SUMMARY NOTES

- Worldwide consumption of dietary supplements, highly fortified foods and so-called 'functional foods' has been increasing dramatically in recent years. This, in turn, has raised questions about 'safe' upper levels of intake.
- FAO and WHO have released a joint report on the process of risk assessment as it relates to high intakes of nutrient substances.
- The report outlines the scientific approach (or model) to be used in establishing upper levels of intake for nutrient substances.
- The model is based on the approaches used for non-nutrient risk assessment and contains the four recognized steps of risk assessment, namely hazard identification, hazard characterization, exposure assessment, and risk characterization.
- The model will assist in promoting international harmonization for this type of risk assessment.

Introduction

In January 2006, a report from a joint FAO/WHO scientific workshop was issued electronically (http://www.who.int/ipcs/highlights/nutrientproject_may18/en/index.html) and will soon be available in hardcopy. The workshop participants were asked to develop an internationally applicable science-based approach -- or model -- for the risk assessment of nutrient substances to identify quantitative 'safe' upper levels of intake of such substances. Their work took into account existing national and regional approaches as well as approaches established for non-nutrient substances. Note that workshop participants were not charged with identifying upper levels of intake for specific nutrient substances, but only to identify an approach or model to do so.

The workshop was convened by FAO and WHO based on interest from Member States who wished to monitor and evaluate nutrient substance intakes given changes in the world's food supply that include increased use of nutrient fortification substances and dietary supplementation. In addition, the Codex Alimentarius Commission had requested FAO and WHO to provide scientific advice about upper limits of intake for vitamins and minerals. This request derives from the Codex mandate to set international recommendations and guidelines to protect the health of the consumer and promote fair trade in food. Further, WHO has a long-standing interest in promoting the harmonization of risk assessment practices, and nutrient risk assessment is an important extension of this work.
Nature of the Report

The report addresses nutrient risk assessment as a ‘marriage’ between nutritional and toxicological sciences. The model is based on the approaches used for non-nutrient risk assessment and contains the four recognized steps of risk assessment, namely hazard identification, hazard characterization, exposure assessment, and risk characterization. In the report, each step is described within the context of the special considerations important for nutrient substances, which as a class uniquely present risks at both low levels of intake in the form of nutrient deficiency and at high levels of intake in the form of toxicity.

In addition, the merging of nutritional and toxicological approaches necessitated an examination of terminology and key definitions. As a result, the report contains clarifications of terms and adjustments to terminology to make them more appropriate for nutrient risk assessment.

At the outset it was recognized that hazard identification/characterization result in an outcome -- notably specification of an 'upper level of intake' or 'UL' -- that is globally relevant, i.e. relevant across wide and diverse populations. On the other hand, exposure assessment and risk characterization produce outcomes that are population relevant. This means that risk characterizations can be inherently different depending upon the target population. From the perspective of harmonization, quantitative ULs have the potential to be harmonized. Dietary intake assessment and risk characterization will have different outcomes around the world, but clearly these assessments would benefit from agreed-upon principles for how they are derived.

The nutrient risk assessment model and its key activities are portrayed schematically in the report (see Figure 1).

Fig. 1 Nutrient Risk Assessment Model
The reports emphasizes the importance of the initial 'problem formulation' step, which ideally should be conducted as a dialogue between nutrient risk assessors and nutrient risk managers. It precedes the activities of nutrient risk assessment and clarifies the needs of the manager as well as ensures that the nutrient risk assessment outcome is maximally useful to the manager. On the other hand, separating the role and specific responsibilities of the assessor from that of the manager is underscored by the report, and discussions are included concerning the types of decisions that reside with assessors and those that reside with managers.

**Key Conclusions of the Report**

**Transparency**
Following their review of the existing national and regional nutrient risk assessment publications, the workshop participants concluded that nutrient risk assessment in general would benefit from more transparent decision-making and better documentation concerning the rationale underpinning the decisions made. It was recognized that scientific judgment is an integral part of risk assessment, but the reasoning associated with such judgments must be evident.

**Nutrient hazard identification/characterization**
The participants described the nutrient hazard identification/characterization process as iterative and requiring considerable refinement of data searches and database development. It begins with the identification of adverse health effects associated with the nutrient substance and makes use of human, animal, and *in vitro* data. The rating of study quality and the use of tables to summarize the data were considered useful and relevant to transparency.

