient risk assessment.

(attachment)

The general principles that make risk assessment appropriate for application to nutrients are mostly the same as for risk assessment of any substance, but with a few significant and important differences.

Hazard identification, causality evaluation and dose-response evaluation are nearly universal. Uncertainty assessment is very different for nutrients. The large uncertainty factors applied to environmental contaminants and food additives can lead to nonsensical UL values for nutrients—“safe” levels below the recommended intakes.

Question 4b: Please provide other comments on the content of the Background Paper.

(attachment)

In addition to the answers to the previous specific questions, CRN offers the comments and editorial suggestions to improve the scope, focus, and precision of the Background Paper.

Page 5

Additional sentence to insert at the end of the first full paragraph on this page:

Internationally recognized upper levels are needed for implementation of the section on maximums in the vitamin and mineral food supplement guideline, now at Step 8, in the Codex Committee on Nutrition and Foods for Special Dietary Uses.

In second full paragraph, last sentence, between “no” and “guidelines” insert the words:
internationally recognized

Page 6

At the end of the last sentence in the first partial paragraph, after “food additives” add the words:
, using the Acceptable Daily Intake (ADI) method, which can lead to safety values less than the recommended intakes for certain nutrients.

In the second sentence of the first paragraph of Section III, add at the end of the sentence:
while recognizing that the scientific outcomes of risk assessment should have major impacts on risk management decisions.

Page 7

Next to last paragraph, add at the end of the last sentence:
and their corresponding range of potential adverse effects.

Last paragraph, next to last sentence, the words “ways they deem appropriate” seems to be an invitation or license to ignore the risk assessment outcomes. Replace with:
ways that are consistent with the scientific outcomes and the needs of particular populations with their documented biological and dietary characteristics.

Page 8

Figure 1 has no discernable meaning and should be deleted. The size, shape and degree of overlap of the circles and the ellipse suggest meaning that is not there. In contrast, the definitions in the boxes just below Figure 1 are quite good.

Page 9

The paragraph just below the UL definition box is quite good but needs more formatting or typographical emphasis—perhaps with bolding or underlining.

Page 10

Line 1: The word “upper” should be inserted before “**quantitative.**”

Paragraph 2, last sentence: The word “term” should be replaced with “procedure” and the following clause should be added at the end of the sentence:
because the usual definition and procedure may lead to identification of upper levels below the usual recommended intakes for some age-gender groups.

Figure 2:

Hazard Characterization box—an additional item should be added to cover situations in which the no adverse effects have been observed:

- **Evaluation of data relevant to safety at the highest levels with appropriate and sufficient data, if no adverse effects have been at any level.**

Paragraph just after Figure 2: Add at the end of first sentence, just after “UL”:
or evaluation of safety if no UL can be identified.

Page 11, Section B:

The first sentence should be rewritten as follows:

The application of a risk assessment approach to nutrients and related substances requires, as mentioned earlier, recognition that these substances provide health benefits, and thus are unlike non-nutrients.

Second sentence: Replace “safety” with “default uncertainty” and replace “data uncertainties” with “dataset.”

First paragraph, sentence beginning with “JECFA”: Replace “appropriate” with “**necessary.**”

First paragraph, add the following sentences at the end and as part of this paragraph:

The UL seems to be identical to the upper end of the AROI. If uncertainty factors sufficient to ensure safety are selected the intake value identified will be the UL or a similar value. If the uncertainty factors selected are larger than necessary to ensure safety, the resulting value will reflect nutritional policy rather than safety.

Page 12

End of third full paragraph, after "related bodies" add:

In order to address comprehensive approaches and reviews in relatively few documents.

Hazard identification paragraph: In the words "with a given" add just after "with" the words "**excessive intakes of.**"

Page 13

Line 6, replace "significance" with "**consequence**".

Line 7, replace "necessary reliance on" with "**application of differing**".

Line 7, replace "on hard data" with "**being required by the data.**"

Line 8, delete the words "the significant".

At the end of the last sentence in this paragraph, add:

are sometimes judged persuasive in the selection or rejection of certain datasets.

At the end of the second paragraph, add the sentence:

The great disadvantage of using animal data is the necessity of quantitative extrapolation to humans.

In the Hazard Characterization section, add a third paragraph that reads:

The consequences of these differing judgments are large. This is especially evidence in the choice to rely upon human data of lower quality that does not require cross-species extrapolation *versus* the choice to use animal data of higher quality but which requires extrapolation with its uncertainties.

In the Exposure Assessment section, add the following sentence at the end of the first paragraph:

Determining exactly how high an intake to evaluate requires judgment, but neither a mean nor a worst-case scenario gives realistic results that adequately protect the public health.

Page 14

Line 5, replace "tendency" with "**practice**".

Line 6, after "overages" add "of nutrients that are likely to degrade during the shelf-life of the product" and delete the remainder of the sentence.

Last sentence in this paragraph, after "consistent" add "and **convincing**".

Risk Characterization section, line 7, replace "the potential" with "**any**" and add after "**harm**" the words "that has occurred".

After the last sentence in the Risk Characterization section, add a new sentence:

They acknowledged, however, that the dose-response relationship seems to be linear and without threshold, thereby making the selected value a judgmental choice.

Add a new paragraph after the third paragraph in the Risk Characterization section:

The relationship between risk assessment and risk management has driven the

choice of datasets for risk assessment for supplements by an industry association (Hathcock, 2004). In this example, the risk assessment was performed on data related to *supplemental* intakes. This direct approach to supplemental intake safety avoids the uncertainties involved in the indirect approach (by *difference* between the UL for total intake and the expected dietary intake). This direct approach requires selection of data related to supplemental intakes in persons who have representative dietary intake of the nutrient under consideration.

Page 15

Footnote: Replace "would be expected to" with "**may**" and add at the end of this first sentence: "**, especially when environmental conditions and culturally based food preferences are substantially different**".

Page 16

End of first paragraph, add the sentence:

The procedures for using the UL and population data to identify justified risk management options should be based on an internationally harmonized set of scientific principles.

Section 1, end of second paragraph, after "LOAEL" add:

", and thus the EC SCF LOAEL should account for greater sensitivity based on preexisting liver disease."

Section 1, after the sentence ending with "in nature" add a new sentence:

Human data, however, have the advantage of not requiring extrapolation between species.

Page 17

Section 2, add a new paragraph after paragraph 1, as follows:

Some genetic anomalies clearly illustrate that the most extremely sensitive individuals cannot be the basis for risk assessment or risk management for the general population. Two well-know examples illustrate this point: (1) persons with Wilson's disease cannot excrete copper and thus can tolerate only extremely low copper intakes that would be severely deficient for health adults, and (2) persons with phenylketonuria (PKU) do not metabolize phenylalanine normally, leading to toxicity of intakes that would be deficient for others.

Section 3, delete the second paragraph or modify it to recognize that these refinements of the 10-fold uncertainty factor are only moderate improvements of the ADI process, and these modifications require toxicokinetic and toxicodynamic data that are commonly available only in animal datasets. This approach has the disadvantage of demanding the extrapolation from animals to humans, with its robust uncertainties.

Page 18

At the end of line 2 ("good health") add a new sentence:

The uncertainty factors must not be arbitrarily adjusted to manipulate to outcomes to be artificially near the recommended intakes, or else the risk assessment is not following sound scientific procedures.