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Joint FAO/WHO
Development of a Scientific Collaboration to Create a Framework
for Risk Assessment of Nutrients and Related Substances

BACKGROUND PAPER
And
REQUEST FOR COMMENT / CALL FOR INFORMATION

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Preface

The need for an internationally relevant or 'harmonized' approach for nutrient risk assessment is well recognized. The increased consumption of fortified foods, formulated so-called 'functional foods,' and dietary/food supplements has made nutrient risk assessment highly relevant to protecting public health and to the practice of setting science-based international standards for food. Just as there has been a need for international nutrient reference values to specify the adequate levels of nutrient intake, there is likewise a need for identification of upper levels of intake which if exceeded may cause harm.

In September 2004, two United Nations organizations, the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), announced their intention to begin activities to address the issue. This Background Paper has served as an informal 'conceptual exercise' to assist the two organizations in identifying key considerations and questions relevant to the development of an international scientific approach for nutrient risk assessment.

*Geneva, Switzerland
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I. INTRODUCTION

Certain nutrients and related substances¹, like other ingested substances (e.g., food additives, contaminants), can produce adverse effects if intake exceeds a certain amount. This potential for harm is described by the process of risk assessment, which is a science-based evaluation of available data followed by a series of decision points. Risk assessment is well established for non-nutrient chemicals in foods. However, nutrients and related substances are unlike non-nutrients in that, within a range of intake, they provide benefit. For this reason, new paradigms have had to be considered that build upon the principles established for assessing the risk from non-nutrients, but also go beyond to incorporate additional or different principles that take into account the special characteristics of nutrients and related substances.

This Background Paper was developed by two United Nations organizations, the Food and Agriculture Organization (FAO) and the World Health Organization (WHO). Its purpose is to raise questions. It is organized to set nutrient risk assessment within the existing approaches for non-nutrients and to highlight the special considerations needed to address nutrients and related substances. The starting point for this paper included general risk assessment approaches as described by FAO/WHO and others, as well as three nutrient risk assessment reports developed at the request of national or regional governments and related bodies.

FAO and WHO are now asking for input on the questions and considerations that have been identified in developing this paper. The responses received will assist the two organizations in planning for a scientific collaboration in the form of a technical expert workshop. Workshop participants will be tasked with developing an international approach for risk assessment of nutrients and related substances.

II. INTEREST IN NUTRIENT RISK ASSESSMENT

Within the international arena, the need for an accepted scientific approach for nutrient risk assessment is apparent. The development of international standards for food products -- such as fortified foods, vitamin-mineral/food/dietary supplements, infant formula, and dietetic foods/foods for special dietary uses -- includes consideration of the so-called upper level of intake from all sources for nutrients and related substances. Risk managers can better address standard-setting if appropriate, science-based risk assessment outcomes are available to inform their decisions. Additionally, numerous public health activities ranging from nutrient intervention programs to establishing dietary guidelines must take into account the potential for harm as well as the benefits associated with nutrients and related substances. Further, the growing use of fortified foods and supplements requires attention be paid to the possibilities of excessive intake of nutrients and related substances.

Several national authorities and related bodies as well as certain private groups and industry organizations have undertaken work designed to address nutrient risk assessment either comprehensively or for a particular issue or concern. These activities have been informative and in many ways ground-breaking. However, their varied assessment outcomes, while not diminishing their value, have made international harmonization challenging. The development of international principles intended to assist in clarifying and harmonizing the approaches for nutrient risk assessment would be useful in this regard.

Interest Related to the Work of Codex²: The Codex Alimentarius (or 'food code') is an international food standards program intended to protect the consumer and facilitate international trade. The Codex Committee

¹ Also referred to as 'nutrients or other substances with a nutritional or physiological effect'; the term is also abbreviated as 'nutrients' as in nutrient risk assessment.

² All Codex reports referenced as Alinorm or CX can be accessed online: www.codexalimentarius.net.

on Nutrition and Foods for Special Dietary Uses (CCNFSDU), as well as the Codex Alimentarius Commission, has expressed interest in topics for which nutrient risk assessment principles would be of value.

The CCNFSDU, beginning in 1991 (17th Session), initiated work to develop guidelines for vitamin and mineral supplements. An aspect of this work now includes the establishment of 'maximum limits' for the vitamins and minerals contained in such supplements. Originally, one view within the Committee had been to set limits based on the level of -- or low multiples thereof -- the recommended nutrient intake. A second view had been that the approach used should be science-based and be derived from a nutrient risk assessment process. The current draft guideline reflects the decision of the 25th Session of the CCNFSDU (2003) to select the latter option that takes into account 'upper safe levels' of vitamins and minerals established by scientific risk assessment. As part of this process, the text of the draft guideline also retains for further consideration by the Committee wording concerning the need to take into account the reference intake values of vitamins and minerals for the population.

However, nutrient risk assessment has also been discussed more broadly within CCNFSDU. The 22nd Session in 2000 included discussions concerning the recommendations of the FAO/WHO Expert Consultation on Food Consumption and Exposure Assessment of Chemicals (Alinorm 01/26, paragraphs 128-131). The interest in nutrient risk assessment as it relates to the work of CCNFSDU was addressed by various delegations. The Committee Chair noted the specificity of risks associated with nutrients and indicated that they would require a relevant methodology. Some delegates stressed the fundamental difference between risk assessment for chemicals and for nutrients and expressed the view that the approach taken for nutrients should not be exclusively toxicological but should also be related to nutrition. It was noted that there were no guidelines for risk assessment for nutrients, but that it would be useful to develop models and methods in this area, especially for the purpose of considering novel foods and upper limits for nutrients.

During its next session (23rd Session) in 2001, the Committee continued its discussion on risk assessment. It was noted that several countries followed a risk-based approach for nutrient assessment at the national level, and some studies were underway to establish safe upper levels of consumption for vitamins and minerals. It was proposed that the Committee should request FAO/WHO to extend their current work on recommended nutrient intakes to 'include upper levels for vitamins and minerals' (Alinorm 03/26, paragraph 138). This proposal was included in the listing *Codex Requests to FAO and WHO on Scientific Advice* developed for the Executive Committee of the Commission (Alinorm 04/27/4). In any case, a set of principles for nutrient risk assessment is one component that would need to be available for consideration in accomplishing this task.

In 2002, the 24th Session of CCNFSDU received and discussed a report from FAO (CX/NFSDU 02/9) on progress towards a risk-based approach for upper limits for nutrients. FAO indicated its intent to produce a general technical report outlining the general principles to be adopted in approaching the topic of upper levels and safety of specific vitamins and minerals (Alinorm 3/26A, paragraph 119).

The Committee, in 2003, considered its response to the larger Commission interest in adopting the *Working Principles for Risk Analysis* (as incorporated into the Procedural Manual (1)), an interest that included the request from the Commission that relevant Codex committees develop or complete specific guidelines on risk analysis in their respective area. One component of risk analysis is risk assessment. A paper concerning the application of risk analysis to the future work of CCNFSDU had been prepared by Australia as requested by the Committee during its 24th Session in 2002 and was discussed at this time. In supporting further discussions within CCNFSDU, some delegations noted that a scientific process should be part of risk management decisions and that some guiding principles and guidelines were necessary especially for the establishment of safe upper levels of nutrients (Alinorm 04/26, paragraph 148).

Interest Related to the Work of JECFA: The need for a nutrient risk assessment approach has also been highlighted by the Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA), a

committee established in 1955 following recommendations made by the Joint FAO/WHO Expert Committee on Nutrition at its fourth session. JECFA was initially tasked with evaluating the safety of food additives, but the scope of its work has expanded to cover contaminants, residues of veterinary drugs in foods, and intrinsic food components. JECFA has evaluated the safety of several substances that were claimed to have nutritional or health benefits. These include eight iron compounds, four calcium compounds, four magnesium compounds, d-alpha-tocopherol, riboflavin, and lutein/zeaxanthin. The Committee has noted that whether such products meet appropriate definitions as nutrients or are worthy of health, nutrient or other claims is outside its remit. The reviews were conducted in the same manner as that for food additives.

The International Programme on Chemical Safety (IPCS) and other organizations have recognized the importance of the harmonization of risk assessment procedures to enhance the quality of risk assessments, achieve greater consistency when evaluating the risks from different sources of exposure, improve the transparency of the risk assessment process and facilitate risk communication. As a direct response to the *Intergovernmental Forum on Chemical Safety Priorities for Action Resolution (2)* adopted at Forum I in 1994, IPCS has undertaken a project to harmonize approaches to the assessment of risk from exposure to chemicals. The goal of this project is to globally harmonize approaches to risk assessment through increased understanding, focusing on specific issues and striving for agreement on basic principles. Harmonization will result in efficient use of resources and consistency among assessments. In addition to the current Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment, as noted above, JECFA has recognized the need for the development of additional guidance for the risk assessment of nutrients and other beneficial food components.

