

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

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Today's Date *

10/12/2004

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)

For chemicals in food, it is generally accepted that information on hazard identification and characterisation is globally applicable. While there may be genetic- and age-based differences in the response of healthy individuals to nutrients, as there are for other chemicals, such differences are likely to be more readily identified for nutrients given the extensive amount of human data available. Intake of nutrients, on the other hand, will vary considerably between population and within populations. The use of supplements will greatly influence intake of nutrients for some groups. As a consequence, risk characterisation for many nutrients will be population and sub-population specific.

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.

For hazard identification and characterisation, the principles currently used for other chemicals in food are equally applicable to nutrients. WHO and national governments have articulated these in various publications.

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.

Unlike other food chemicals, the majority of the data for nutrients on hazard identification and characterisation is based on human studies. While this provides a significant advantage in relation to the relevance of the data, it is likely to introduce further uncertainty in relation to the quality of the data. Data quality will be influenced by many factors, including the study design, number of participants, strength of the cause-effect relationship, applicability to the general population, and peer review of the data. Bioavailability will also be a more significant issue for nutrients than for other food chemicals. Scientific judgement will always play an important part in the final decision

regarding the acceptability of the data, although where used, this should be stated.

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

Extrapolation to age/gender groups will depend on the nature of the various adverse endpoints and whether it is appropriate to use the same endpoint for all age and gender groups. Gender differences are unlikely to be common, except for specific life stages (e.g. pregnancy and postmenopausal women), while age differences are common, and therefore specific studies on different age groups are preferable to extrapolations based on bodyweight. For most nutrients, there is a reasonable understanding of age-related differences and therefore specific studies on different age groups are generally required.

Question 2c: Determination and use of uncertainty factors.

Establishing the uncertainty factor used to extrapolate limited data to the general population is probably the most contentious element of the hazard characterisation of nutrients. This may be helped if there was a better understanding of the dose-response relationship curve, particularly at the lower end of the curve where adverse effects begin to appear. If data were available, it may be possible to establish a benchmark dose rather than relying on a NOEL or a LOEL. Compared to other food ingredients, more toxicokinetics and toxicodynamics information is generally available for nutrients.. This may assist in reducing the uncertainty factor for interspecies variation. The use of an uncertainty factor to account for poor data may not be an option for nutrients.

Question 2d: Other

The severity of the adverse effect is another issue that requires scientific judgement. In many cases, there is debate as to whether the observed effect is truly adverse or whether it may be an adaptive response. While most effects are measured using objective criteria, in some cases, subjective criteria may also be considered. The clinical significance of a particular observed effect may be assisted by reference to animal models.

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.

There are a number of general principles relevant to the process of determining exposure (or intake) for a nutrient or related substance. Intake estimates for nutrients would be most appropriate at the specific country level, given the different food consumption patterns and nutrient content of foods between different countries. One limitation of conducting nutrient intake estimates at the global level is the lack of relevant food consumption data at this level. The GEMS/Food Regional Diets focus primarily on consumption of raw agricultural commodities, which is more relevant for assessing exposure to contaminants and pesticides. They lack coverage of a wide range of processed foods, which would be required if fortification had to be considered in the intake assessment. There are also different foods fortified and different nutrients used for fortification in different countries, which would also cause difficulties if trying to estimate global intakes.

One principle of importance to nutrient intakes has already been highlighted in the Background Paper, namely, estimating 'usual' nutrient intakes. This would generally require food consumption data for more than one day. However, this would also need to be reliant on the toxicological endpoint determined for the particular nutrient. If acute/short term effects occur, then one-day food consumption data would be better to assess intake for this nutrient. The other consideration in relation to the toxicological endpoint is that the intake assessment must be calculated for the form of the nutrient for which the endpoint has been derived. For example, if it is only the supplementary use of the nutrient that is assessed, then supplementary use should form the basis of the intake assessment. If assessing supplementary use, the frequency of taking supplements needs to be considered. If fortified foods are included in the assessment, the market share of the fortified products may need to be considered.

All sources of the nutrient should be included, where relevant to the assessment, such as naturally occurring sources, fortified foods, and supplements. The latter two may have a significant impact on the estimated nutrient intakes and the foods/sources contributing the most to the estimated intake. The bioavailability of the nutrient should also be considered in the context of the intake estimates, however, in some instances this may be difficult to factor into the actual calculations, and may just be used as supplementary text when presenting intake assessment results.

At a country level, regulatory agencies may determine a policy on when to take regulatory action in relation to nutrient intake estimates, for example, if there are 5% or more of the population that has exceeded the upper level. This would need to be determined based on the consumption data and the composition data used for the estimate and the level of certainty or confidence there is in these datasets.

Another factor that needs to be considered for nutrient intake assessments is the age groups for which the assessment will be conducted. It is likely that there will be certain groups for which an assessment should always be conducted (eg, children), but there may be other age groups for which an upper level has been set.

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.

The consequences of exceeding the UL for the general population will depend on the nature of the adverse endpoint and our understanding of the dose-response curve, particularly at the low dose end. Furthermore, it is important to quantify whether any group in the population might be at risk of more serious adverse effects other than the adverse effect that was used as the basis for setting the UL. Principles will be based around the need for accurate data to support the adverse endpoint chosen and the uncertainty factor used to establish the UL. For the more sensitive groups in the population, which may be related to age and/or life-stage, separate ULs may be

needed. The intake distribution and number of individuals potentially over the UL will be critical factors.

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.

In general, the methodology normally used in chemical risk assessment is applicable to nutrients. At the risk characterisation stage, for all chemicals, it is essential to consider and discuss with risk managers the available management options in order to achieve a workable outcome. This is particularly the case with nutrients where the risk management options may be more limited and the need to ensure that the full benefits of an adequate intake of nutrients are achieved.

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

The discussion document presents a reasonable overview of the issues relevant to the risk assessment of nutrients.