

Opportunity to Respond to Questions

This form provides the opportunity to respond to the questions posed in the Background Paper: Joint FAO/WHO Development of a Scientific Collaboration to Create a Framework for Risk Assessment of Nutrients and Related Substances.

Responses may be typed in to the form directly or appended as an 'attachment' to each question (use 'Upload file'). Fields with asterisks are required. Responses and your name/organization will be available for public viewing.

Name/Organization

Title

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Alliance for Natural Health

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

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13/12/2004

Question 1

The Background Paper discusses the possibility that hazard identification and hazard characterization have global relevance, while exposure assessment and risk characterization are relevant to populations. If such a conceptual framework for the four steps is appropriate, then scientific principles could be organized and considered along these same lines.

Question 1a: Is the distinction between global relevance and population relevance for the four risk assessment steps a meaningful consideration for the purposes of developing an international nutrient risk assessment approach? (Please indicate why or why not)

2.1.1 Yes. However, broad distinctions between global and population levels could obfuscate data at 'lower' levels that could result in misinterpretation of risk assessments that, following risk management and imposition of regulations, might result in negative impacts on significant numbers of individuals. The terms 'global' and 'population' need to be accurately defined in the context of the risk assessment and there needs to be sufficient latitude to encompass the dietary needs of specific *population subsets* and *individuals*, taking into account:

- a) lower than average consumption rates of specific nutrients
- b) lower than average absorption rates of specific nutrients
- c) greater than average genetic requirements for specific nutrients
- d) variations in nutrient requirements for persons with disease
- e) variations in individual responses to specific nutrient forms, in particular their dose-dependent functional effects on target tissues
- f) variations in the fate of specific nutrient forms from consumption, events in the gut, absorption and distribution of nutrients between individuals as well as by population groups (age, gender, ethnicity, etc).

2.1.2 For example, there are substantial variations in the ability of different individuals to absorb folic acid (as well as other nutrients). A significant sector of the population (perhaps as much as 30% in some countries, the rate varying according to genetic differences and ethnicity) appear to have an impaired ability to convert folates from food (or synthetic, 'pharmaceutical-grade' folic acid containing the monoglutamate form, not the predominant form in foods) into the bioactive form of folic acid (5-methyltetrahydrofolate) in their bodies.¹ This genetic uniqueness puts this subset of the population at risk of birth defects, cardiovascular disease, dementia, cancer and other illnesses due to a functional folate deficiency. Oral folic acid requirements in this subset of the population may be over 100 times the average oral intake of folic acid sufficient for the population at large. Also, biological responses vary considerably between different forms of nutrients. Thus, supplementation with the bioactive tetrahydro form of folic acid (rather than monoglutamate form, widely used in mainstream dietary supplements), avoids the need for bioactivation via the

¹ Duell PB, Malinow MR. Effects of folic acid on homocysteine in persons classified by methylenetetrahydrofolate reductase genotype. *American Journal of Clinical Nutrition*, 1999; 69 (6), 1287-1289.

vitamin B12-dependent methionine synthase cycle, so preventing masking of the haematologic indicators of vitamin B12 deficiency.²

- 2.1.3 **Inter-individual variability in nutrient absorption** is well known. For example in one study, absorption of alpha-tocopherol (a form of Vitamin E) following supplementation, as measured in plasma, was found to vary 40-fold between individuals, while the levels were more stable within individuals over time.³
- 2.1.4 The need to focus on the **specific requirements of individuals (not just averages for whole populations or particular, standard population groups)** could be prioritised following detailed analysis of relevant data. Although some relevant data is available in peer-reviewed journals, considerable amounts of such data are unpublished, forming part of the medical records of doctors specialising in clinical nutrition or orthomolecular medicine. It is the view of the ANH, that ignoring such data in the form of medical records jeopardises the accuracy of the risk assessment. Its use could be vital in filling in many data gaps between published studies.
- 2.1.2 Apart from taking into account variance within populations and nutrient requirements for individuals, **temporal changes in nutrient requirements** should also be addressed. For example, one study which compared two discrete data sets, one from the Netherlands, another from Queensland, Australia, showed that seasonal effects of reduced sunlight exposure, and hence vitamin D deficiency, result in increased rates of schizophrenia.⁴ Such problems could be reduced by taking into account nutritional needs among certain population groups at specific times. Such an approach was in essence advocated by McKenna in 1992,⁵ but this related only to vitamin D and did not take into account *interactions* between other nutrients such as vitamin A, calcium and magnesium.
- 2.1.3 Another example of problems that could result from inappropriate scaling is the differences in relative consumption rates of nutrients such as vitamin A and vitamin

² Venn BJ, Green TJ, Moser R, Mann JI. Comparison of the effect of low-dose supplementation with L-5-methyltetrahydrofolate or folic acid on plasma homocysteine: a randomized placebo-controlled study. *American Journal of Clinical Nutrition*, 2003; 77(3): 658-62.

³ Roxborough HE, Burton GW, Kelly FJ. Inter- and intra-individual variation in plasma and red blood cell vitamin E after supplementation. *Free Radical Research*, 2000; 33(4): 437-45.

⁴ McGrath J, Selten JP, Chant D. Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first registration - data from Australia and the Netherlands. *Schizophrenia Research*, 2002; 54 (3): 199-212.

⁵ McKenna MJ. Differences in vitamin-D status between countries in young-adults and the elderly. *American Journal of Medicine*, 1992; 93 (1): 69-77.

⁶ Anon. Excess retinol intake may explain the high incidence of osteoporosis in northern Europe, 1999; *Nutrition Reviews* 57 (6): 192-195.

⁷ Melhus H, Michaelsson K, Kindmark A, Bergström R, Holmberg L, Mallmin H, Wolk A, Ljunghall S. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Annals of Internal Medicine*, 1998; 129, 770-778.

⁸ The term 'nutrient forms' is used distinctly from 'nutrients', in recognition that there are considerable differences in effects between individual forms of vitamins (e.g. retinol vs synthetic beta-carotene vs natural carotenoids) and minerals (e.g. calcium oxide vs calcium citrate malate, sodium selenate vs selenomethionine). If nutrients are grouped (e.g. vitamin A and all precursors considered as a single group, all forms of calcium or selenium considered as distinct groups) the risk assessment will have the effect of yielding levels which are excessively low for 'safer' nutrient forms, and could then be deemed unscientific.

⁹ Schaafsma A, de Vries PJF, Saris WHM. Delay of natural bone loss by higher intakes of specific minerals and vitamins. *Critical Reviews in Food Science and Nutrition*, 2001; 41 (4): 225-249.

D between different populations, e.g. northern and southern Europeans. There is an abundance of published studies demonstrating the health promoting properties associated with the southern European diet, but such diets are not generally available to northern Europeans. In the absence of sufficient vitamin D and calcium (and potentially other nutrient co-factors), it has been suggested that the relatively high levels of vitamin A present in the diet (through consumption of foods such as liver and fortified milk) may cause adverse effects such as increased rates of bone fracture.^{6,7} However most studies have not taken into account nutrient interactions, the role of confounding factors such as smoking, physical activity or fluoride intake, or differences between different ethnic groups, or other population subsets.

2.1.4 Therefore, in conducting risk assessments, there is a real need to take into account global, population *and* **individual dietary requirements** for specific **nutrient forms**,⁸ to ensure that such assessments are **accurate and non-discriminatory**.