III. FAO/WHO RESPONSE TO INTEREST

FAO and WHO note their role in providing scientific advice to assist the Codex Alimentarius and member countries (3) and anticipate that their work may also be useful to other organizations such as JECFA. In doing so, FAO/WHO are aware of the importance of distinguishing between the role of the risk assessor and the risk manager. In undertaking work related to the development of a nutrient risk assessment approach, FAO/WHO will ensure that the tasks addressed fit clearly within the scope of risk assessment and do not encompass tasks to be addressed by risk managers. The organizations also recognize that the work should not only be developed to meet the scientific needs of the risk manager but that the final outcome should also be appropriately organized and presented so as to be readily understandable and useable by risk managers.

In acknowledging the broad interest in work to address international nutrient risk assessment, FAO/WHO also note in particular that the listing *Codex Requests to FAO and WHO on Scientific Advice (Alinorm 04/27/4)* includes the request for FAO/WHO to take on tasks related to providing upper levels for vitamins and minerals. Further, a FAO report to the 24th Session of CCNFSU (CX/NFSU 02/9) specified the intention to outline general principles related to upper levels and the safety of vitamins and minerals. The focus of the report was progress towards a risk-based approach for upper 'limits' for nutrients.

At this time, FAO/WHO are beginning a nutrient risk assessment project that will include an international scientific collaboration in the form of a technical expert workshop.

This FAO/WHO project will be organized in a step-wise and transparent process. It is initiated now with a Call for Information as well as a request for specific comments on several key issues. Interested parties are invited to comment.

These starting activities will be followed by a Call for Experts. Next steps include the development of discussion papers for consideration during the workshop and the identification of workshop participants.

It is anticipated that the workshop will be convened in 2005. The report of the workshop will be made available in draft form with the opportunity for public comment before the report is finalized and distributed.

IV. GOAL OF THE JOINT FAO/WHO TECHNICAL EXPERT WORKSHOP

The tasks to be undertaken by the participants of the workshop are two-fold:

- Based on discussion papers to be developed, workshop participants will be asked to formulate an internationally-relevant scientific approach for nutrient risk assessment;
- Then, to test and demonstrate the application of the approach, workshop participants will apply the approach to a subset of nutrients, specifically several selected vitamins and minerals. The approach will then be refined based on this experience.

The scientific approach (also referred to as a framework or model) should have applicability across the range of dietary substances known to be essential and/or beneficial, but which may also cause harm when their intake exceeds a specified level. Much of the available data on nutrient risk assessment focuses on vitamins and minerals, so it is expected that these substances will provide a fertile experience for informing the approach development process. However, if the over-arching interest is dietary substances that provide benefit but may cause harm at a different level of intake, principles related to vitamin and mineral risk assessment should have applicability to other nutrients and related substances. Furthermore, it is recognized that there are nutrients and related substances beyond vitamins and minerals for which risk assessment needs have already been identified. Certain types of dietary fibers, amino acids, fatty acids, and dietary antioxidants have all been suggested as subjects for nutrient risk assessment.

In short, the outcome of the workshop has the potential to be relevant to all nutrients and related substances. Nonetheless, the development of an approach for nutrient risk assessment generally must take into consideration the inevitability that the endpoints of interest will vary considerably across the different types of nutrient categories (e.g., macronutrients versus vitamins/minerals). While this undoubtedly will present challenges in developing the approach, it does not suggest that a general model is impossible. Rather, the workshop efforts should include identification of both the components of the approach that will vary depending upon the target nutrient category and the nature of the adaptations or modifications that are needed for the various nutrient categories.

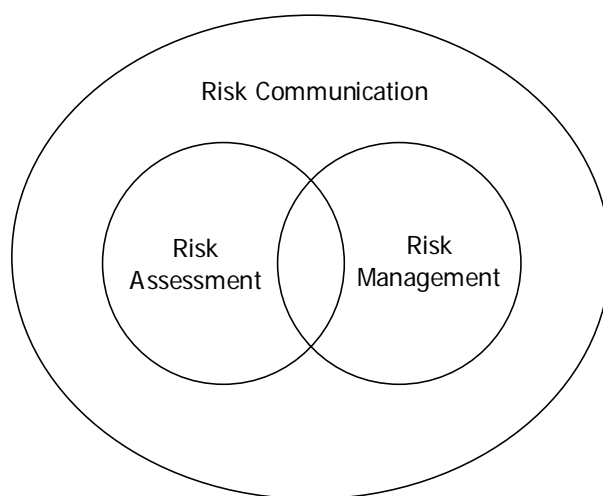
As part of the workshop tasks, the utility and validity of the approach will need to be demonstrated by first testing and then illustrating the approach via its application to several vitamins and minerals. Additional validation will be sought through the use of a public comment period before the report of the workshop is finalized. It will remain, of course, for risk managers in the Codex process as well as the risk assessors and managers at national levels or within other organizations to make use of the workshop outcomes in ways they deem appropriate. Should resources allow, FAO/WHO may continue work to develop a set of upper levels for vitamins and minerals.

V. SCIENTIFIC CHALLENGES: DEVELOPMENT OF A NUTRIENT RISK ASSESSMENT APPROACH

A. Overview of Risk Assessment and Relevant Terminology

The process of risk assessment is a component of the larger process of risk analysis. The paradigm is applicable whether the interest is a nutrient or a non-nutrient. The schematic in Figure 1 shows the relationships among the risk analysis components.

Figure 1: Components of risk analysis



The following are definitions for these components taken from the Procedural Manual (13th Edition) of the Codex Alimentarius Commission (1).

Risk Analysis	A process consisting of three components: risk assessment, risk management and risk communication.
Risk Assessment	A scientifically based process consisting of the following steps: i) hazard identification; ii) hazard characterization; iii) exposure assessment; and iv) risk characterization. It should be noted that often a full RA according to the Codex protocol is not necessary or not possible for different reasons.
Risk Management	The process, distinct from risk assessment, of weighing policy alternatives in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.
Risk Communication	The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.

Regarding food safety and non-nutrients, a number of organizations have considered paradigms for risk analysis, and in turn risk assessment. FAO and WHO in particular have played a role in the development of international food safety risk analysis. A conference sponsored by FAO/WHO recommended in 1991 that the Codex Alimentarius Commission incorporate risk assessment principles into its decision-making process, and Codex adopted such principles in 1991 and 1993. Currently, the Procedural Manual of the Codex Alimentarius Commission (1) includes *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius*. JECFA has also established international safety assessment principles for additives and contaminants in food (4). Examples of work at the national level include a report from Health Canada issued in 1993 and known as the *Health Risk Determination - The Challenge of Health Protection* (5), as well as the 1983 publication from the National Research Council in the United States entitled *Risk Assessment in the Federal Government: Managing the Process* (6). Discussions describing nutrient risk assessment specifically can be found in several regional or national reports (7)(8).

Risk assessment addresses the relationships between exposure to a substance and the likelihood that adverse effect/adverse health effects³ will occur in the exposed population. In essence, risk assessment is a scientific undertaking to characterize the nature and likelihood of harm resulting from human exposure to "agents in the environment." The process of classic risk assessment involves scientific judgments/decisions made during a four-step process. Uncertainties and variability in the data available are identified and discussed as part of the risk assessment. The uncertainties are usually either due to questions about the available data or questions about the appropriateness of inferences made in the absence of sufficient data.

The four generally recognized steps (labelled differently by some) are:

- | |
|---|
| <p>(i) hazard identification
 (ii) hazard characterization
 (iii) exposure assessment
 (iv) risk characterization</p> |
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A key quantitative outcome resulting from the hazard characterization step is the specification of a level of intake -- usually referred to as an 'upper level' -- at which, or below, no harm is likely to occur. Or, alternatively, it is the level above which there is the potential for harm. Since nutrients and related substances may also 'cause harm' if their intake levels are too low, a possible addition to the definition would note the assumption that nutrient needs are adequately met.

<p>Upper Level of Intake (UL): A quantitative level of total intake at which, or below, no harm is expected to occur assuming nutrient adequacy is met.</p>
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For the purposes of accomplishing its conceptual exercise, this Background Paper refers to the quantified outcome of nutrient risk assessment as an 'upper level' or UL. It is important to note that the UL is neither a recommended intake nor a fortification or supplementation levels. Further, an important hallmark of the UL is that it is not a regulatory limit. Rather, it is a piece of information to assist in decision-making.

Depending upon the data available, the UL may be given for different life stage or age/gender groupings. Also, depending upon the data available, the UL may reflect intake from all sources or intake only from selected sources. Ideally, nutrient risk assessment is based on intake from all sources.

