

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

American Society for Nutritional Sciences & American Society for Clinical Nutrition

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

Professional Association

Today's Date *

12/10/2004

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)

The American Society for Nutritional Sciences (ASNS) and the American Society for Clinical Nutrition (ASCN) would like to thank Drs. Sanford Miller, Ian Munro, Joseph Rodricks and Allison Yates for their help in drafting our responses to these questions.

ASNS and ASCN believe that it is important that users of the international nutrient risk assessment approach developed as a result of the deliberations and workshop understand that a quantitative reference value (in this case, a UL) is an estimate, based on data available, of a level of intake thought to not present increased risk of identified adverse effects to almost all of the individuals to which the UL applies. The ability to tolerate a nutrient biologically should be similar on a global basis, given the expected variability in response based on body size and metabolism. This constitutes the first two steps of risk assessment: hazard identification and characterization.

While exposure (a third step in risk assessment) will vary depending on geographic location, food supply, food habits, etc., data on intake from similar populations is also useful to the review and evaluation of the assumptions used in characterizing the hazard in step 2 of the process. Thus the exposure assessment, while specific to various populations and not critical to the hazard characterization, does play a role in global considerations of hazard analysis, and thus can't be considered to be only relevant to the specific populations for which it is developed. Since there are global and regional differences in nutrient intake, sources, and bioavailability (for some nutrients), it may not be possible to completely dissociate the aspects of hazard characterization and of risk characterization.

Regardless of whether exposure assessment is considered to be global or population based, it is important for the international nutrient risk assessment working group to include in its task the development of guidance on uniform methods to collect data on intake and on its evaluation relative to characterizing risk.

In terms of importance to the development and use of an international risk assessment methodology, this consideration (global versus population based) is of less importance than is developing a method to evaluate the limited data that is typically available. It will be necessary to establish an easily understood way of explaining the differences in what is done globally versus in regional areas if the four steps are disjointed and developed under different protocols.

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.

The scientific principles in nutrient risk assessment should not be 'different' whether globally determined or population specific; however, it is possible that the resulting risk characterization may be different due to different or limited data on exposure applicable to specific populations. It

would seem that one aspect needed in the discussion at the workshop would be to evaluate what additional assumptions are needed when exposure data are limited or lacking, which might then result in a different risk characterization. It also is probable that the risk analysis/management may be quite different depending on the population of interest as well as competing risks of inadequacy. These issues follow the nutrient risk assessment, but are not included in it.

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.

The members of ASNS and ASCN know that the ranking of scientific evidence and a determination of criteria to evaluate relevance is an arduous task. It is, however, the most important aspect of developing useful science-based nutrient risk assessments that can then serve as the basis for good risk management policy development. There are an increasing number of methods that have been put to ranking scientific information, all of which should be reviewed in preparation for the workshop. They include older criteria for ranking diet and disease relationships (Hill, AB. 1971. Principles of Medical Statistics, 9th ed., New York: Oxford University Press.) as well as methods recently issued as interim guidance by the U.S. Food and Drug Administration for ranking of evidence relative to health claims (www.cfsan.fda.gov/~dms/hclmgui4.html), the U.S. Preventive Services Task Force methods to evaluate evidence (www.ahcpr.gov/clinic/uspstfix.htm), and others, including the U.S. Agency for Healthcare Research and Quality (at <http://www.ahrq.gov>), the American Dietetic Association (at <http://www.eatright.org/>), the Canadian Task Force on Preventive Health Care (at <http://www.ctfphc.org/>), the Center for Evidence Based Medicine (at <http://www.cebm.utoronto.ca>), the Cochrane Collaboration/Cochrane Reviews (at <http://www.cochrane.org>), Evidence-based Practice Internet Resources (at <http://www-hsl.mcmaster.ca/ebm/>), etc.

Such evaluation methodologies, while arduous and time consuming, should be strongly considered as a way to minimize subjectivity in evaluating available data, given the variety and unevenness of data typically available relative to adverse effects associated with consumption of specific nutrients, as described in the Background Paper.