2.1.5 In considering data for use in risk assessments for whole populations, it is generally *inappropriate* to rely on data derived from clinical trials **using single or very limited combinations of nutrients** given interactions and synergy between nutrients, especially where such trials are related to high-risk population groups such as smokers or those with pre-existing diseases. In trials assessing interventions against multi-factorial diseases such as cardiovascular disease, cancer and osteoporosis⁹ it is particularly important to assess the effects of supplemental nutrient combinations, which may include phytonutrients, vitamins and minerals. In addition, trials utilising **synthetic or non-food form nutrients** should be viewed with caution, given, in some instances, known differences in their effects on the body compared with naturally-sourced nutrients. Furthermore, risk assessments would need to include consideration of **seasonal effects** caused by differences in nutrient consumption/requirement and metabolic processes affecting nutrient production, assimilation or excretion.

Question 1b: If so, please provide specific suggestions about how best to further articulate and make good use of the differences in identifying the scientific principles for nutrient risk assessment.

Science-based risk assessment, undertaken properly, is a time-consuming and costly process. In the view of the ANH, risk assessments should be conducted properly, using the necessary data, and only for those **nutrient forms** where it is deemed relevant and proportionate.

3.1.2 Therefore, the first step in developing a risk management approach for nutrients is to identify which **nutrient forms**, in addition to nutrient groups, should be included for risk assessment (see also Section 8.1.6). This selective approach parallels in principle one used by the Netherlands government which, prior to the implementation of the EU Food Supplements Directive (Directive 2002/46/EC), considered upper levels only for a limited range of nutrients, such as fat-soluble vitamins (notably preformed vitamin A) which have the ability to accumulate in the body and cause potential harm if taken regularly in excessive dosages.

3.1.3 **Science-based** risk assessment *cannot* be justified for a large number of nutrient forms where; a) nutrients are known to be safe even when consumed in high dosages, *and*; b) there is no evidence that the nutrient form has caused any significant adverse effects in a population despite the fact that they are consumed

by hundreds of millions of people around the world on a daily basis.

- 3.1.4 Rodricks reviews the difficulties encountered by the Institute of Medicine (USA) in its risk assessment of nutrients and nutritional supplements and emphasises that, owing to the **absence of adequate methodology**, upper intake levels could not be established for nutrients such as amino acids.¹⁰ This demonstrates **technical challenges** in performing risk assessments even using limited criteria; the difficulties and potential for inaccuracy become substantially greater if risk assessments are to be conducted in a scientifically rational and meaningful manner.
- 3.1.5 Using the above criteria to select **nutrient forms** for risk assessment would ensure a degree of proportionality with respect to the risk assessments which in turn can be used in risk management and development of international guidelines (e.g. through Codex Alimentarius) and regulations (e.g. EU Food Supplements Directive). Such consideration of proportionality is itself an accepted and necessary criterion in risk management science.¹¹
- 3.1.6 **Different nutrient forms should be viewed as individual nutrients** given that their effects on the body can differ to a great extent; there can be no adequate scientific justification to include nutrients containing common minerals or vitamins into groups for risk assessment purposes, in the manner undertaken to-date by the US Institute of Medicine (IOM), the European Commission, Scientific Committee on Food (SCF), the UK Expert Group on Vitamins and Minerals (EVM), the Council for Responsible Nutrition (CRN) and the International Alliance of Dietary/Food Supplement Associations (IADSA). Such grouping would only be scientifically rational if it were shown that nutrient forms within groups of vitamins or minerals had similar biological responses, which is clearly not the case (see Table 1).

Table 1. Examples of differences in biological response by different forms of nutrient

Nutrient group	Nutrient form	Relative Risk^a	Source
Vitamin B12	Cyanocobalamin	Greater	Andersson & Shapira, 1998 ¹²
	Hydroxycobalamin, Methylcobalamin	Less	Freeman, 1996 ¹³
Calcium	Magnesium oxide	Greater	McGuire <i>et al.</i> , 2000 ¹⁴
	Magnesium pidolate	Less	Paolisso <i>et al.</i> , 1992 ¹⁵
Iron	Ferrous sulphate	Greater	Shatrugna <i>et al.</i> , 1999 ¹⁶
	Iron bisglycinate	Less	Jeppsen & Borzelleca, 1999 ¹⁷
Selenium	Sodium selenate	Greater	Schrauzer, 2001 ¹⁸
	Selenomethionine	Less	Schrauzer, 2001 ¹²
Chromium	Chromium picolinate	Greater	Stearns <i>et al.</i> 1995 ¹⁹
	Chromium polynicotinate	Less	Vincent, 2003 ²⁰

^a Relative risk of different forms of the same nutrient group, based on available toxicological data, at dosages typically used (including supplementary intake).

- 3.1.7 In addition to assessing risks associated with consumption of particular nutrients, it is of paramount importance **to assess the risks which may be associated with the implementation of regulations based on the risk assessment**. For example, an extract from a UK Cabinet Office document on risk assessment in relation to regulation reads as follows:

“As well as assessing the risk that the proposed regulations are addressing, you should also consider the risks associated with the implementation of the options, and:

- *the potential for policy to exacerbate or mitigate risks to human health, property, finances, environment, reputation etc; any*
- *risks to policy delivery; and*
- *use this information to inform policy development and implementation.*

The likely sources of risk for each option should be spelled out along with an estimation of the likelihood of these risks occurring. The consequences of these risks for the proper implementation of the options and the likely outcomes ensuing should be examined.”²¹

It is clear that in the risk assessments conducted by the IOM, SCF, EVM, CRN and IADSA, such risks have not been contemplated and it seems unlikely, given the texts of the EU Food Supplements Directive (Article 5), which in turn is identical in principle to that adopted by the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU), that their consideration has yet been anticipated viz:

“Maximum amounts of vitamins and minerals present in food supplements per daily portion of consumption as recommended by the manufacturer shall be set, taking the following into account:

- a) “Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups;*
- b) intake of vitamins and minerals from other dietary sources.”²²*

3.1.8 Risk management exercises conducted by the IOM, SCF, EVM, CRN and IADSA have relied specifically on toxicological data supporting adverse effects of nutrients. These data tend to be highly selective and there has been no attempt to consider any benefits of the nutrients.

3.1.9 As shown in Figure 3 in the Background Paper (‘Two-tailed ‘risk’ for nutrients: inadequacy and toxicity’), the risks and benefits of specific nutrients are dose-dependent, although in many cases the dosages known to cause toxicity are well above those typically yielded from diet *and* supplementary intake. However, scientific opinion on what constitutes nutritional deficiency is increasingly varied, particularly as there appear to be threshold dosages at which classic symptoms of nutrient deficiency (e.g. scurvy, rickets, beri-beri, pellagra) arise and higher dosages which represent the minimum levels required for ‘optimum nutrition’, which reduce the incidence of common degenerative diseases. Furthermore, the model in the case of some nutrients is more complex, as shown by the example of vitamin B6 / homocysteine interactions. The EVM recommended limiting vitamin B6 to 10 mg/day, based to a large extent on flawed or irrelevant studies (e.g. Dalton & Dalton, 1987²³). However, 10 mg/day is not effective against hyperhomocysteinaemia, while 100 mg/day is effective.²⁴ Therefore, in this situation the two curves depicted in Figure 3 (Background Paper) would overlap. Clearly, the conceptual model should be altered (Figure 3, Background Paper) to take these complications into account.

3.1.10 ‘Optimum nutrition’, as described by Powers, has “evolved from a perceived need to

base recommendations for nutrient intakes firmly in the context of function. It follows that 'optimum nutritional status' for individual nutrients should be defined in terms of biochemical or physiological markers having some functional value but also showing an appropriate relationship to nutrient intake."²⁵ Andrews and Dobeck demonstrate the importance of consideration of risks *and* benefits in risk management for the licensing of medications, stressing the significance of inadequate consideration of benefits and how this can impact negatively on patients.²⁶ In the case of risk assessments on food (dietary) supplements carried out to-date, where any consideration of benefits has specifically been excluded, potential inaccuracies are even more likely. In the absence of consideration of benefits, any adverse report (e.g. from studies using high dosages, on susceptible groups, such as in the Beta-Carotene and Retinol Efficacy Trial (CARET)²⁷ and the Alpha-Tocopherol and Beta-Carotene (ATBC) study²⁸ on Finnish smokers, will tend to be viewed negatively owing to lack of 'balance' from positive studies demonstrating benefit. The ANH therefore argues that benefits must be considered in the risk management process.