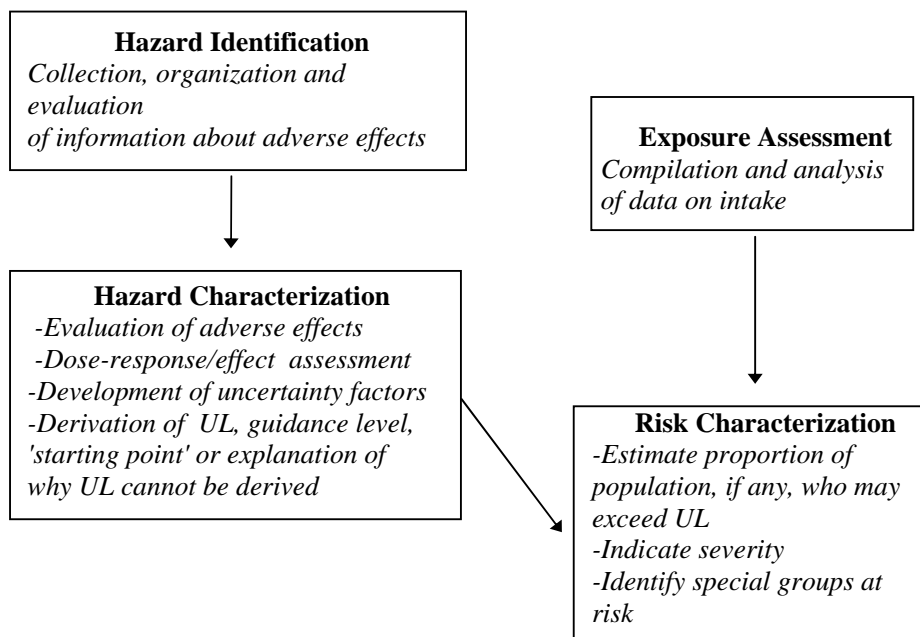
³Change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (See Annex I). The term 'adverse health effects' is also used by some has not been specifically defined. Both terms are used interchangeably in available texts.

Some refer to these quantitative intake levels as safety-based guidance levels. Others identify them as starting points so as to indicate they represent scientific information that the risk manager can use, among other considerations, in the development of policies and standards. And still others draw a distinction between an upper level and a guidance level by attributing more uncertainty to a guidance level.

In any case, a variety of terms are used (not all synonymous) including 'tolerable upper levels,' 'tolerable daily intake,' 'safe upper levels,' and 'upper range of safe intake.' Many risk assessors are familiar with the term Acceptable Daily Intake (ADI) which is defined as the estimated maximum amount of an agent, expressed on a body mass basis, to which an individual in a (sub)population may be exposed daily over its lifetime without appreciable health risk. This term has not been extensively used in nutrient risk assessment.

The sequencing of the four steps of risk assessment may vary as described by others, and available graphics include an array of back-and-forth steps as well as overlapping circles. Moreover, many risk assessment descriptions begin the task of risk assessment with problem formulation, a series of considerations often involving both risk assessors and risk managers that precedes the formal risk assessment. At its most basic, the 'flow' for risk assessment is shown in Figure 2 (below).

Figure 2. Steps in risk assessment



Hazard identification is followed by hazard characterization and produces an UL. An exposure assessment is carried out to compile and analyze information about the exposure within the population of interest. The information obtained from the exposure assessment is combined with the UL and other hazard characterization information to produce a risk characterization that identifies the proportion of the population likely to exceed the UL. Risk characterization also highlights important considerations including the severity and nature of the adverse effect and the identification of any special groups at risk.

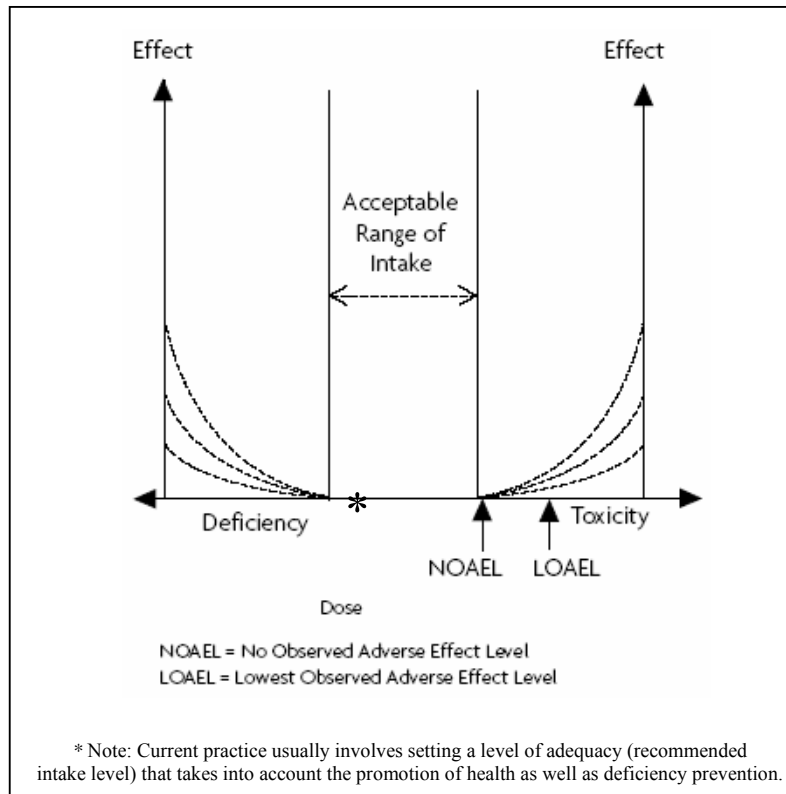
Annex I lists generic terms used in hazard/risk assessment and was developed as part of an international project to harmonize terminology. A glossary of terms used in food safety risk analysis is provided in Annex II. Annex III lists characteristics of a good risk assessment. The specific relevance of such commonly used terms and characteristics to nutrient risk assessment needs to be considered and clarified.

B. The Risk Assessment Approach in the Nutrition Context

The application of a risk assessment approach to nutrients and related substances requires, as mentioned earlier, recognition that nutrients and related substances are unlike non-nutrients in that they provide health benefits. The application requires particular attention to uncertainty factors. The use of the standard safety factors for non-nutrient data uncertainties to ensure toxicological safety⁴ could result in UL values that are the same or less than the nutrient adequacy levels, a nonsensical outcome. In their evaluations concerning several substances purported to have nutritional benefit, JECFA applied the food additive safety assessment paradigm. The approach used the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse effect level (LOAEL) from human or animal studies with a safety or uncertainty factor to arrive at an ADI. The standard default safety factor is 100. JECFA determined that in the case of nutrients and other substances necessary for health and well-being, the use of a lower safety factor may be appropriate so as to result in a level of nutrient intake high enough to satisfy nutritional needs and to maintain health. Additionally, the IPCS has developed an approach for the assessment of risk from essential trace elements which uses an acceptable-range-of-oral intake (AROI) (9).

The application of risk assessment to nutrients and related substances is complicated by the fact that ‘harm’ relative to nutrient intake has two aspects: Harm resulting from excessive intakes and harm resulting from intakes that are too low. Between these two points is the ‘acceptable range of intake.’ The two-tail aspect of the potential for harm associated with nutrients and related substances is illustrated in Figure 3.

Figure 3. Two-tailed 'risk' for nutrients: Inadequacy and Toxicity⁵



⁴ Ref (4), page 81.

⁵ Modified from Ref (7), page 21.

While a graphic representation such as that found in Figure 3 above is helpful in making the point about the two-tailed potential for harm, the relationships themselves may not be symmetrical. The dotted lines in the figure are meant to indicate that the shape of the curves may differ.

The acceptable range of intake is not specifically defined except as a range of intake believed to be 'safe.' The definition of 'nutrient adequacy', which is included in the lower end of the acceptable range of intake (as shown with an asterisk in the figure), is not universally agreed upon,⁶ but the current practice is to refer to it as a level of intake that maintains life and/or promotes health.⁷ However, in what ways these considerations affect nutrient risk assessment is unclear.

With these nutrition-oriented considerations in mind, the specific tasks accomplished in the four steps of risk assessment can next be considered. To aid in the identification of nutrition-related issues associated with each of these steps, FAO/WHO examined the work of several expert panels that had been requested by regional/national government authorities and related bodies. In order to provide meaningful comparisons, the panel reports needed to be quantitative in outcome and relatively comprehensive in scope.

