

## 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.

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### *Name/Organization*

#### **Title**

Ms

#### **First name \***

Cath

#### **Last name \***

Mulholland

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

Food Standards Agency

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

Government

#### **Today's Date \***

10/12/2004

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## **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)**

Yes it is appropriate to consider risk assessment of nutrients in this way.

**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 identification and characterisation of risk from over or under consumption of nutrients is likely to be universal within a population (subject to the variation of particular sub-populations). In some cases the risk may only apply to a sub-population. However, risk characterisation needs to take into account background exposure to the nutrient which will be variable due to population differences in dietary exposure and exposure to the nutrient from other sources (eg mineral content in local water). This will affect the likelihood of both over and under-consumption of nutrients depending on the dietary pattern.

The diet of the population concerned may also modify the hazard. For example the adverse effects of excess iodine intake will depend on previous exposure (or lack of exposure) to iodine. It is also possible to hypothesise that adverse effects could be modified by antagonistic and synergistic interactions between particular nutrients, particularly competing minerals, or by intake of other dietary components such as protein. These sorts of interactions would need to be considered on a population.

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## **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.**

As noted in the document, there are standard references, which provide objective criteria to assess the quality of particular studies. However, many of the studies in the database for

nutrients are non-standard and need to be considered individually in the context of the overall data set. Additionally data from different types of investigations will have to be brought together. For example large intervention trials are unlikely to contain data on biochemical parameters, whereas small scale trials will look at the effects of particular nutrients in vivo but will not have large numbers of participants or long follow up times.

When seeking information or further work, preferences for particular study designs can be specified, but the suitability of the design will be affected by the quality of the conduct and reporting of the study.

In general terms, the risk assessment will need to consider the appropriateness of the design, conduct and reporting and also the statistical power. Studies where data are present on background exposure to a particular nutrient are particularly important.

In the interests of transparency, criteria for the evaluation and assessment of data should be set out in advance as far as possible.

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

Extrapolation of the findings to different ages or genders needs to be considered case by case as it will depend on different factors for different nutrients. Some examples are considered below.

Extrapolation to children may be problematic because of their increased requirements compared to adults. For different nutrients, body surface area rather than weight could be appropriate. However the developing renal and nervous systems of infants may be more sensitivity to particular effects.

Older adults – deficiency of some nutrients such as vitamin D are more likely, equally reduced kidney function may pre-dispose to mineral or trace element toxicity.

Gender is most likely to be an issue if high levels of a nutrient could have a specific reproductive or developmental effect. Generally nutrient requirements would not differ much, with the exception of iron.

#### **Question 2c: Determination and use of uncertainty factors.**

The rationale supporting the use of uncertainty factors should be established in advance and should be consistent as far as possible. A decision should be taken on what to do when the uncertainty factors for adverse effects result in an upper level below known dietary requirements.

The final decision on which, if any, factors should be applied will have to be taken for each individual nutrient depending on the database. Where possible data-derived uncertainty factors should be used. If this is not possible, standard default factors should be used - however, it should be possible to modify the uncertainty factors to some extent. For example, extrapolation from LOAEL to NOAEL could take into account the severity of the adverse effect, similarly, an uncertainty factor applied to account for a limited database could reflect the severity of the data deficiency. While much of this can be agreed in advance of the assessment, there will still be a need for scientific judgement, for example, to decide how severe an effect is.

#### Question 2d: Other

There will need to be consideration of what to do when an upper level cannot be agreed due to either an absence of adverse effects or a lack of data. For example, is it useful or possible to indicate some sort of safe intake, possibly with the use of additional uncertainty factors.

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### 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.

Nutrition- ideally, survey data from different geographic populations should be comparable.

It will be necessary to consider intakes of nutrients from all sources and model appropriately. High consumers of dietary nutrients are often high consumers of supplements.

Exposure data will also be needed for local water if not covered by dietary data and other sources

It will be necessary to have the best quantitative dietary data available that gives intake estimates for individuals and is representative of the population. Reliable, comprehensive composition data are required to estimate nutrient intakes. The best data available may differ depending on the nutrient being considered.

#### 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.

This will depend on the nature of the effect, the shape of the dose-response curve (which is rarely known) and the uncertainties involved in setting the upper level.

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## **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 definition of nutritional requirements (prevention of deficiency vs optimum health) will need to be carefully considered, as it should be consistent.

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

In general terms, the paper focuses almost entirely on toxicological aspects of nutrient risk assessment, although it is acknowledged that the hazards associated with nutrients are two-tailed. It might be better to concentrate on a toxicological risk assessment (and title the document accordingly) but note where the assessment affects nutritional considerations (uncertainty factors, determining exposure levels etc). If the idea is to take a two tailed approach to risk assessment, then much greater consideration needs to be given to nutritional concerns.

The databases available for nutrition and toxicology will be different. For nutrition, there is a standard hierarchy of data with human work generally the primary consideration with randomized controlled trials as the gold standard. The next level of evidence is prospective cohort studies, with other forms of epidemiological evidence, e.g. cross sectional studies and case-control studies, being considered as less robust. While this hierarchy would also apply to toxicology, it is rare that this kind of data would exist and so toxicology tends to be based on retrospective human data, or more usually, animal studies. The EVM experience was that the databases tended to be a mix of human and animal studies, none of which were precisely designed for nutrient risk assessment. Consequently a great deal of scientific judgement is required to integrate these data and this will make harmonisation challenging.

The risk assessments conducted by the SCF, EVM and IOM do not differ that much in term of process. However, the emphasis placed on different aspects of the database does vary and it is difficult to see how that can be harmonised without being very prescriptive as each nutrient will have a different data set.