3.1.11 The **key problem areas in risk assessments** undertaken to-date are described briefly in Table 2.

3.1.12 In summary, to best use the **scientific principles of risk assessment**, there should not be adverse risk assigned to nutrient forms with a **history of safe use** by a significant subset of the population and a **lack of reliable evidence demonstrating that risk** exists. The majority of vitamins, minerals, food ingredients, and even herbal ingredients have a remarkable record of safety even though they have been consumed by millions of people for 30 or more, in some cases hundreds, of years. However, where there is reliable evidence that risk does exist for a nutrient, an **objective evaluation of all relevant data** regarding the specific nutrient's risks and benefits should be conducted and the decision regarding intake limits should be based upon the data rather than the effects of political pressure or the agenda of special interests.

Table 2. Summary of key problem areas in risk assessments carried out to-date by IOM, SCF and EVM.^a

Problem area	Justification
Study selection criteria	Study selection criteria for the development of upper safe levels have not been adequately prescribed. Therefore there is a risk that key scientific data are ignored, as in the case of the UK Expert Group on Vitamins and Minerals in its 2003 report on <i>Safe Upper Levels of Vitamins and Minerals</i> . Critical missing data were identified by the Alliance for Natural Health in its consultation response to the Food Standards Agency in November 2002. ²⁹
Paucity of relevant human data	The bulk of published data from human studies available for use in such risk assessments are derived from studies of interventions with single or very limited combinations of nutrients, frequently in synthetic form. This is almost certainly one reason why some of these intervention studies on supplements have failed to show the same health benefits as studies on foods, where nutrients are delivered in different forms and complex combinations. Nutritional science, clinical nutrition, functional medicine and related disciplines are young sciences and there may be insufficient data in the published arena on which to undertake meaningful risk assessments.

<p>Failure to consider clinical data</p>	<p>In the absence of available data from clinical trials, risk assessments have failed to examine the large body of evidence built up over several decades by clinical nutrition and 'orthomolecular' practitioners. A so-called evidence-based approach has been used to exempt such data, but there is no adequate scientific justification to ignore such an invaluable resource of empirical data, given the large numbers of cases involved. Owing to lack of funding and government priority, sufficient effort has yet to be expended on collating such data for the purposes of publication.</p>
<p>Overuse of animal data</p>	<p>Owing to the paucity of relevant human studies, risk assessments conducted on nutrients tend to be over-reliant on animal data, which have sometimes been shown to be non-applicable to human risk and which themselves are subject to great variation.³⁰</p>
<p>Nutrient groups vs forms</p>	<p>Upper safe levels are proposed for nutrient groups, such as individual vitamins or minerals. However, both toxicity and therapeutic ranges vary considerably between different forms, so a risk assessment procedure based on nutrient groups would inevitably select for the 'most toxic' forms of nutrients and thereby may prevent 'safer' nutrients being used at appropriate dosages. Such an approach cannot be considered rational scientifically.</p>
<p>High susceptibility groups</p>	<p>The No Observable Adverse Effect Level (NOAEL), used as a key statistic in the risk assessment protocols, is generally set on the basis of the most susceptible population groups. Risk management based on NOAELs means that, in some cases, the majority of the population is unable to consume dosages which are in the 'optimum' range. In the case of beta-carotene, this means that the safety of beta-carotene, even when delivered in its natural context alongside other carotenoids, would be based heavily on two trials on beta-carotene (ATBC and CARET: see Section 3.1.10), in which marginal adverse effects were noted in smokers or asbestos workers and which may themselves be artifacts of the experimental designs. Accordingly, whole populations would be treated as if they were members of a high risk population subset.</p>
<p>Inappropriate estimation of dietary intakes</p>	<p>The proposed upper safe levels (USLs) will be moderated to maximum permitted levels (MPLs) following assessment of dietary intakes. This will take into account highest intake scenarios which might be derived from consumption of fortified foods. There is no evidence that those that consume higher levels of supplemental nutrients also consume the highest levels of fortified foods. Therefore, such an approach is irrational and would prevent those wishing to supplement a healthy, whole-food diet with optimum dosages of micronutrients.</p>
<p>Lack of weighting of adverse effects</p>	<p>In most risk assessments, different types of adverse effect are considered equally, triggering a NOAEL or a Lowest Observable Adverse Effect Level (LOAEL). However, flushing from niacin or stomach discomfort from vitamin C, should not be regarded in the</p>

	same way as hepatotoxicity caused by retinol, or other serious adverse effects.
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Lack of consideration of benefits	Health benefits of food supplements are ignored in risk assessments carried out to-date, despite the fact that risk/benefit evaluation is a standard criterion used in risk assessment science. At least within the European Union, avoidance of benefits is linked to the inability for any health claims to be made for food supplements, in turn linked to long-standing medicinal laws which state that claims can only be made for medicinal products. Such barriers are irrational given that health benefits can clearly be attributed to foods and food supplements. For benefits to be considered fully, it would be necessary to modify existing definitions for medicinal products (e.g. EU Directive 2001/83/EC).
Risk of using inappropriate or invalid studies	There is a real risk that use of inappropriate or invalid studies (e.g. Dalton & Dalton, 1987, for vitamin B6) in risk assessment could result in maximum permitted levels that deprive many individuals of the dosages required to maintain good health.

^a The CRN and IADSA³¹ risk assessments include safety evaluation of supplemental intakes of nutrients only.

Question 2

Hazard identification and characterization involve a number of decision points that require scientific judgment in order to derive a UL. Please provide input as to how guidelines for these judgments can be developed for the following decision points:

Question 2a: Criteria for the evaluation of the quality and utility of relevant scientific evidence.

4.1.1 There is a wide range of potential sources of data that might be relevant to risk assessments. These include:

- Molecular studies: published, peer reviewed research
- Cellular studies: published, peer reviewed research
- Animal studies: published, peer reviewed research
- Controlled clinical studies: published, peer reviewed research
- Uncontrolled clinical studies: published, peer reviewed research
- Epidemiological studies: published, peer reviewed research
- Meta-analyses: published, peer reviewed research
- Government, university or other reports: published / unpublished

- Case reports: published
- Case reports: unpublished
- Commercial data: conference proceedings
- Commercial data: unpublished

All the above sources could be said to offer scientific evidence of relevance to nutrient risk assessment, but evidence **should not be regarded as conclusive unless it has been corroborated by multiple studies**, in a range of different formats.