FAO/WHO were able to identify three expert panels that had been tasked with evaluating the safety of intakes of vitamins and minerals (7)(8; see Annex V)(10; see Annex IV). In each case, the report of the panel reflected the deliberations and conclusions of an expert body convened at the request of a government authority or related body. The focus of the informal comparison was the general approach used for hazard identification and hazard characterization as well as the resulting quantitative outcomes and conclusions. One vitamin (vitamin A (7)(11)(12)) and one mineral (selenium (7)(13)(14)) were examined in particular. While there are additional descriptions of risk assessment approaches available in the public domain, FAO/WHO limited their focus to those from governments or related bodies.

The abbreviations used in this Background Paper for the three government-requested expert panels are:

EU-SCF: European Union, Scientific Committee on Food (Note: Activities formerly the responsibility of SCF now rest with the European Food Safety Authority)

EVM: Expert Group on Vitamins and Minerals. United Kingdom, Food Standards Agency.

IOM: Institute of Medicine. United States, National Academies of Science.

A discussion of the four steps of risk assessment as applied to nutrient risk assessment follows.

▪ ***Hazard identification*** involves the collection, organization, and evaluation of all information pertaining to the adverse effects associated with a given nutrient or related substance. It provides an overview of the ability of the nutrient or related substance to cause one or more types of 'toxicity' in humans. Usually the process includes the selection of the most critical or sensitive endpoint (or adverse effect) upon which to base the assessment.

⁶ Some nations or regions define adequacy based on levels to prevent deficiency.

⁷ Also referred to as 'optimal health'

The three expert panel reports examined used the same data bases for their risk assessments although the timing of the reports varied enough that some studies relied upon by later panels were not available to earlier panels for a given nutrient. Even with the possibility that different data affected outcomes for some nutrients, the conclusions they reached as to the hazards identified and the weight to give to particular hazards varied across the three reports. Sometimes these variations resulted in quite different conclusions; in other cases the variations were of minor significance. The differences --beyond those attributable to information from newer data -- likely reflect the necessary reliance on scientific judgment rather than on 'hard' data. This, of course, occurs because of the significant inadequacies in and uncertainties arising from the available data bases addressing the adverse effects and related information for nutrients and related substances.

One report noted that the overall quality of the data base for evaluating nutrient safety was generally poor as compared to data bases available for non-nutrients such as food additives. For example, the report commented that both human and animals studies were generally not designed for evaluating adverse effects or toxicities. Instead, they have been designed to evaluate beneficial or metabolic effects of nutrients and related substances. Thus, information on potential hazards tended to be incomplete and difficult to interpret since it was not systematically and objectively developed. Data on vulnerable groups (e.g., young children, elderly) were particularly scarce. Most animal studies were of an investigative nature and intended to evaluate a very specific question. As such, they did not result in the comprehensive set of toxicology studies normally done to support regulatory requirements.

For reasons such as these, the nature and types of uncertainties associated with nutrient risk assessment can be exceptionally varied and challenging. Given the lack of consistency in the quality and numbers of studies available for individual nutrients or related substances, a case by case approach has been taken. A formal systematic review methodology across nutrients and across reports is lacking. Its development, while challenging, may be useful especially in the international context.

- **Hazard characterization** is the detailed evaluation of the nature of the adverse effects associated with the nutrient or related substance. It rests largely on the assessment of a dose-response, sometimes referred to as dose-effect assessment. In fact, some groups refer to hazard characterization as 'dose-response assessment.' A dose-response assessment is a process whereby scientific evidence (experimental/medical) is used to specify the relationship or 'data curve' between increasing intake and increasing likelihood of a response or adverse effect. Based on these evaluations, an UL is derived taking into account uncertainties such as those related to the data base and those associated with variability between species and individuals.

The three expert panels laid out similar general approaches and criteria for evaluating and weighing the scientific evidence and had access to many, but not all, of the same studies. Nonetheless, taking into account adjustments in outcomes that may have resulted from newer data available to certain panels, they sometimes came to different conclusions as to the nature and adequacy of the data base for selecting specific hazards as critical endpoints and threshold levels (LOAEL or NOAEL). In short, there were decision points at which the panels diverged. This resulted, in some cases, in differences in conclusions.

- **Exposure assessment** or intake assessment is the process of compiling and analyzing data on the intake of the substance for the population of interest. Typically the analysis includes the application of statistical adjustment factors and other intake assessment tools that allow conclusions about the amount of a substance being consumed on a 'usual' basis and prevent the tails of the intake distributions from inflating the estimates. Analysis can not be limited to estimates of mean intake alone, but needs to include estimates of the distributions of intakes so that the intakes of consumers at the high end of the intake distribution curve can be evaluated in comparison to the UL.

The many difficulties associated with collecting accurate and representative food intake data reflect methodological challenges that in turn cause uncertainties. These include inadequate composition tables by which to estimate the intakes of specific nutrients from foods (particularly as related to changes in

availability of fortified foods), difficulty in obtaining information on usual intakes from one-day or short time periods, and inaccuracies in reporting the types and amounts of foods consumed. Additionally, there are only limited data on intakes from dietary supplements.

Further, compositional data for dietary supplements and some fortified foods are usually based on declared label values, which may represent significant underestimates because of the tendency of manufacturers to add overages⁸ and the ease with which their formulations can be changed to meet market demand. The intake data on dietary supplement use usually differ from the intake data available for foods, for example they may cover different time periods or they are obtained from different surveys. This is complicated by the fact that it is often inappropriate to estimate total intakes by summing across intakes from foods plus supplements. Where intake estimates are given for both diets and supplements, they are generally given as separate estimates. A consistent approach for arriving at total nutrient intake estimates from foods and supplements has not been specifically identified.

- **Risk characterization** pulls together all the pieces of the previous steps of risk assessment in order to characterize and describe the risk. It is referred to by some as advice for decision-making. The tasks focus on the integration of the hazard characterization and its resulting UL with the intake/exposure assessments for the general population of interest or vulnerable population subgroups (e.g., children). Therefore, in risk characterization, the proportion of the population who may have intakes that exceed the UL is identified as well as the degree to which their intakes exceed the UL. Usually there is a discussion of the severity of the adverse effect and the likely reversibility of the potential harm if intakes are reduced below the UL. Some risk characterizations may include indications as to the overall public health significance of the possible harm to population subgroups of interest and the identification of other special groups 'at risk.' Any other scientific information that could be taken into account in managing the problem is included in the risk characterization product. In short, the significance of the risk of excessive nutrient intake cannot be evaluated only by identifying the percent of the population above the UL, but must carefully consider all of the factors described above.

To provide a specific example of how risk characterization has been done for nutrient risk assessment, one report on vitamin A included a clearly identified discussion section on this segment of risk assessment. The hazard characterization step had concluded that an UL intake level of >3000 µg RE/day would be protective for women of child-bearing age against the risk of teratogenicity and also protective for all other age/gender groups against the risk of hepatotoxicity. Using these outcomes, the risk characterization section included statements that clarified that the UL applies to both dietary and supplemental intakes of vitamin A and determined that the 97.5th percentile of intakes for adults in Europe exceeded the UL of 3000 µg RE/Day. The report stated that because alterations of embryogenesis may occur following a single or a small number of doses of vitamin A, for women of child bearing age, the UL should be compared with intake estimates that reflect short-term rather than long term exposure. They also stated that because the UL of >3000 µg RE/day may not adequately address the possible risk of bone fracture in particularly vulnerable groups, it would be advisable for postmenopausal women who are at greater risk of osteoporosis and fracture, to restrict their intake to 1500 µg RE/day.

Risk characterization is a step within risk assessment that illustrates readily the interface between risk assessment and risk management. It could be described as a 'hand-off' from the risk assessors to the risk managers. Available examples as to where nutrient risk assessment ends and nutrient risk management begins tend to offer different scenarios. It would likely be helpful to the elucidation of process of risk assessment for nutrients and related substances if this issue were to receive more attention and further clarification.

⁸ Ref (7), page 341, Table 7. The table reports over-formulations for an array of nutrients ranging from 30-100%.

C. Nutrient Risk Assessment in the International Context

The subject of this Background Paper is the development of an international nutrient risk assessment approach. For work intended to be useful internationally, it would be helpful to clarify whether the outcomes of the four steps of risk assessment as applied to nutrients and related substances can be harmonized. That is, which are those steps that could be considered globally and which are those steps that may be less universal in scope. A consideration that may help in this regard is to focus on the nature of the data to be used during the execution of the specific steps.

