

**ALLIANCE FOR NATURAL HEALTH INTERNATIONAL
SUBMISSION TO EFSA CONSULTATION:**

Public consultation on Guidance on human health risk benefit assessment of foods

The discussion document on which comments are sought can be found at the following link:

<http://www.efsa.europa.eu/en/consultations/call/sc100226.htm>

The following comments for each relevant subsection of the EFSA guidance document were made by the Alliance for Natural Health International and submitted electronically on the EFSA website on 15th April 2010.

Terms of reference as provided by EFSA

Line 162: The term "risk benefit assessment" should be expressed either as "risk/benefit assessment" or as "risk-benefit assessment". This change should be made throughout the document.

Line 169: Instead of "Consideration of methods and approaches needed to assess the risks and benefits...", we suggest instead: "Evaluation and validation of methods and approaches appropriate to the assessment of the risks and benefits...". This helps to focus the work more, and allows for comparing and contrasting methods when utilised with real data, rather than simply their "consideration".

Risk benefit assessment - Definition

Line 262: the word "generalised" should be inserted before the word "approach, as it is only the general approach of using the 3-step approach that is similar. Other aspects of the approach cannot therefore be mirrored as the Codex or FAO/WHO nutrient risk assessment project do not take benefits into account.

Proposed approach for risk benefit assessment 296

Examples of situations for which a risk benefit assessment might be appropriate

Line 304-327: Given that these examples allude to policy decisions such as folic acid fortification and fluoridation, there should also be reference to policies which would restrict amounts of nutrients that are based on risk. Therefore we propose the addition of an additional example, as follows:

- Where statutory limitation of nutrients based on risk (and not benefit) has occurred or is contemplated.

Step 1 – Initial assessment

We have serious concerns about this approach. First, it presupposes that risks and benefits can be directly compared, implying that the comparisons are based on the same currencies. There are very great subjective elements in any such assessment. An example is nicotinic acid: how would the assessor compare a flushing reaction against that might occur at just 100 mg intake, with the benefits associated with blood cholesterol management at daily dosages 10 times this amount.

See: Verkerk, R.H.J., The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. *Toxicology* (2010), doi:10.1016/j.tox.2010.02.011 for a much more in depth discussion of this example, along with three others.

We propose that the most appropriate forward is to evaluate the full pattern of risks and benefits that are associated with different dosages of intake that reflect known use-patterns. This allows the data to be collated centrally and to be referenced at any later stage during the process. The notion of discarding the approach if there is “no appreciable health risk (based on scenario 1) or no appreciable health benefit 30 (based on scenario 2)” is also problematic, given there are many possible interpretations over what is “appreciable”.

We support the continuation of the risk-benefit assessment and the use of modelling approaches for this. However, the modelling approaches are not defined and therefore of little value.

2.4. Metrics used in risk benefit assessment

When developing any metric for a food or food ingredient, it is essential that the food or food ingredient is accurately characterised. For example, the risks and benefits of canned versus fresh tomatoes or fish are quite different, as those for raw vs deep fried fish. This same situation applies for food ingredients, where the ingredient and its specific molecular form are critically important to the evaluation of both risks and benefits. For example, the risks and benefits of synthetic folic acid commonly used in supplements and fortified foods, as compared with polyglutamate folates as found in green-leaved vegetables or in botanical extracts in food supplements, are quite different. The same can be said for the majority of other nutrients. Accordingly, we propose that this the guidance should be much more specific in terms of the characterisation of the food or food ingredient and it should at least make reference to the molecular form of the latter.

The significance of this issue is explained further by our group in the following two papers:

Verkerk, R.H.J., Hickey, S., A critique of prevailing approaches to nutrient risk analysis pertaining to food supplements with specific reference to the European Union. *Toxicology* (2010), doi:10.1016/j.tox.2009.12.017

Verkerk, R.H.J., The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. *Toxicology* (2010), doi:10.1016/j.tox.2010.02.011

The issue of the problems over finding suitable metrics is reasonably handled in this section — and the statement that further work is recommended (lines 93-94) is of utmost importance. It should be realized that for many nutrients (food ingredients) it will generally not be possible to utilize QALYs and DALYs. In fact, most metrics of interest will not in any way involve mortality (e.g. risks will not include mortality rates, and benefits will not include lifespan). These data will simply not be able to be generated in any reasonable time for the vast majority of nutrients. However, where the data are available, such as from national poisons databases, these should be used (e.g. National Poison Data System in the USA, and/or equivalents elsewhere).

However, there are ways in which semi-quantitative weightings of risks and benefits could be fairly simply developed and agreed for comparative purposes. It is recognized that such weighting involves considerable subjective decision-making, but assuming adequate expertise in such decision-making, using not only peer reviewed literature but also clinical experience (particular from the field of nutrition) this is not necessarily a major problem. It is critical that such evaluations are undertaken taking into account dose responses.

Adverse effects for particular levels of exposure/intake can be classified and negatively weighted according to specific sub-populations as follows:

- Onset: acute, chronic or delayed (including metagenicity, carcinogenicity, teratogenicity)
- Severity: mild, moderate or severe
- Reversibility: reversible in short-term, medium-term, long-term, or not reversible
- Nature of effect: organ or body part affected, symptomatology, etc.

Benefits can be similarly classified, and positively weighted, using a numeric weighting scale. For example:

- Locality of benefit: local, general
- Nature of benefit: minor, moderate or major health benefit (including disease risk reduction potential)

The sum of the weightings for specific levels of exposure/intake provides some general guidance over the interplay of various risks and benefits.

Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment

Lines 137-138: The statement: “the obvious benefit endpoint will be the absence of risk for nutrient deficiency” is incorrect. A benefit cannot be simply an absence of risk. An absence of risk simply nullifies risk and does not establish benefit. However, at a particular level of exposure, risk of inadequacy might be nullified and in addition, further benefits may be encountered. For example, taking 18 mg of niacin daily is likely to eliminate any risk of inadequacy (pellagra). However, benefits may occur in a diverse range of body systems (e.g. eye health, blood cholesterol management) with intakes in excess of 100 mg. However, at this exposure/intake level, some individuals might experience skin flushing, which is generally seen as a minor, reversible complaint which disappears or declines with habitual use of higher dosages of niacin.

This is considered in further details in:

Verkerk, R.H.J., The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. *Toxicology* (2010), doi:10.1016/j.tox.2010.02.011

3.1.1. Types of data

Human intervention studies are generally few and far between for foods given many have been presumed safe and beneficial through their historic use. Most intervention studies with foods and in particular food ingredients have been undertaken with diseased populations and these studies are not necessarily directly relevant to healthy populations.

Given this paucity of data, it is of great importance that all available data sources are utilised. This issue was considered at EFSA Colloquium 6 and it was recommended that medical records be included as possible data source. There is a wealth of data from dietitians, clinical nutritionists and other health professionals that pertains to the relationship between foods and nutrients and physiological responses. This should be utilised.

5.1. Risk benefit assessment of an indispensable nutrient: Selenium

The example mentions different forms of selenium present in natural foods (e.g. selenocysteine), but fails to discuss the implications of different molecular forms on risk or benefit.

Other benefits such as the effects of selenium on immuno-competence and male fertility have been ignored. They should be factored in to the example.

It would be useful to have a further example included, perhaps the example of folate being of particular relevance.

For further information see:

Verkerk, R.H.J., The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. *Toxicology* (2010), doi:10.1016/j.tox.2010.02.011