- 4.1.2 The ANH supports an approach which relies on the **totality of evidence**, assuming the evidence is relevant to the population group in question. For example, on this basis, clinical studies on smoker populations (with cancer, pre-clinical or with metastasis, or with high cancer risk) and the effects of intervention with beta-carotene supplements could not be used to inform risk assessments relevant to a national population. Furthermore, it would not be possible to ignore large numbers of relevant studies, as demonstrated by the ANH in its critique of the UK EVM Group report.²¹
- 4.1.3 **Evidence should not be selected exclusively from peer reviewed journals**, because clinical studies in particular may be: a) limited in number; b) limited in their scope, often dealing with interventions with single or limited combinations of nutrients; c) potentially biased, which in turn will be influenced especially by the research funding organisation.³²
- 4.1.4 **It is wholly appropriate to utilise unpublished work** (see Section 4.2.1) **for additional, supporting information, on the proviso that the data are relevant and their quality can be substantiated**. In the case of medical case reports, for example, such unpublished case data can offer far more meaningful data than is frequently the case with some of the published studies. For example, if there is doubt about the safety of a vitamin (e.g. vitamin B6 at doses in excess of 10 mg/day), it would be useful to gather data from clinical nutritionists to glean views from their own long-term medical records.³³
- 4.1.5 Criteria need to be adopted in order to accept certain thresholds of data. In principle, **the larger the study, the greater the need for vigilance** in determining its acceptability. Particularly problematic are clinical and epidemiological studies, considered below.
- 4.1.6 Some of the **key issues that should be considered in selection of clinical and epidemiological studies** for risk assessment include:
- a) Proper randomisation
 - b) Proper trial design (for clinical trials)
 - c) Information on participant selection
 - d) Information on participant refusal
 - e) Proper group or cohort selection
 - f) Clarification of confounding variables
 - g) Tests of multifactorial interaction
 - h) Proper statistical analyses, including data transformation as necessary, confidence limits and statistical significance
- 4.1.7 **Many studies are open to wide interpretation** and the authors conclusions may in fact not be the correct conclusions; for example, a trend or association which may be cited in a study as a causal factor, may not necessarily be one, given the multi-factorial and complex nature of such studies. Therefore due diligence needs to be taken during interpretation. Factors³⁴ to be considered in particular are:

- a) **Strength of association**; where a relationship between the intake of a nutrient appears to be associated with a given health indicator, the extent of that relationship gives some indication as to its likely significance (e.g. does the nutrient apparently cause 1.2-fold or 20-fold effects on the specified health indicator?)
- b) **Dose-response**; given the dose-dependent relationship between any substance and its toxicity, studies which demonstrate increased severity of a given health indicator with increased dosage are more convincing.
- c) **Consistency**; this implies a degree of reproducibility of the effect demonstrated in one study, which is also shown to occur in other studies with different populations, hence giving stronger evidence of a causal relationship.
- d) **Biological plausibility**; where data from epidemiological studies shows weak associations, molecular or cellular studies can be very useful as a means of testing the underlying mechanisms which may give rise to a particular effect.
- e) **Reliability of exposure information**; this factor has clearly been considered in the Background Paper (Question 3) and is of great relevance. In some cases it may be inappropriate to quantify total intakes and effects of nutrients from conventional foods, water/beverages and supplements in a simplistic additive manner owing to differences in bioavailability, metabolism and excretion of different forms. Exposures may be short-term or long-term, seasonal, etc. This issue is considered in greater detail in Sections 7.2 and 8.1 of this report. Furthermore, the duration of exposure is a critical factor in clinical intervention trials, as are the nutrient forms, dosages and confounding factors such as health status of the participants before commencement of the trial.
- f) **Confounding**; there are numerous factors which may contribute to confounding. These may include the initiation of disease in a pre-clinical state prior to the start of the study, interactions between different dietary or environmental factors, drug interactions, socio-economic factors, the role of exercise or physical activity, alcohol consumption, smoking, etc. In many clinical and epidemiological studies, such factors are not adequately taken into account (or may not be possible to evaluate given resource availability) and may explain certain negative responses that may have been wrongly attributed to supplements or supplement interventions.
- g) **Statistical significance**; some studies do not include appropriate statistical testing of significance of results, in terms of *P*-values, as compared with the null hypothesis, which reflects the results that would be expected by chance alone with no effect of treatment. These, together with confidence limits are essential, but can only be relied upon on the basis that appropriate assumptions are made and, where necessary, appropriate transformation of the data has been undertaken prior to the statistical analysis.
- h) **Meta-analysis**; meta-analyses are increasingly used³⁵ as a means of combining quantitative data, usually summary statistics derived directly from a variety of published studies on the same subject area. Although they are useful as a means of assessing empirical data, and can complement a manual review of the literature, there are a variety of

problems that may be associated with them. Even if the trial selection criteria are reasonable, and studies are viewed as 'high quality', the results will be very dependent on factors such as the nature of the treatments and the relative scale of the trials (large trials clearly weighting the results more heavily). In both the recent antioxidant and vitamin E meta-analyses,²⁶ the treatments in the trials selected did not include the most beneficial forms of either antioxidants or vitamin E (i.e. phytonutrients and natural vitamin combinations in the former study and full-spectrum, natural vitamin E including mixed tocopherols and tocotrienols in the latter one). Apart from this experimental bias, the studies were also numerically biased by very limited, large and non-representative studies. Accordingly, many of the respective authors' conclusions were incorrect or misleading (see the ANH comments on the antioxidants³⁶ and vitamin E³⁷ meta-analyses respectively). In the case of the vitamin E meta-analysis, there has been a general misinterpretation of the study's results, which may or may not have been deliberately orchestrated for political and commercial purposes; the Relative Risk derived by the authors was 1.06, but because the 95% confidence interval did not cross over unity, the authors were able to claim that the risk was "significant", meaning statistically significant. This was interpreted by the media and lay people to mean a subjectively significant rise, which of course could not be justified epidemiologically. Given pharmaceutical sector's financial capacity to conduct clinical trials, most to-date have used an intervention-based approach synonymous with orthodox medicine, and have included use of single or limited combinations of mainly synthetic vitamin analogues and inorganic minerals. As a result, clinical studies evaluating the effects of healthy balanced diets supplemented with a range of food-state supplements, are wanting.

- i) **Pooled analysis**; this methodology is different from meta-analysis in that it does not rely on summary data, but on primary (unanalysed) data derived from individual trials, which in many cases may be difficult to extract from the original authors. However, pooled analyses could, in the future, be more relevant than meta-analyses as a means of comparing multiple, smaller, high quality studies in a more meaningful way than is possible with meta-analyses. The recently published pooled analysis undertaken by Knekt *et al.* (2004)³⁸ is a landmark study, following tight criteria for study selection, including a 10-year follow-up, and reveals a marked positive effect of higher dose (> 700 mg/day) supplementation with vitamin C on reduced incidence of cardiovascular disease (CVD) events. This is all the more remarkable as this dose for most participants was probably achieved with a single dose of vitamin C, which had a relatively short half-life in blood. More pronounced effects could potentially be derived from multiple daily doses. In any event, this cohort analysis of 9 prospective studies offers further evidence that the RDA for vitamin C should be raised dramatically if disease reduction by nutrition is to be seriously contemplated by health authorities. The lack of apparent effect of vitamin E in reducing CVD events in these pooled studies may have been attributed to alpha-tocopherol being the primary form consumed as a food supplement as opposed to the natural, mixed tocopherol/tocotrienol form which has undoubtedly greater antioxidant capacity.³⁹

4.1.8 Other important factors that should be considered include:

- a) **Physiological relevance**, the extent to which the body responds to the introduced supplementary nutrients in a way similar to the response to

nutrients derived from food, where vitamins and other nutrients are always present in combinations. For example, in the presence of vitamin C, oxidised alpha-tocopherol can be regenerated efficiently, resulting in increased availability of alpha-tocopherol. It may be that vitamin C supplementation increases alpha-tocopherol plasma concentrations, at least in subjects with low vitamin C status, or that supplementation with the combination of vitamin E and C may yield relatively higher alpha-tocopherol plasma concentrations than supplementation with vitamin E alone^{40,41};

- b) **data quality**; there are serious risks associated with use of poor quality data, e.g. Dalton & Dalton, 1987 for vitamin B6, and:
- c) the **duration of exposure** of intervention and **length of follow-up**.

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

5.1.1 It is simply not scientifically rational to extrapolate data from whole populations to particular age or gender cohorts. However, where primary data are available for specific age/gender cohorts, limited extrapolations may be feasible to closely related cohorts in the same or similar populations. Age and gender, among other factors, have both been found to greatly influence nutrient requirements, and dietary patterns tend to vary considerably according to age, gender, as well as according to other factors such as ethnicity,⁴² lifestyle, dietary habits, season and disease status.⁴³ Some of these factors may be clustered within particular socio-economic groupings.