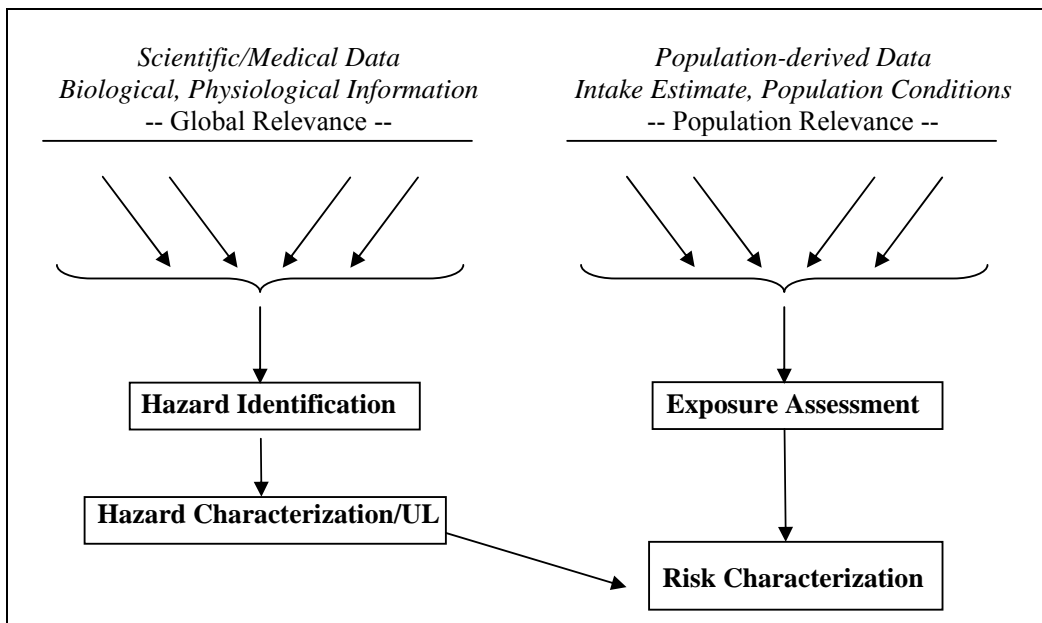
If the type of data inputted into each step is used as a starting point, it is possible to divide the steps into two categories.

First, there are those steps that are based on the available scientific/medical literature and intended to identify and interpret the biological, physiological and chemical evidence for the relationship between intake and the potential for harm to humans. These data by their nature are relevant across wide and diverse populations, i.e. they tend to reflect the science pertaining to all humans. They have global relevance.

Second, there are those steps based on information about the population⁹ targeted for risk assessment. This information would include data about dietary consumption patterns and food composition, which in turn underpin the exposure assessment step. The exposure assessment is population relevant, i.e., is dependent on the types of foods consumed and dietary patterns within a region or nation-state. Risk characterization includes considerations of the globally relevant hazard characterization within the context of the exposure assessment. This would cause risk characterization to be population relevant.

These differences are illustrated in Figure 4.

Figure 4. Steps in risk assessment: Global versus population relevance



⁹ The term 'population' in discussions pertaining to nutrient risk assessment in the international context refers to nations/regions with a common food supply and dietary patterns and which would be expected to differ from other nations/regions in this respect. Elsewhere in this paper or in other documents the term may be used to refer to special or vulnerable groups ('populations' or 'sub-populations') such as children or women of childbearing age.

This consideration does not preclude an international nutrient risk assessment workshop addressing principles for all four steps of risk assessment. However, what it does suggest is that the use of the principles for hazard identification/characterization results in outcomes, notably the UL, that could be globally relevant. In the case of exposure assessment and risk characterization, the application of the principles produces outcomes that are population relevant. That is, risk characterizations -- even when conducted in a consistent manner using internationally-applicable guiding principles -- can inherently be different depending upon the target population.

D. Scientific Challenges Identified

As a general rule, the broad scientific challenges associated with the four steps of nutrient risk assessment are the same as those common to all risk assessments. In the case of nutrient risk assessment, the challenges can appear somewhat daunting given the generally poor quality of the data available for nutrients and related substances particularly when compared to food additives. But it is worth noting that these difficulties are like those faced in an earlier international nutrition-related activity – specifically, establishing international recommended nutrient intakes. The clear need for such reference values spurred the international nutrition scientific community to work toward the necessary scientific advice, guidance and outcomes.

The issues raised by observations noted in the discussions above can be organized into four broad categories. The categories identified clearly do not cover all or perhaps even many of the scientific challenges faced by nutrient risk assessment, but they serve as a starting point for further discussion.

1. Challenge: Criteria for data evaluation

Developing criteria for the evaluation of the quality and utility of relevant scientific evidence brings into play a large and complex set of issues. As a transparent science-based process, risk assessment is best served when the criteria for selecting, evaluating and weighing the scientific evidence are clearly articulated and followed. There are commonly accepted general criteria for evaluating and weighing different types of evidence and all three of the reports reviewed for this Background Paper indicated use of these criteria. Yet, as noted earlier, despite the fact that the three reports reviewed stated adherence to these commonly accepted criteria, variations occurred in how they evaluated and weighed the available studies.

When considering the potential hazard for hepatotoxicity from high intakes of vitamin A, the IOM selected a LOAEL of 14,000 µg /day. This threshold was chosen after selecting data sets that allowed for an evaluation of whether other potential causes of liver abnormalities could have confounded results. Studies that failed to provide information on predisposing or confounding factors other than high intakes of vitamin A (e.g., alcohol intake, use of drugs and medications, and history of viral hepatitis infection) were not weighed as heavily in identifying the LOAEL as were studies that provided information on possible confounders. Conversely, the EU-SCF report identified a LOAEL of 7500 µg RE/day. They did not indicate that they had taken into account the potential for these types of confounders in the studies they used to determine the LOAEL.

Some of the differences in evaluating scientific evidence may have arisen because the available evidence is limited for purposes of risk assessment. The data bases tended to represent a mixture of available information, but most notably nutrition studies designed to evaluate beneficial or metabolic functions of nutrients, rather than safety and toxicology studies. That is, the available studies usually were not conducted in a manner consistent with the systematic approach commonly used for other substances that are frequently the focus of risk assessment such as food additives. In short, available data bases are generally of poor quality for purposes of risk assessment, and nutrient risk assessment is quite multidisciplinary in nature. It is also likely that historically there has been infrequent collaboration between nutrition and toxicology. This would suggest it is worthwhile to augment the traditional criteria for scientific evaluation with criteria or

guidance that is specific to the types of evidence available for, and the unique aspects of, nutrient risk assessment.

2. Challenge: Criteria for extrapolation to vulnerable groups.

A major purpose of ULs is to protect the most sensitive members of the general population from the adverse effects of excessive nutrient intake. For example, some individuals in certain life stage or other sub-groups (e.g., pregnant women, young children, genetically diverse sub-groups) may be biologically sensitive to the nutrient under consideration. An UL for the general population may not be protective for these vulnerable groups. It is important from a safety perspective that vulnerable groups be identified and their risks assessed.

It is preferable that the ULs for different life stage group or other vulnerable groups be derived from relevant data. However, as noted previously, the available data bases rarely provide adequate consideration of potentially vulnerable groups and information upon which to base a UL is very limited. In the absence of data for a particular vulnerable group, extrapolations are often made from the ULs for other groups on the basis of known differences in body size, physiology, metabolism, absorption and excretion of a nutrient. For example, when data are not available for children and adolescents, extrapolations may be made on the basis of body weight in comparison to a reference weight.

Given the paucity of data specific to vulnerable groups and the importance of setting ULs to protect these groups, it is important that particular consideration be given for how best to derive ULs for vulnerable groups during the development of a nutrient risk assessment approach. Consideration should also be given to how best to deal with those cases where the range of intake between the reference intake level needed to maintain good health and the UL above which toxicities can occur is narrow (e.g., zinc).

3. Challenge: Criteria for determination and use of uncertainty factors

A key step in the hazard characterization component of risk assessment is the assessment of uncertainty. Uncertainty factors are empirical values applied to take into account uncertainties in the data. For example, uncertainty factors may need to be applied when extrapolating from results in experimental animals to humans or when extrapolating results from selected individuals to another group. These factors allow for differences in sensitivity between individuals and between species that may result from such differences as absorption, metabolism, or biological effect of the substance under consideration. Uncertainty factors may also be applied to account for uncertainties due to data base deficiencies (e.g., absence of a NOAEL requiring extrapolation from a LOAEL), a poor data base (e.g., absence of data on chronic or reproductive toxicities), studies without small numbers of subjects, or because of the nature of a particular adverse effect.

It is common practice in risk assessments to use separate factors for each area of uncertainty, with typical values being 10 for inter-individual variation, 10 for species differences and 3 for extrapolation of a LOAEL to a NOAEL. More recently, the process has allowed for the use of chemical-specific adjustment factors by sub-dividing the 10-fold factors into separate components representing toxicokinetic and toxicodynamic differences. For these latter types of refinements, extensive information on toxicokinetics and/or mode of toxicity is necessary.