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

One the largest gaps in the currently available nutrient risk assessments is the amount of data on various age and gender groups. It should be possible to develop better methods of extrapolating the limited data available to these groups when no data are available about their experiences relative to the adverse effects in such groups. Based on the differences in nutrient distribution and metabolism among individuals of different body sizes, physiological ages, and gender, it should be possible to develop an applicable model. It should take into account the mechanism of excretion of excess amounts of the nutrient, the body pool size, the relationship to storage compartments, etc. Unless significant evidence is to the contrary, it should be assumed that if one age/gender or

lifestage group has shown evidence of adverse effects, there is a high probability that all individuals will show adverse effect at some level of intake.

Question 2c: Determination and use of uncertainty factors.

The hazard characterization step includes the use of an uncertainty factor (UF), which is the collective judgment of 'certainty' with regard to the data available. It may be very difficult to develop a quantitative model that establishes a UF based on weighing the available factors that must be taken into account. For example, seriousness of the adverse effect is different than lack of toxicology studies, or irreversibility of the effect, but all three are considered in developing the UF. This will probably be the most difficult aspect of the task for the workshop group: developing a quantitative metric that can include and weigh the different aspects of concern that go into establishing risk.

Review of the experience documented in the three nutrient risk approaches reviewed in the background paper should aid the group in dissecting how UF's are derived and frame, through inductive reasoning, the necessary process and its component parts.

Question 2d: Other

Consideration should be given to determining what should be the mechanism when there isn't adequate data to develop a UL. Should there be a minimum data set for a UL recommendation? If not, then should there be another reference value that is designed to impart information to the user that 1) caution is warranted, and/or 2) more data is needed before the UL can be provided? Other international bodies (e.g., FAO/WHO Joint Expert Committee on Food Additives) have indicated when there is inadequate data to set an Adequate Daily Intake (ADI)---such as a temporary ADI.

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.

The American Society for Nutritional Sciences and the American Society for Clinical Nutrition believe that while there is limited data on adverse effects of many nutrients, in many situations

there is also limited data on dietary intake and intake of dietary supplements upon which to evaluate exposure. In almost all instances, data on family or household consumption is of limited value. There may be a tendency to misuse similar data unless specific guidance is included in the international nutrient risk assessment protocol about the types of data and methods of collection necessary to estimate exposure when characterizing risk.

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 development of the UL should include consideration of the severity of the effect as part of determining the UF. To enhance uniformity of approach, there should be a categorization of the severity or seriousness of the adverse effect as well as its reversibility that leads to determination of the UF. It is also necessary to establish whether the data indicate that intake from all sources is of concern, or just from large bolus amounts consumed in a relatively short time period. Similarly, the form of the nutrient may make a major difference in its toxicity or ability to elicit an adverse effect, and thus the specific chemical forms to which the UL applies are important to delineate.

The risk characterization step should be used both as a basis for public policy, but also as a mechanism by which the UL can be reviewed to ascertain that assumptions used in its development are well-founded. Large percentages of the population of interest with chronic intakes above the UL should lead one to question the derivation of the UL as well as the exposure estimates if there is no evidence of the adverse effect or early signs or markers of its development. This doesn't mean that the hazard characterization is incorrect, but merely means that it should be reviewed carefully.

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.

The American Society for Nutritional Sciences and the American Society for Clinical Nutrition believe that the international nutrient risk assessment group should consider the issue of what to do when data is of lowest quality and relevance; should there be a temporary UL as with food additives (JECFA)?

While the UL is meant to establish a level at which the most sensitive in the population group will not experience adverse effects, it is possible that this level of intake may not meet the needs of others. This risk of adverse effects, compared to the risk of inadequate intake, must be also considered in establishing a UL. There are usually more and better quality data on requirements, so that fewer assumptions and thus smaller safety factors are needed to establish the range of requirements in a population group. Given that larger 'safety' or uncertainty factors will be used in developing the UL, principles need to be included that focus on this issue.

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

In general, the background paper represents a good summary of the issues involved in applying risk assessment methodology to nutrients. To advance the utility of such assessments, aspects of modern biology should also be investigated (e.g., proteomics or metabolomics). While there is probably not yet a great deal of data available, one of the functions of conducting a risk assessment is to point out where data are lacking and thus needed to improve the utility of the assessment.

While not included in the background paper, given the serious lack of data useful to determining ULs, significant consideration needs to be given to developing appropriate experimental models for studying the adverse effects of chronic high dose exposure to nutrients that are applicable to humans. Many aspects of the traditional toxicology models are not useful and consensus on modifications needed to obtain appropriate data for studying nutrient excess is needed.