5.1.2 For example, in a **UK government dietary survey**, the following foods were found to be most commonly consumed by 4 to 18-year-olds; "white bread, savoury snacks, chips [French fries], biscuits, boiled, mashed and jacket potatoes and chocolate confectionery"⁴⁴; while adult UK men were found, in a separate survey, to consume 2.7 portions of fruit and vegetables a day, compared with the 2.9 daily portions consumed by adult women.⁴⁵ These and other data show distinct gender patterns.

5.1.3 With regards to the **total antioxidant capacity (TAC)** of serum, a useful biomarker for nutritional health, as measured by the ABEL® total antioxidant capacity assay with peroxynitrite,⁴⁶ significantly higher TAC scores, expressed as $\mu\text{mol L}^{-1}$ vitamin E analogue (VEA) equivalent values were measured in men than in women⁴⁷ in 173 apparently healthy, 'normal' men and women (age range 21-76) and 14 London Marathon runners (age range 20-59), with no correlations evident with age.⁴⁸ A different assay measured higher levels in 22 male and 21 female healthy students.⁴⁹

5.1.4 Dietary patterns not only vary within age and gender cohorts within national populations, they also vary to an even greater extent between national populations. For example, there are very substantial differences between macronutrient and, in particular, micronutrient intakes, between northern and southern Europe, and within and between regions, such as Europe, Africa, North America, Central America, South America, Asia, Australasia, etc.

- 5.1.5 Socio-economic factors** (and education) have a large bearing on dietary choices.⁵⁰ For example, respondents in the UK National Diet and Nutrition Survey (2002) were significantly more likely to be taking supplements if they were from a non-manual rather than manual home background.⁵¹
- 5.1.6 A range of other factors, such as lifestyle, dietary habits, ethnicity and disease status, may readily confound data.** For example, one meta-analysis has demonstrated that smokers declared significantly higher intakes of energy (+4.9%), total fat (+3.5%), saturated fat (+8.9%), cholesterol (+10.8%) and alcohol (+77.5%) and lower intakes of polyunsaturated fat (-6.5%), fibre (-12.4%), vitamin C (-16.5%), vitamin E (-10.8%) and beta-carotene (-11.8%) compared with non-smokers.⁵²
- 5.1.7** Finally, since ULs are determined as non-regulatory reference levels, which should relate to specific population groups (which may in turn include age, gender, ethnicity, lifestyle factors, nutrient intakes, activity levels, etc.), **great care should be taken in calculating nutrient intake from *all sources***, given the wide array of nutrient forms that may be consumed in foods, beverages and in supplements. In short, **from a pharmacokinetic or toxicological perspective, different nutrient forms consumed in conventional foods, beverages and supplements cannot necessarily be assumed to be *additive in their effect***. For example, consuming synthetic beta-carotene from supplements is not directly comparable with consuming equivalent amounts of beta-carotene derived from natural carotenoids in supplements and foods;⁵³ similarly, consumption of calcium oxide in a supplement cannot be regarded as equivalent to consuming the same total amount of calcium derived from food sources together with a calcium citrate-malate supplement formulated with vitamin D and magnesium.

Question 2c: Determination and use of uncertainty factors.

- 6.1.1 Generally in risk assessments on non-cancer causing chemical agents, typical values for uncertainty (or 'safety') factors (UF) of 10 for inter-human variation, 10 for animal to human (inter-species) extrapolations and less than 10 for LOAEL to a NOAEL extrapolations are used.⁵⁴ These are more or less identical to those used by the SCF and EVM for vitamins and minerals, although a UF of 3 is typically selected for LOAEL to NOAEL extrapolations (as per Background Paper). This suggests excessive conservatism, given that in instances where more data are available for known toxins such as pesticides, a more accurate estimate of uncertainty for differences between LOAEL and NOAEL has been shown in some cases to be significantly less than 2.⁵⁴
- 6.1.2 There is a real risk of misinterpretation of study findings, as per the Vitamin E meta-analysis [see Section 4.2.7 h)], thus giving rise to unnecessarily large UFs.
- 6.1.3 For nutrient forms where there is very little or no evidence of toxicity, the UF should be minimised, and should certainly be < 2 and may approach 1. In this regard, some of the less restrictive UFs suggested by IADSA should be considered in place of the often over-restrictive UFs suggested by the EVM or SCF.

- 6.1.4 There can be no justification for *not* attempting to improve the reliability of data as a means of eliminating the need for large UFs. A UF in excess of 2 or 3 may make the difference between a particular nutrient being of benefit and it not being of benefit.
- 6.1.5 In conclusion, where there are ample, relevant data, there is no justification for the use of UFs for nutrients, ULs being drawn directly from the data.

Question 2d: Other

Question 3

The conduct of exposure assessment and risk characterization also requires sound scientific principles that can be applied to the various decision points, including but not limited to compilation and collection of intake data and decision-making for summarizing the potential for harm.

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

- 7.1.1 **Nutrient exposure must be determined from assessments of intake derived from conventional foods, food supplements and beverages.** Global averages will have very little real meaning owing to substantial differences in nutrient exposure in different parts of the world. Regional and local data will be of much greater relevance. There are a wide variety of databases available, many of which have been populated, particularly in industrialised countries, by data collected from self-reporting **questionnaires**⁵⁵, **but such self-reported data are well known to be subject to error.**⁵⁶ The Joint Institute for Food Safety and Applied Nutrition (USA) has access to a range of tools that may be used to determine nutrient exposure.⁵⁷
- 7.1.2 Apart from reporting errors, further problems are caused by **excessive pooling of data**. So where national data are pooled even within particular age classes, as is typical, variations in dietary intakes caused as a result of ethnicity, socio-economic grouping, energy expenditure and other factors are ignored. As food fortification becomes more common, this will have the effect of increasing mean intake levels for specific nutrients; however, there is no evidence to suggest that those who consume the largest amounts of fortified foods, also consume the largest quantities of nutrients via supplements. It is likely, in the absence of empirical evidence, that the reverse is true.

- 7.1.3 Given continuing **trends towards food processing, convenience foods, fast foods, as well as intensification of agriculture**, particularly in industrialised countries, **intakes of trace and ultra-trace minerals, which are not commonly supplemented, are almost certainly set to continue to decline**. Many of these are likely to be banned under the forthcoming Food Supplements Directive, unless a legal challenge in the European Court of Justice by the ANH is successful in January 2005.
- 7.1.4 In the UK, levels of a range of **important dietary minerals have declined by between 15% and 76% during the period 1940 to 1991** (see successive editions of McCance and Widdowson's *The Composition of Foods*, Food Standards Agency, UK).⁵⁸ The amount of selenium in the European diet has declined dramatically, owing to mineral depletion of agricultural soils over the past decades, as well as owing to changes in wheat supply from North America (high selenium content in soil and wheat products) to Europe (low selenium content). Selenium levels have declined to such an alarming extent in the UK and Belgium even between 1983 and 1993 (trends are likely to be similar in many other countries), that a wide range of health problems are to be expected in the population as a result of selenium deficiency.⁵⁹ Declines in trace mineral content of foods in the US can be determined by interrogation of US Department of Agriculture (USDA) databases.⁶⁰
- 7.1.5 In order to assess accuracy of questionnaire-based data on nutrient exposure, **random sampling of specific biomarkers** (e.g. gamma-tocopherol, beta-carotene, vitamin C, vitamin D) should be undertaken in specific population groups to provide accurate reference values. Reference values would be made more accurate by assessing biomarker concentrations in individuals in which nutrient intakes have been determined, so taking into account bioavailability. This approach would allow the application of correction factors to improve accuracy of the questionnaire-based data. An evaluation of biomarkers (plasma ascorbic acid, beta-carotene and alpha-tocopherol 24-hour urinary potassium excretion) was undertaken and compared with data obtained via a self-reporting questionnaire in the UK, focusing on fruit and vegetable consumption and was shown to be valid.⁶¹
- 7.1.6 There are number of ways of considering the effect of food supplements in the body. The **measurement of the individual nutrient forms in the plasma** using HPCL with either direct UV- or fluorometric detection following derivatisation is well established as are other colorimetric methods. The measurement of some **metabolic markers** reflects to a certain extent the consumption and utilisation by the body of the specific nutrients ingested. However, the treatment of samples as well the inherent instability of ascorbate and dehydroascorbate, which have half lives of only a few minutes, makes the measurement of actual concentrations less useful.
- 7.1.7 The use of particular **biomarkers that are relatively stable in terms of intra-individual analyses is particularly relevant**, given that nutrient concentrations fluctuate considerably within the day according to time since last meal, diet, metabolic stress, hydration and a host of other factors. **Antioxidant analysis** (plasma) is potentially a particularly important tool in this respect.
- 7.1.8 During a lifetime, the body is exposed to a variety of potentially damaging oxidative stresses. Some of these arise naturally as a byproduct of cellular respiration as well as during infection and inflammation when phagocytic white blood cells release large quantities of reactive oxygen species (ROS), including free radicals (highly reactive unstable species with unpaired electrons). Others arise from diet, environmental pollution, including cigarette smoke, exhaust fumes and ionising radiation⁶². ROS are essential to human wellbeing but if produced in excess can lead to destruction of cells, disabling of enzymes and damage to DNA. In order to protect the body against potential damage of ROS, the body has adopted a range of antioxidant measures,