One report noted that there are few nutrients where the available data bases provide this kind of information. The numerical value assigned to the uncertainty factor depends on the size and type of the population to be protected, the quality of the data base, and the various uncertainties that have to be taken into account. The greater the uncertainty, the UF is larger; a smaller UF results with less uncertainty. This is consistent with the ultimate goal of the risk assessment which is to provide an estimate of a level of intake that will protect the health of virtually all members of the healthy population. The numerical UF levels could range from a value of 1 if adequate data were available up to 100 or more if the safe intake had to be based on an animal study because of the inadequacy of human data. Yet, a unique aspect of nutrient risk assessment is that the

uncertainty factor selected can not be so large that the UL is set at or below the intake required for maintenance and promotion of good health.

Using vitamin A as an example, of the three reports, only the IOM developed specific numeric UFs for the age/gender and life stage groups for which they eventually provided ULs. Their UFs ranged from a value of 1.5 for women of reproductive age to a UF value of 10 for infants. The UF for adults 19 years and older was 5.0. The inconsistencies in dealing with UFs among the three reports illustrates that, despite the use of generally similar criteria for developing UFs, the significance of the role played by scientific judgment in deriving these factors. Additionally, the final UL is very significantly affected by the UF since the UL is often the result of dividing the LOAEL or NOAEL by the UF.

Close attention to the approaches and criteria for deriving UFs in order to enhance international harmonization for hazard characterization decisions thus becomes an important issue as an international risk assessment approach is developed.

4. Challenge: Guiding principles for global versus regional applications

The interest in and utility of a globally relevant risk assessment for nutrients and related substances was highlighted earlier in this Background Paper. An international approach can be used for international standard-setting. It can also foster harmony in the conduct of risk assessment not only across risk assessments for a single nutrient, but among risk assessments for nutrients and related substances in general.

As already discussed, there may be (a) those components of risk assessment for which a universal quantitative conclusion can be reached and that will have general applicability and (b) those components that require a consistent set of principles and processes, but take into account population differences in food supplies, consumer dietary patterns, and baseline nutriture.

This perspective would suggest that hazard identification and hazard characterization appear to have global applicability. Where the available science is of sufficient quality, this process can result in ULs (i.e., quantitative values) for specified age/gender or life stage groups that can be applied internationally.

Conversely, exposure assessment and risk characterization are largely dependent on the types of foods available for consumption and the dietary patterns of consumers as well as the baseline nutritional status of the population. The risk assessment process for these two components will, by necessity, vary from one region to another. However, to encourage international harmonization, it would be valuable to establish a set of principles and criteria to guide national/regional risk assessors in conducting exposure assessment and risk characterization. Moreover, the availability of such guiding principles could also provide a scientific basis for discussing disagreements, if and when they occur, as to conclusions reached.

Using vitamin A as an example, the three reports agreed that a level of 3000 µg preformed vitamin A was an intake at or above which increased risk of teratogenicity, a serious and irreversible hazard, could occur. Although the reports differed in whether to designate this as the endpoint for deriving an UL, these determinations and conclusions occurred during the first two steps of their respective risk assessment process that is hazard identification and hazard characterization. Thus, the consistency in concluding that intakes at or above 3000 µg/d posed a risk of teratogenicity in women of child-bearing age is the type outcome that has global applicability; it relies on a common and international scientific data base.

Additionally, again using vitamin A as an example, each of the reports compared this level of 3000 µg/day with estimates of intake of preformed vitamin A from foods and supplements for women of child-bearing age in their respective countries or regions. These evaluations occurred during the exposure assessment and risk characterization steps of the process. The EU-SCF noted that the 97th percentile intake of adults in most of Europe exceeded the UL level and therefore recommended that careful consideration should be given to

the appropriateness of enrichment of human foods with vitamin A. The EVM noted that the maximum estimated intakes from food and supplements by UK residents was 8450 µg RE/day, a value in excess of the threshold for teratogenicity of 3000 µg RE/day. Therefore, they supported the current advice that women who are pregnant or who wish to become pregnant should not take dietary supplements containing vitamin A except on medical advice. Conversely, the IOM noted that the risk of exceeding the UL for vitamin A in the United States appears to be small based on estimated intakes for the U.S. populations.

These examples illustrate two critical points. One, the process of conducting and evaluating exposure assessments across the three reports differed. For example, the EVM added the 97.5th percentile intakes for vitamin A from foods to the highest available supplemental dose to estimate a total diet maximum intake, but noted that high levels from food and/or supplements may exceed intakes at which adverse effects had been reported. The IOM also estimated intakes separately for supplements and foods, but they did not combine the two estimates to obtain a total intake estimate.

Scientific challenges pertaining to hazard identification and hazard characterization have been discussed above. In the case of scientific challenges for exposure assessments, a set of general principles for analyzing and evaluating the intake estimates from different types of data bases would facilitate consistency in approaches and procedures used among nation states and regions. In subsequent risk characterization, the actual conclusions as to the nature and magnitude of the risk must also take into account the food and dietary patterns and baseline nutritional status of consumers. This can be guided by common approaches to data analysis and evaluation and types of factors to be considered in resulting decisions, but must by necessity also be relevant to the populations for which it is to be applied.

VI. QUESTIONS: REQUEST FOR COMMENT

As a result of the considerations highlighted in this Background Paper and in anticipation of convening a technical workshop on nutrient risk assessment, FAO/WHO are seeking input on several key issues related to the development of an international approach for nutrient risk assessment.

Responses to the questions below are being accepted electronically through 10 December 2004.

(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 (1)(a) 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)

▪Question (1)(b) 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.

(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 (2)(a) Criteria for the evaluation of the quality and utility of relevant scientific evidence.

▪Question (2)(b) Extrapolation to various age/gender groups.

▪Question (2)(c) Determination and use of uncertainty factors.

▪Question (2)(d) Other

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

▪Questions (3)(b) 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.

(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 (4)(a) 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.

▪Question (4)(b) Please provide other comments on the content of the Background Paper.

If you wish to respond to these questions, please access the Nutrient Risk Assessment Project web page available on the International Programme on Chemical Safety (IPCS) web site (www.who.int/ipcs/en).

VII. CALL FOR INFORMATION

If you are aware of other resources, information or documents that would be useful, we would appreciate your providing them or calling them to our attention. The **Call for Information** is included on the Nutrient Risk Assessment Project web page. Persons who wish to submit information are informed that they can forward such submissions to the following address:

ATTN: Nutrient Risk Assessment Project
International Programme on Chemical Safety
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27 Switzerland
or nrproject@who.int

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¹ This listing is not comprehensive and reflects resources brought to the attention of FAO/WHO at this time. The Call for Information is expected to identify other resources, information or documents pertinent to the Nutrient Risk Assessment Project.

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ANNEX I

**Alphabetical List of Selected Generic Terms
in Hazard and Risk Assessment and their Definitions¹**

Term	Description
Acceptable Daily Intake	Estimated maximum amount of an agent, expressed on a body mass basis, to which an individual in a (sub) population may be exposed daily over its lifetime without appreciable health risk. Related terms: <i>Reference Dose, Tolerable Daily Intake</i>
Acceptable Risk	This is a risk management term. The acceptability of the risk depends on scientific data, social, economic, and political factors, and on the perceived benefits arising from exposure to an agent.
Adverse Effect	Change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.
Analysis	Detailed examination of anything complex, made in order to understand its nature or to determine its essential features.
Assessment	Evaluation or appraisal of an analysis of facts and the inference of possible consequences concerning a particular object or process.
Assessment Endpoint	Qualitative/Quantitative expression of a specific factor with which a risk may be associated as determined through an appropriate risk assessment.
Assessment Factor	Numerical adjustment used to extrapolate from experimentally determined (dose response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur. Related terms: <i>Safety Factor, Uncertainty Factor.</i>
Concentration	Amount of a material or agent dissolved or contained in unit quantity in a given medium or system.
Concentration-Effect Relationship	Relationship between the exposure, expressed in concentration, of a given organism, system or (sub) population to an agent in a specific pattern during a given time and the magnitude of a continuously-graded effect to that organism, system or (sub) population. Related terms: <i>Effect Assessment, Dose-Response Relationship</i>
Dose	Total amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population.