A pivotal point in the hazard identification/characterization process is the selection of the critical adverse health effect. This is the effect upon which the UL is based. The participants concluded that the selection process should be driven primarily by the interest in providing maximum public health protection, which usually means selecting the adverse health effect that occurs at the lowest level of intake. In turn, the basis for selection does not focus on the severity of the effect or necessarily on the effect with the 'strongest' evidence.

Workshop participants acknowledged the desirability of deriving ULs using a 'benchmark dose' (or, for this report, a benchmark intake) because such values are based on information gleaned from a range of studied intake levels. However, they concluded this is not generally feasible in the case of nutrient risk assessment. Available data are often very limited and therefore often fail to specify effects within the context of a range of intakes. Therefore, *No Observed Adverse Effect Levels* or *Lowest Observed Adverse Effect Levels* are usually used and will require careful consideration of correction for uncertainty.

**Dietary Intake Assessment**
By providing a quantitative estimate of intake for the nutrient substance within the population of interest, dietary intake assessment gives the information needed to estimate the proportion of the population that is likely to exceed the UL. When combined with other information from the hazard identification/characterization process, the dietary intake assessment is essential to describing the risk associated with excessive intake. A critical goal of the workshop was to identify general principles for dietary intake assessment for the purpose of harmonizing the process of such assessments. It had been noted that differences in the approaches used to estimate intake of nutrient substances was an aspect of existing nutrient risk assessments most likely to vary. These principles are laid out within the report as recommendations for practice.

Further, it was observed that the nature of available consumption databases frequently precludes the ability to derive an estimate of total intake using a single database. So, there is often the need to combine different types of consumption data or data obtained from different surveys using different samples in order to estimate total intake. In particular, it is common practice to 'add on' an estimate of supplement intake to an estimate of intake from foods. This shifts the food intake distribution by a fixed amount and can result in serious over-estimation of intake, especially if the maximum supplement 'dose' available (or even the 95th
percentile) is used as the ‘add on’. Participants suggested that this ‘add on’ be no more than the median or perhaps a weighted average across the range of available supplement ‘doses.’

**Risk Characterization**

Nutrient risk characterization functions to integrate the outcomes of the earlier steps into a set of conclusions that address the nutrient risk managers' need for scientific information to make risk management decisions. The information is both quantitative and qualitative. A concern identified during the workshop is that risk characterization has to be tailored for and useable by risk managers; it must serve as more than a summary intended for risk assessors. It was concluded that improved understanding of nutrient risk managers' needs would reduce the chance that relevant information might be overlooked during the development of risk characterization.

**Threshold Model versus Non-threshold Model**

Because the model is based on the identification of the point along the continuum of increasing intake at which risk may occur, the model is applicable to substances that demonstrate a threshold effect, i.e. an intake level above which adverse health effects occur and below which they do not. While this appears to be the vast majority of nutrient substances, there are some substances, such as saturated fatty acids, that are generally regarded as having adverse health effects at any level of intake. In these cases, different models or special modifications to the threshold model need to be explored and were identified as a future research need.

**Special Populations**

Nutrient risk assessment has been most widely used with populations that are adequately nourished and generally healthy. However, workshop participants also considered the model as it may relate to inadequately nourished or diseased populations. It was agreed that the process identified for establishing a UL was appropriate for use with special populations. However, if scientific information about the metabolic states of these populations were used in the model, it was anticipated that ULs established for such populations would be different from those established for adequately nourished and generally healthy populations.

**Data Gaps and Research Needs**

The report repeatedly points out that the database needed for nutrient risk assessment is very limited at present and attention should be given to filling the data gaps and increasing the scientific knowledge in this topic area. The final chapter of the report describes the current research needs. It calls for studies on the general metabolism of nutrient substances, for studies to clarify the nature of adverse health effects, and for research targeted to identifying meaningful biomarkers of effect. Further, it highlights the need for work to articulate guidelines for data evaluation including the selections and interpretation of available data and the process for dealing with data uncertainties. In the area of dietary intake assessment, methodologies applicable worldwide for estimating dietary intake are lacking. And importantly, additional discussions are needed to enhance the interface between nutrient risk assessors and nutrient risk managers particularly in identifying the key elements of the problem formulation process in order to better specify the needs and expectations of the risk manager.

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