including utilisation of vitamins and other nutrients as antioxidants.⁶²

- 7.1.9 A **definition of an antioxidant** is a compound that at relatively low concentrations prevents or delays the oxidation of another compound by employing strategies or scavenging, prevention of radical formation and induction of antioxidant enzymes.⁶²
- 7.1.10 Antioxidants are important components of a healthy diet, and are derived naturally particularly from plant sources. The FAO/WHO risk assessment project applies initially only to vitamins and minerals, but there are a large number of **phytonutrients**, with which vitamins and minerals interact, that are of key importance as antioxidants in the diet. **Vitamin antioxidants** include vitamin A, β -carotene, vitamin C, the vitamin E group (tocopherols and tocotrienols) and Vitamin D. Vitamins A, C and E act by scavenging ROS, while other antioxidants, yet to be included in the risk assessment project, employ strategies of chelating free iron and copper thus removing their potential to create extremely reactive hydroxyl by reactions with hydrogen peroxide. Antioxidants such as selenium are co-factors in antioxidant enzyme glutathione peroxidase.
- 7.1.11 A variety of **antioxidant capacity assays** have been developed in order to assess the capacity of a sample to scavenge free radicals. Most of these, for example the ORAC, TEAC, FRAP and the Randox commercial version of the TEAC assay have been assessed in great detail in the EUROFEDA Concerted Action⁶³ and for a variety of reasons they have been found wanting.
- 7.1.12 The issue of **optimum intake of vitamins**, beyond their role in avoiding deficiency diseases, is probably the issue of most relevance in seeking methods to assess the risk and benefits of taking food supplements. And while vitamins can act as ROS scavengers in the process, they can themselves be converted into free radicals or pro-oxidants in which enhanced production of free radicals occurs when they are attacked by free radicals. These antioxidants converted to pro-oxidants then have the capacity to be harmful.
- 7.1.13 **Dose-response studies** with regard to antioxidant functions are of crucial importance when assessing risks and benefit associated with ingredients used in food supplements, as well as functional foods. This is of particular interest if an ingredient at low concentrations is pro-oxidant but at sufficiently high concentration can exhibit very effective antioxidant capacity.⁶⁴ With such behaviour, determination of specific doses for individuals can be critical.
- 7.1.14 Some **novel diagnostic tests** have been developed which could be used to assist in the risk assessment of food supplements:
- **Metabonomics** involves analysing biological fluids, tissue extracts, drugs or dietary supplements with techniques of nuclear magnetic resonance spectroscopy (NMR), mass spectrometry, or infrared spectroscopy, providing many data points simultaneously which give a complete metabolic profile of the substance under investigation.⁶⁵
 - **EXATEST™**: elemental X-ray analysis processed by Scanning Electron Microscopy, as a highly accurate and rapid means of assessing intracellular electrolyte levels.⁶⁶
 - **ABEL®** (Analysis By Emitted Light) range of oxidative stress tests incorporating Pholasin® (a light-emitting protein derived from a marine rock-boring mollusc, *Pholas dactylus*),⁶⁷ as follows:
 - Total antioxidant capacity (TAC) assay of serum or plasma using peroxyxynitrite and vitamin E analogue standards to produce a VEA

- equivalent score for individuals and measure subsequent changes in response to antioxidant supplementation (even in horses)^{55, 68}
- o ABEL® antioxidant assay for superoxide, a rapid flash assay suitable for near patient testing and especially for measurement of ascorbic acid without interference from uric acid;
 - o ABEL® antioxidant assay for hydroxyl radicals, especially for assessing antioxidants derived from plants;
 - o ABEL® antioxidant assay for halogenated oxidants, for assessing organic antioxidants;
 - o ABEL® cell activation assays, for use with blood and isolated cells to measure the real-time production of free radicals from living cells and assess the effect of vitamins exposed to free radicals produced by cells;
 - o Combination of ABEL® assays to produce data for use in quality assurance, assessment of batch to batch uniformity and possible changes that might occur during production.

Question 3b: Please provide input on general scientific principles for the characterization of the severity and the degree to which intakes exceed the UL or other aspects of risk characterization.

8.1.1 As per the FAO website, "*The Risk Assessment process provides an estimate of the probability and severity of illnesses attributable to a particular hazard related to food.*"⁶⁹ Accordingly, it is necessary to provide some parameter which expresses the severity of the risk, together with the probability of that risk occurring, as a function of risk characterization. This parameter would need to be specific to a given population. The risk assessments undertaken to-date by the SCF, EVM and trade associations do not characterise risk in this way.

8.1.2 An appropriate formula is given in Figure 1:

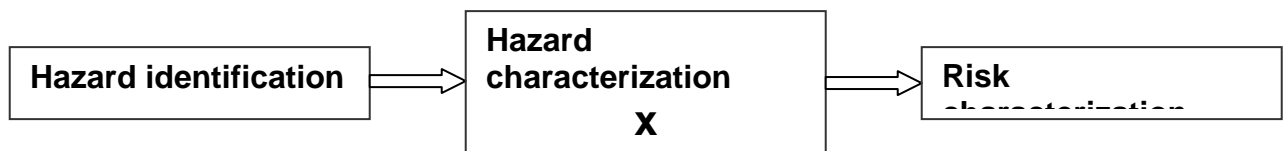


Figure 1. The components of risk characterization (adapted from Sumner & Ross⁷⁰)

Figure 2 in the Background Paper is misleading in that it implies that hazard characterisation and exposure assessment (contrary to Figure 1 above, and other sources⁷¹) are independent of each other. Risk characterisation, as shown in Figure

1, is a direct function of hazard characterisation *and* exposure assessment.