¹ IPCS (International Programme on Chemical Safety). *Descriptions of Selected Key Generic Terms Used In Chemical Hazard/Risk Assessment: Joint Project with OECD on the Harmonisation of Hazard/Risk Assessment Terminology.* Access online: http://www.who.int/ipcs/publications/methods/harmonization/definitions_terms/en/

Dose-Effect Relationship	<p>Relationship between the total amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the magnitude of a continuously-graded effect to that organism, system or (sub)population.</p> <p>Related terms: <i>Effect Assessment, Dose-Response Relationship, Concentration-Effect Relationship.</i></p>
Dose-Related Effect	<p>Any effect to an organism, system or (sub) population as a result of the quantity of an agent administered to, taken up or absorbed by that organism, system or (sub)population.</p>
Dose Response	<p>Relationship between the amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the change developed in that organism, system or (sub) population in reaction to the agent.</p> <p>Synonymous with Dose-response relationship.</p> <p>Related Term: <i>Dose-Effect Relationship, Effect Assessment, Concentration-Effect Relationship.</i></p>
Dose-Response Assessment	<p>Analysis of the relationship between the total amount of an agent administered to, taken up or absorbed by an organism, system or (sub)population and the changes developed in that organism, system or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose-Response Assessment is the second of four steps in risk assessment.</p> <p>Related terms: <i>Hazard Characterisation, Dose-Effect Relationship, Effect Assessment, Dose-Response Relationship, Concentration-Effect Relationship.</i></p>
Dose-Response Curve	<p>Graphical presentation of a dose-response relationship.</p>
Dose-Response Relationship	<p>Relationship between the amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the change developed in that organism, system or (sub) population in reaction to the agent.</p> <p>Related Term: <i>Dose-Effect Relationship, Effect Assessment, Concentration-Effect Relationship.</i></p>
Effect	<p>Change in the state or dynamics of an organism, system or (sub) population caused by the exposure to an agent.</p>
Effect Assessment	<p>Combination of analysis and inference of possible consequences of the exposure to a particular agent based on knowledge of the dose-effect relationship associated with that agent in a specific target organism, system or (sub) population.</p>
Expert Judgement	<p>Opinion of an authoritative person on a particular subject.</p>
Exposure	<p>Concentration or amount of a particular agent that reaches a target organism, system or (sub) population in a specific frequency for a defined duration.</p>

Exposure Assessment	<p>Evaluation of the exposure of an organism, system or (sub) population to an agent (and its derivatives).</p> <p>Exposure Assessment is the third step in the process of Risk Assessment.</p>
Exposure Scenario	<p>A set of conditions or assumptions about sources, exposure pathways, amount or concentrations of agent(s) involved, and exposed organism, system or (sub)population (i.e. numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation.</p>
Fate	<p>Pattern of distribution of an agent, its derivatives or metabolites in an organism, system, compartment or (sub) population of concern as a result of transport, partitioning, transformation or degradation.</p>
Guidance Value	<p>Value, such as concentration in air or water, which is derived after allocation of the reference dose among the different possible media (routes) of exposure.</p> <p>The aim of the guidance value is to provide quantitative information from risk assessment to the risk managers to enable them to make decisions. (See also: reference dose)</p>
Hazard	<p>Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub) population is exposed to that agent.</p>
Hazard Assessment	<p>A process designed to determine the possible adverse effects of an agent or situation to which an organism, system or (sub) population could be exposed.</p> <p>The process includes hazard identification and hazard characterization. The process focuses on the hazard in contrast to risk assessment where exposure assessment is a distinct additional step.</p>
Hazard Characterization	<p>The qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose-response assessment and its attendant uncertainties.</p> <p>Hazard Characterisation is the second stage in the process of Hazard Assessment, and the second step in Risk Assessment.</p> <p>Related terms: <i>Dose-Effect Relationship, Effect Assessment, Dose-Response Relationship, Concentration -Effect Relationship.</i></p>
Hazard Identification	<p>The identification of the type and nature of adverse effects that an agent has as inherent capacity to cause in an organism, system or (sub) population. Hazard identification is the first stage in hazard assessment and the first step in the process of Risk Assessment</p>
Margin of Exposure	<p>Ratio of the no-observed-adverse-effect level (NOAEL) for the critical effect to the theoretical, predicted or estimated exposure dose or concentration.</p> <p>Related term: <i>Margin of Safety</i></p>

Margin of Safety	<p>For some experts the Margin of Safety has the same meaning as the Margin of Exposure, while for others, the Margin of Safety means the margin between the reference dose and the actual exposure dose or concentration.</p> <p>Related term: <i>Margin of Exposure</i></p>
Measurement Endpoint	Measurable (ecological) characteristic that is related to the valued characteristic chosen as an assessment point.
Reference Dose	<p>An estimate of the daily exposure dose that is likely to be without deleterious effect even if continued exposure occurs over a lifetime.</p> <p>Related term: <i>Acceptable Daily Intake</i>.</p>
Response	Change developed in the state or dynamics of an organism, system or (sub) population in reaction to exposure to an agent.
Risk	The probability of an adverse effect in an organism, system or (sub) population caused under specified circumstances by exposure to an agent.
Risk Analysis	<p>A process for controlling situations where an organism, system or (sub) population could be exposed to a hazard.</p> <p>The Risk Analysis process consists of three components: risk assessment, risk management and risk communication.</p>
Risk Assessment	<p>A process intended to calculate or estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.</p> <p>The Risk Assessment process includes four steps: hazard identification, hazard characterisation (related term: dose-response assessment), exposure assessment, and risk characterization. It is the first component in a risk analysis process.</p>
Risk Characterization	<p>The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system or (sub)population, under defined exposure conditions.</p> <p>Risk Characterisation is the fourth step in the Risk Assessment process.</p>
Risk Communication	Interactive exchange of information about (health or environmental) risks among risk assessors, managers, news media, interested groups and the general public.
Risk Estimation	Quantification of the probability, including attendant uncertainties, that specific adverse effects will occur in an organism, system or (sub)population due to actual or predicted exposure.

Risk Evaluation	<p>Establishment of a qualitative or quantitative relationship between risks and benefits of exposure to an agent, involving the complex process of determining the significance of the identified hazards and estimated risks to the system concerned or affected by the exposure, as well as the significance of the benefits brought about by the agent.</p> <p>It is an element of risk management. Risk Evaluation is synonymous with Risk-Benefit evaluation</p>
Risk Management	<p>Decision-making process involving considerations of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, and compare regulatory and non-regulatory options and to select and implement appropriate regulatory response to that hazard.</p> <p>Risk management comprises three elements: risk evaluation; emission and exposure control; risk monitoring.</p>
Risk Monitoring	<p>Process of following up the decisions and actions within risk management in order to ascertain that risk containment or reduction with respect to a particular hazard is assured.</p> <p>Risk monitoring is an element of risk management.</p>
Safety	<p>Practical certainty that adverse effects will not result from exposure to an agent under defined circumstances. It is the reciprocal of risk.</p>
Safety Factor	<p>Composite (reductive) factor by which an observed or estimated no-observed-adverse effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk.</p> <p>Related terms: <i>Assessment Factor, Uncertainty Factor.</i></p>
Threshold	<p>Dose or exposure concentration of an agent below that a stated effect is not observed or expected to occur.</p>
Tolerable daily Intake	<p>Analogous to Acceptable Daily Intake. The term Tolerable is used for agents which are not deliberately added such as contaminants in food.</p>
Tolerable Intake	<p>Estimated maximum amount of an agent, expressed on a body mass basis, to which each individual in a (sub) population may be exposed over a specified period without appreciable risk.</p>
Toxicity	<p>Inherent property of an agent to cause an adverse biological effect.</p>
Uncertainty	<p>Imperfect knowledge concerning the present or future state of an organism, system or (sub) population under consideration.</p>
Uncertainty Factor	<p>Reductive factor by which an observed or estimated no-observed-adverse effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk.</p> <p>Related terms: <i>Assessment Factor, Safety Factor.</i></p>

<p>Validation</p>	<p>Process by which the reliability and relevance of a particular approach, method, process or assessment is established for a defined purpose.</p> <p>Different parties define “Reliability” as establishing the reproducibility of the outcome of the approach, method, process or assessment over time. "Relevance" is defined as establishing the meaningfulness and usefulness of the approach, method, process or assessment for the defined purpose.</p>
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ANNEX II

Glossary: Risk Analysis Terms Related to Food Safety for the Purposes of the Codex Alimentarius¹

Hazard: A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.

Hazard Identification: The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.

Hazard Characterization: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.

Dose-Response Assessment: The determination of the relationship between the magnitude of exposure (dose) to a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response).

Exposure Assessment: The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food.

Risk Analysis: A process consisting of three components: risk assessment, risk management and risk communication.

Risk Assessment: A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization.

Risk Assessment Policy: Documented guidelines on the choice of options and associated judgements for their application at appropriate decision points in the risk assessment such that the scientific integrity of the process is maintained.

Risk Characterization: The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

Risk Communication: The interactive exchange of information and opinions throughout the risk analysis process concerning risks, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.