- 8.1.3 This approach characterises risk for a given population only. Thus, **total risk** depends on hazard exposure (hazard x exposure) and susceptibility to a variety of population groups.
- 8.1.4 Accordingly, data are required for the following parameters (Table 3), and these could be developed for at least two population groups according to susceptibility: vulnerable (high-susceptibility) populations (e.g. young, elderly, pregnant, lactating, etc.) and average-susceptibility populations (mean of population groups of varying susceptibility):

Table 3. Parameters for semi-quantitative risk characterization of nutrient forms⁷²

Risk criteria	Parameter	High susceptibility population groups	Average-susceptibility populations
Severity	Hazard severity		
	Susceptibility		
Probability of exposure ^a	Frequency/duration of consumption		
	Proportion of population consuming		
	Size of population		

^a Exposures should be calculated for total intakes (conventional food and supplements) of nutrient groups where effects are additive (known dose-response) or separately for conventional foods and supplements where responses are known to be different between food-forms and supplement-forms.

- 8.1.5 **Hazard severity**, an evaluation of the nature of adverse effects, should be determined for those nutrient forms prioritised for the risk assessment. These could be ranked semi-quantitatively, so that, for example, hepatotoxicity as a result of excessive preformed vitamin A consumption would be given a much higher ranking than flushing from niacin or mild diarrhoea from vitamin C. Such rankings should be developed for both average-susceptibility and high-susceptibility population groups.
- 8.1.6 Having **characterised risk for the various nutrient forms**, ranking should again be undertaken to assist in determining priorities. This may done via an arbitrary, semi-quantitative Relative Risk Index (RRI). For example, some nutrients and nutrient forms, which may be attributed a relatively high RRI, may be regarded as intrinsically toxic even at relatively low concentrations (e.g. selenium, zinc, molybdenum), but they are highly beneficial (essential) at specific dosage rates. Dose-response data is needed to establish the margin between beneficial dosages

and dosages which have the potential to induce adverse effects in both susceptible and normal populations.

- 8.1.7 **Policy or regulations** taking into account different susceptibilities and exposures, developed on the basis of a risk management process for nutrients which addresses properly the parameters given in Table 3, including confidence limits for each parameter, would serve to avoid limiting average populations to the highest dosages deemed safe for high-susceptibility groups. Such an approach is likely to enable members of most population groups to consume dosages of nutrients that are likely to promote optimum health and is important for the development of preventative health management strategies. However, as indicated above (Sections 4.2.7 and 5.1.7), caution needs to be applied when determining total intakes, given that nutrient forms within a given nutrient group do not necessarily respond additively in the body, given differences in assimilation, metabolism and excretion between nutrient forms.
- 8.1.8 **Such risk characterization and assessment should be reserved for those nutrient forms where there is sufficient evidence of a genuine and significant risk.** Qualitative or rudimentary, semi-quantitative risk ranking (using for example an RRI) may be undertaken to determine the threshold for which more detailed, quantitative risk assessment should be undertaken. Such a scheme would give rise to three distinct levels of risk assessment, as shown in Table 4.

Table 4. Prioritization of risk assessment and management strategies following proper risk characterisation

Low priority	Moderate priority	High priority
<i>Estimated Relative Risk beneath de minimis level (negligible)</i>	<i>Estimated Relative Risk seen to pose some risk, at least to high-susceptibility population groups</i>	Estimated Relative Risk considered to pose significant risk to some or all population groups at threshold dosages
UL may be set as $> x$, where x is the highest NOAEL known	Progress risk assessment, semi-quantitatively	Progress risk assessment with highest degree of quantification
No regulated maximum levels prescribed	Agree ULs	Agree ULs
No further action required, other than on-going adverse event monitoring	Prescribe maximum levels through risk management (maximum permitted levels)	Prescribe maximum levels through risk management (maximum permitted levels)
		Consider prioritising further research
		Consider legitimising access to highest doses via

		practitioners only
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- 8.1.9 When an 'action threshold' for detailed risk assessment is reached, above the *de minimis* risk threshold (Table 4), risk management decision-making may be assisted by parallel assessment of risks *and* benefits (such a principle is alluded to in Figure 3 in the Background Paper). Benefits, as well as hierarchical approaches to quantification (as suggested here), have consistently been ignored in all nutrient risk assessments undertaken to-date.
- 8.1.10 Using these suggested scientific principles would also mean that intakes for some population groups may exceed ULs set for vulnerable groups, but the risk to each respective group would nonetheless be minimised. It would also allow the establishment of safety margins between LOAELs and optimal (beneficial) doses.⁷³
- 8.1.11 To assess the efficacy of the risk characterisation process, the results should be compared with **existing adverse event reports**, where these are available, although it should be appreciated that these will tend to bias short-term, acute effects. Interestingly, there extremely low numbers of reported adverse events related to vitamin and mineral supplementation. In the UK, the Medical Toxicology

Unit studies⁷⁴ represent a valuable, although now slightly dated, database of adverse events for pharmaceutical products and dietary supplements, yet this resource was not referred to by the EVM in their risk assessment. Data sets are generally more complete in the US than elsewhere. A very comprehensive survey by the US government (Ervin *et al* 1999) showed that approximately 40% of the US population took supplements in the month prior to being interviewed.

- 8.1.12 The US Federal Drugs Administration (FDA) has on file approximately 2,500 adverse event reports (AERs), including 79 deaths, that may be related to dietary supplements, these having been collected over a 20-year period.⁷⁵ Forty four of the 79 reported deaths were apparently attributable to ephedrine-containing products.⁷⁶
- 8.1.13 These data continue to be unavailable for public scrutiny after being withdrawn from the FDA website over two years ago.⁷⁷ Further data on the frequency of reported adverse events in the US can be found in reports of the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers, the only comprehensive poisoning surveillance database in the United States. These data show that vitamin and mineral supplements are among the safest products taken orally. They are many times safer than alcoholic beverages, tobacco and even caffeine (TESS Annual Reports from 1983 to 2003 inclusive are accessible from the TESS website⁷⁸). These and other data⁷⁹ show clearly that pharmaceutical products present by far the greatest risk of poisoning.
- 8.1.14 Food and Drug Administration's Center for Food Safety and Applied Nutrition (CFSAN) has recently launched a new adverse event reporting system for dietary supplements, prompted particularly by concerns over the safety of ephedra (rather than nutrients).⁸⁰
- 8.1.15 It is estimated that food-borne diseases contribute to approximately 76 million illnesses, 323,000 hospitalisations, and 5,200 deaths in the United States each year,⁸¹ while properly prescribed and administered prescription and over-the-counter drugs are estimated in the to cause annually 2.2 million serious adverse events, and some 106,000 deaths in the USA.⁸²

The Background Paper reflects a 'thought process' and is intended to inform a longer process for the development of a technical expert workshop. Clearly the process will benefit from additional input.

Question 4a: Please provide comments on other general factors or considerations that could be taken into account during the process of identifying principles for nutrient risk assessment.

- 9.1.1 **There are serious weaknesses in any risk assessment approach which evaluates selectively the safety and toxicology of nutrients in isolation from their essential and health promoting properties, and then applies risk management decision-making to whole populations on the basis of results from studies on the most susceptible or vulnerable population groups.**
- 9.1.2 Some may argue that the degree of uncertainty caused by data limitations (in the case of some nutrients and forms) could warrant application of the **precautionary principle**,⁸³ but the apparent safety record of food supplements would suggest that such an approach might be **disproportionate**. Additionally, should the precautionary principle be applied, it should be seen in the context both of exposing populations to nutrients, as well as depriving them of nutrients should risk management have the effect of restricting particular nutrient forms or dosages.
- 9.1.3 Data limitations and use of selective data are very evident with risk assessments carried out to-date. For example, the CARET²⁷ and ATBC²⁸ trials involving beta-carotene and limited other nutrients, where the trial participants were smokers or asbestos workers and therefore highly susceptible to lung cancer cannot be applied to whole populations. At most, a risk management approach in which warning labels are applied to products indicating safety concerns for susceptible groups, as is common practice with certain foodstuffs, would surely be a more rational risk management strategy than blanket imposition of a restrictive dose that may limit substantial sectors of the population from gaining adequate quantities of a nutrient? As shown in a meta-analysis exploring relationships between smokers and diet,⁸⁴ smokers appear to consume less beta-carotene than non-smokers in any case, so there can be no scientific rationale in applying maximum levels of beta-carotene that are deemed safe for smokers to non-smokers, particularly given that the dosages, forms and combinations of nutrients used in the treatment groups within the studies appear to have been inappropriate.

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

- 10.1.1 Dietary reference values and risk management.** National nutritional surveys, in which the data are compared with dietary reference values, are widely used to assess nutritional inadequacy or excess. Reference values have been identified as an important criterion for use in risk management, as evidenced by texts in both the Food Supplements Directive (Article 5) and the proposed Codex Alimentarius guidelines for vitamins and minerals. However, there is often a failure to appreciate

the concepts on which these reference values, are based and depending on which values are used, thoroughly different perspectives on micronutrient deficiency emerge.⁸⁵

10.1.2 Prioritisation of risk management. There is a great need to ensure that risk assessment is undertaken in such a way that allows prioritisation of proportionate risk management approaches (see Section 11.11). **It is crucial that recent politicisation and mis-interpretation of studies concerning nutrients (e.g. antioxidants, vitamin E, folic acid) are not used to rail-road risk management approaches by unnecessarily restricting nutrient availability; such risk 'mis-management' in itself creates new risks that can only be deduced if benefits are included in overall decision-making, and it runs counter to the development of preventative healthcare strategies that are so keenly required globally.**

11. CONCLUSIONS OF ANH SUBMISSION TO FAO/WHO NUTRIENT RISK ASSESSMENT PROJECT CONSULTATION

11.1 For risk assessment purposes, **nutrients cannot be regarded in the same way as environmental chemicals**, which are not associated with beneficial effects, **or even pharmaceutical drugs**, which are aimed specifically at unhealthy populations and are well-known to be associated with serious iatrogenic risk.

11.2 **Food supplements are clearly a category of food, being concentrated sources of nutrients.**⁸⁶ There is no evidence that they pose more risk than foods, in fact, existing evidence suggests they pose significantly less risk to humans than foods, even in countries such as the US, UK or New Zealand, where around 50% or more of the population consume them regularly (see New Zealand data, compiled by Ron Law⁸⁷) As such, from a risk management viewpoint, it is rational to treat supplements in a more similar manner to conventional foods, rather than as synthetic food additives, environmental chemicals or medicinal products.

11.3 From a standpoint of **scientific rationality**, nutrients, unlike the xenobiotics mentioned above, need to be considered in a **unique** way, given that they are essential not only for the maintenance of health, but also to the promotion of health.

11.4 As the human diet alters, given the monumental changes that have occurred during the last century as a result of agricultural intensification, plant breeding, genetic engineering, food processing, food choices, lifestyles and other factors, **it is crucial that an approach to risk assessment and management is adopted that takes fully into account the huge range of *interacting* and *changing* factors.**

11.5 There has been an increasing push for vitamin, mineral and other nutrient intervention approaches to be determined using an **evidence-based rationale**. Put simply, an evidence-based rationale is only as good as the evidence on which the risk assessments are based. Low quality evidence implies low quality risk assessment. Further, an evidence-based approach can be interpreted in such a way that it promotes the use of highly selective data which have the effect of skewing results in favour of unnecessarily low ULs and guidance levels. This appears to be the case particularly in the EVM guidance for key nutrients such as beta-carotene, pantothenic acid, biotin, vitamin B6, vitamin C, vitamin D, niacin, iron and manganese.

11.6 Perhaps, a more appropriate paradigm is one based on **scientific rationality**, which is the approach that has been adopted in the present submission. This approach promotes a fundamental re-appraisal of risk assessment and management approaches to vitamins and minerals, and related substances.

- 11.7 In essence, there is a need to address risk assessment at the **nutrient form, rather than nutrient group level**, and develop a range of **qualitative, semi-quantitative and quantitative tools** that enable **rational priority setting** and subsequent risk assessment. As with risk assessments in other areas, it is necessary to determine the **probability** as well as **severity** of potential risks, these data being of direct relevance to risk management.
- 11.8 Risk assessment needs to be conducted using the **totality of available, relevant evidence**, including sources of evidence from interventions with humans which have been derived from the **practice of clinical nutrition**. Such evidence is of much greater relevance than extrapolations from animal studies, approximated by application of uncertainty factors, or data from weak or only marginally relevant human studies. A **major inherent weakness of typical controlled, intervention studies** is that they fail to assess in to any substantial degree (if at all) complex interactions between nutrients, as they occur in foods or in more 'advanced' supplements.
- 11.9 Interestingly, **clinical nutrition data**, present in the medical records of hundreds of doctors and practitioners in a number of countries (e.g. USA, Canada, UK, the Netherlands, Sweden, Denmark, Germany, Australia, South Africa, etc.) would 'fit' the criteria for use in existing risk assessment if they were collated and published in peer-reviewed journals. The difficulty is that most of these data are not published and therefore are ignored. Thus far, there have been very few organisations prepared to fund such **collation and publication of clinical data** – does it mean that these invaluable empirical data sets are less valuable because they are largely unpublished? If very substantial resources are to be expended on the risk assessment and management of nutrients, **should governments not prioritise such funding?** Clearly, views on the value and usage of data from various sources can change quite dramatically depending on whether a so-called 'evidence-based' approach (utilising data only from peer-reviewed studies with an emphasis on clinical trials) or a scientifically rational approach, as advocated here, is adopted.
- 11.10 In developing **global standards**, it is essential that a 'one-size fits all' approach is not adopted on the basis of studies largely on populations in the western world. There are immense differences in both macro- and micro-nutrition in different parts of the world. Just as recent trends among 'industrialised populations' are showing dramatic health impacts caused by fast and convenience foods, high-yielding variety staples in developing countries appear to be giving rise to different effects, some caused by their poor absorption of nutrients compared with older, lower-yielding varieties.⁸⁸
- 11.11 Risk assessment is capable of producing **a range of risk thresholds to trigger different and proportionate responses of risk management**. Restricting availability of nutrients and dosages appears to be the key proposed strategy of the European Commission, but this response is likely to be disproportionate in many cases. The use of voluntary or compulsory **warning labels (depending on risk assessment for a given nutrient), improved labelling and use of child-proof containers** (e.g. for certain forms of iron supplement), are among the range of risk management options that may be used.
- 11.12 Given the **rapid expansion and changing nature of research and information** in the field of nutritional research, very substantial **information gaps**, and the **unprecedented transition in global health on epidemiological, nutritional and demographic fronts**,⁸⁹ it is of paramount importance that the results of risk assessment, and their consequent translation in to policy, are **reviewed on a regular basis**.

- 11.13 Finally, given the critical relationship between nutrients and human health and evolution, **any rational risk management approach cannot be solely reliant on Upper Levels and estimates of existing dietary intakes.** This is particularly the case given that **average dietary intakes of micronutrients appear to be inadequate and appear to be strongly related to the recent cataclysmic rise of degenerative diseases such as cancer, cardiovascular disease, osteoporosis, diabetes and obesity, all of which have roots in inappropriate macro- and micro-nutrition and are targets in the WHO's Global Strategy.**⁹⁰ Risk management should, therefore, also include assessment of nutrient **benefits**, as well as the **costs (health, economic, social, etc.) of limiting dosages and forms to different population groups.**
- 11.14 **The recent emergence of high quality nutrition and food supplementation as a strategy in healthcare, being increasingly adopted as the primary healthcare strategy by millions of people around the world, may be a genuine evolutionary adaptation to depleting micronutrients in the food supply. As such, any attempt to limit consumer access to nutrients must be considered with great care and only after detailed consideration of all data, risks and benefits.**

ACKNOWLEDGMENT

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R. Verkerk