¹ Codex Alimentarius Commission. Joint FAO/WHO Food Standards Programme: Procedural Manual. Thirteenth edition. Rome: Food and Agriculture Organization of the United Nations and World Health Organization, 2004.

Risk Estimate: The quantitative estimation of risk resulting from risk characterization.

Risk Management: The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

Risk Profile: The description of the food safety problem and its context.

ANNEX III

Characteristics of a Good Risk Assessment¹

A good risk assessment helps food safety regulators and other officials to make effective decisions about a food safety risk. It improves the quality of the decision-making process and informs the decision for which it was prepared. Although there is not one particular type of ‘best’ risk assessment, a good risk assessment has a number of essential characteristics:

- ***Clearly identifies the questions to be answered***
A good risk assessment ensures that both the questions asked and the responses identified are the most appropriate. Although the questions to be answered by the risk assessment come from the risk managers, risk assessors must spend time understanding, defining and, if necessary, clarifying and refining them together with risk managers. The questions to be answered should be documented and understood by all members of the risk analysis team.
- ***Is a collaborative and interdisciplinary team effort***
A good risk assessment involves a range of scientific and non-scientific experts working together in order to respond to the questions asked. The best teams are interdisciplinary ones where experts’ roles are complementary and their contributions together exceed the sum of their individual parts.
- ***Has adequate resources***
A good risk assessment has adequate resources (time, money, personnel and expertise) that reflect the importance of the food safety problem under consideration and that are sufficient to answer all the questions posed.
- ***Is based on scientific evidence and sound assumptions***
A good risk assessment is based on scientific evidence and clearly formulated, unbiased assumptions. Sound assumptions are important to help bridge data gaps. Risk assessors should try to clearly formulate implicit assumptions (i.e., ones that are not expressed explicitly but reside inside thoughts or actions) as well as explicit ones (i.e., assumptions made knowingly). The assumptions used should be rigorously challenged and should clearly identify any weaknesses. Good assumptions are revised or discarded as necessary are based on the most likely outcomes rather than the worst-case scenarios.
- ***Uses the best available data***
A good risk assessment uses high-quality, accurate and reliable quantitative, qualitative and/or semi-quantitative data. Risk assessors need to be able to transform facts and evidence into useful information, which can be used to support, inform and guide decision-making. They should pay adequate attention to the collection, analysis and mining of data, and ensure the use of good conceptual and computer models. Risk assessors should also ensure that analysis is explicitly tied to existing evidence, clearly presented, and supported by references and bibliographic information.

¹ Reproduced with permission: FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization). *Draft Version* (uncirculated): *Food Safety Risk Analysis: An Overview and Framework Manual*.

- ***Explicitly acknowledges, identifies and addresses uncertainty***
A good risk assessment explicitly acknowledges, identifies, describes and addresses the magnitude, importance, types and sources of uncertainty. It seeks to eliminate uncertainty or reduce it to a minimum, and address any remaining uncertainty by the most appropriate means (e.g., expert knowledge, primary research, and qualitative and quantitative techniques such as sensitivity analysis, probabilistic techniques and Monte Carlo analysis). If necessary, variability is addressed separately and explicitly.
- ***Considers all the relevant risks***
A good risk assessment considers all the explicit and implicit risks that are relevant in any particular situation. It identifies and quantifies residual risks (i.e., the risk that remains after a management action is taken) as far as possible, and puts them into perspective. Good risk assessment also takes account of changes or transformation in risks due to management measures. For instance, chlorine in the water supply reduces microbial risks but increases chemical risks. Banning the use of antibiotics in animal feed reduces risks of antibiotic resistance but may increase the risk of food-borne illness. Risk assessors must ensure that when risks are transformed they are carefully explained so that proper risk-risk trade-offs can be made.
- ***Is objective, unbiased and transparent***
A good risk assessment is honest, unbiased, clear and objective. It should be based on a scientific approach and carried out with objectivity and neutrality. Opinions or value judgements (for instance on economic, political, legal or environmental aspects of the risk) should not be allowed to influence the outcome of a risk assessment. A good risk assessment should explicitly and openly identify and discuss any controversies in the science or uncertainties in the analysis.
- ***Is clearly and comprehensively documented***
A good risk assessment should clearly document the assumptions, logic, models used, calculations, and results obtained so that they are comprehensible to risk managers and other stakeholders despite their complexity. The risk assessment process should produce a coherent narrative report that puts risks into a proper perspective and explains how they should be managed and why. It should be comprehensive and detailed enough to meet all the risk managers' needs for decision-making.
- ***Is reviewed and evaluated***
A good risk assessment has a separate quality assurance process, which may include some sort of peer or independent review. The results are estimates and should be subject to independent evaluation and review. Good risk assessment is open to evaluation and is flexible enough to change when opportunities for improvements are identified.
- ***Has educational value***
A good risk assessment helps managers to understand food safety problems and learn about related issues. It helps managers to identify the limits of knowledge and enables resources to be directed towards narrowing information gaps. Good risk assessment is conducive to learning and the process is as important as the result.

ANNEX IV

Relevant Institute of Medicine Reports

Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington D.C.: National Academy Press, 1997.

Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline*. Washington D.C.: National Academy Press, 1998.

Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington D.C.: National Academy Press, 2001.

Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington D.C.: National Academy Press, 2000.

ANNEX V

Opinions requested by the European Commission¹

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Beta Carotene*. SCF/CS/NUT/UPPLEV/37 Final. 28 November 2000.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Biotin*. SCF/CS/NUT/UPPLEV/55 Final. 10 October 2001.

European Commission, Scientific Panel on Dietetic Products, Nutrition and Allergies. *Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid)*. 8 July 2004. (Request N° EFSA-Q-2003-018). In *The EFSA Journal*. Volume 80. 2004. 1-22. (not available at online reference)

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium*. SCF/CS/NUT/UPPLEV/64 Final. 23 April 2003.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Copper*. SCF/CS/NUT/UPPLEV/57 Final. 27 March 2003

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Folate*. SCF/CS/NUT/UPPLEV/18 Final. 28 November 2000.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Iodine*. SCF/CS/NUT/UPPLEV/26 Final. 7 October 2002.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Magnesium*. SCF/CS/NUT/UPPLEV/54 Final. 11 October 2001.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Manganese*. SCF/CS/NUT/UPPLEV/21 Final. 28 November 2000.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Molybdenum* SCF/CS/NUT/UPPLEV/22 Final. 28 November 2000.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Nicotinic Acid and Nicotinamide (Niacin)*. SCF/CS/NUT/UPPLEV/39 Final. 6 May 2002.

¹ Access online: http://europa.eu.int/comm/food/fs/sc/scf/out80_en.html

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Pantothenic Acid*. SCF/CS/NUT/UPPLEV/61 Final. 18 April 2002.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Preformed Vitamin A (retinol and retinyl esters)*. SCF/CS/NUT/UPPLEV/24 Final. 7 October 2002.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Selenium*. SCF/CS/NUT/UPPLEV/25 Final. 28 November 2000.

European Commission, Scientific Panel on Dietetic Products, Nutrition and Allergies. *Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Silicon*. 28 April 2004. (Request N° EFSA-Q-2003-018). In *The EFSA Journal*. Volume 60. 2004. 1-11. (not available at online reference)

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Trivalent Chromium*. SCF/CS/NUT/UPPLEV/67 Final. 23 April 2003.

European Commission, Scientific Panel on Dietetic Products, Nutrition and Allergies. *Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Vanadium*. 19 February 2004. (Request N° EFSA-Q-2003-018). In *The EFSA Journal*. Volume 33. 2004. 1-22. (not available at online reference)

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B₁*. SCF/CS/NUT/UPPLEV/46 Final. 16 July 2001.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B₂*. SCF/CS/NUT/UPPLEV/33 final. 7 December 2000.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B₆*. SCF/CS/NUT/UPPLEV/16 Final. 28 November 2000.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B₁₂*. SCF/CS/NUT/UPPLEV/42 Final. 28 November 2000.

European Commission, Scientific Panel on Dietetic Products, Nutrition and Allergies. *Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Vitamin C (L-Ascorbic acid, its calcium, potassium and sodium salts and L-ascorbyl-6-palmitate)*. 28 April 2004. (Request N° EFSA-Q-2003-018). In *The EFSA Journal*. Volume 59. 2004. 1-21. (not available at online reference)

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin D*. SCF/CS/NUT/UPPLEV/38 Final. 16 December 2002.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin E*. SCF/CS/NUT/UPPLEV/31 Final. 23 April 2003.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin K*. SCF/CS/NUT/UPPLEV/32 Final. 24 April 2003.

European Commission, Scientific Committee on Food. *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Zinc*. SCF/CS/NUT/UPPLEV/62 Final. 19 March 2003.