CRN
COUNCIL for RESPONSIBLE NUTRITION

29th September 2006

CRN response to the European Commission on the setting of maximum and minimum levels of vitamins and minerals in foodstuffs

1. **Where there is not yet a scientifically established numerical tolerable upper intake levels for several nutrients, what should be the upper safe levels for those nutrients that should be taken into account in setting their maximum levels?**

Response
Each nutrient must be taken on a case-by-case basis and be the subject of scientific risk assessment as required by Directive 2002/46/EC and the proposed Regulation on the addition of vitamins, minerals and certain other substances to foods.

In certain cases, the safety assessment of vitamins and minerals by the SCF/EFSA resulted in no tolerable upper levels for total dietary intake being set. For many nutrients such as vitamins B_1, B_2, B_{12}, biotin, pantothenic acid, vitamin K and trivalent chromium, there was no evidence of risk of adverse effects and these nutrients do not represent a risk to human health for normal healthy people. For some nutrients, such as vitamin C and manganese, there were insufficient data to set a UL, but in these cases there is evidence of potential risk at excessive intakes.

In circumstances where no ULs have been set, evidence from other international risk assessments should be considered including the UK Food Standards Agency Expert Group on Vitamins and Minerals (EVM) risk assessment.

For upper levels in food supplements, in 2003 the UK Food Standards Agency EVM set safe upper levels (SULs), where supported by adequate data, and Guidance Levels (GLs) were given on safe levels of intake when the establishment of an SUL was not possible. Guidance Levels represent an approximate indication of levels that would not be expected to cause adverse effects, but were derived from limited data and are less secure than SULs. Nevertheless, SULs and GLs are the amounts of vitamins and minerals that susceptible individuals could take daily on a lifelong basis without medical supervision.

The CRN supports the EVM statement that the SULs and GLs have been derived so that consumers can have confidence that harm should not ensue from daily supplemental intake of the nutrient up to that level. The CRN also supports the findings of the EVM report which is the only international scientific risk assessment that specifically focuses on the SULs and GLs for all the vitamins and minerals permitted for use in food supplements.

67 Upshire Road, Waltham Abbey EN9 3NZ, UK

Tel: +44 20 8807 4247

The inclusion, endorsement and critical analysis of the UK's EVM report in the World Health Organisation review adds further credibility to the approaches taken by the EVM risk assessors.[1]

It should also be noted that the international food supplements industry has been working with the concept of upper safe levels for nearly 20 years, and the European Federation of Associations of Health Product Manufacturers (EHPM) and, in 1997, the Council for Responsible Nutrition (CRN) in the UK, established safe upper levels for 25 vitamins and minerals (Shrimpton, 1997). These EHPM/CRN levels for food supplements have been used safely and effectively for nearly 2 decades and industry current practice follows these guidelines.

The values produced by the international risk assessments are consistent with the industry guidelines and current practice.

Two recently published reports from FAO/WHO and IADSA propose methods of qualitative risk assessments that can contribute to an understanding of current usage without reported adverse effects.

The FAO/WHO report recommends an approach based on the **H**ighest **O**bserved **I**ntake (HOI) where there is no recognised adverse effect. IADSA has developed a similar approach that uses the term **O**bserved **S**afe **L**evel (OSL).

The criteria for obtaining an HOI/OSL are:

- No adverse health effects have been established.
- One or more satisfactory studies on humans are available.
- The highest intake reliably observed that has no recognised adverse effect is taken as the HOI/OSL.
- Supporting evidence can also be derived from animal studies if reliable data are available.

For all cases, a review mechanism should be put in place to re-evaluate any maximum level in the light of new evidence.

2. For some vitamins and minerals the risk of adverse effects, even at high levels of intakes, appears to be extremely low or non-existent according to available data. Is there any reason to set maximum levels for these vitamins and minerals?

Response

The answer is no. For some nutrients, there is no evidence of risk or observations of adverse effects at current cumulative intakes from food, food with added nutrients (fortified food) and food

[1] 'A model for establishing Upper Levels of intake for nutrients and related substances' Internet issues 13th January 2006 and hard copy from 30th June 2006. Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment, Geneva 2nd to 6th May 2006.

supplement consumption. These nutrients do not represent a risk to human health, and in the absence of any evidence to set a SUL, there may be no scientific rationale for setting a maximum level for food fortification or for food supplements. This approach could apply to vitamins B_1, B_2, B_{12}, biotin, pantothenic acid, vitamin K and trivalent chromium.

Whilst in theory there should be no reason to set maximum levels for some nutrients, such as those mentioned above, in practice the consumer may feel more comfortable if all micronutrients were assigned an upper level. In this context it should be noted that the EVM set either upper safe levels or guidance levels for all assessed vitamins and minerals. Furthermore, the HOI/OSL procedures described under question 1 could provide an approach, should the risk manager decide that setting maximum levels would be appropriate. The levels should reflect current practice and industry guidelines of safe practice.

3. **Where we set maximum levels, do we inevitably also have to set maximum amounts for vitamins and minerals separately for food supplements and fortified foods in order to safeguard both a high level of public health protection and the legitimate expectations of the various food business operators? Are there alternatives?**

Response

The answer is no. The ULs set by the SCF/EFSA represent total amounts of vitamins and minerals from conventional foods, fortified foods and food supplements that can be ingested safely over a lifetime. The setting of maximum levels should be considered on a case-by-case basis, and the development of maximum levels based on arbitrary proportions that are split between fortified foods and food supplements is unscientific and is not consistent with internationally accepted risk analysis procedures.

The UK EVM risk assessments and exposure assessments were based on food and food supplement consumption and nutrient intakes from the UK NDNS. The EVM included the mean and high levels (97.5 percentile estimates) of intake from food and fortified food for each nutrient for adults, and the risk assessors separately derived SULs and GLs for food supplements on a case-by-case basis. The SULs and GLs are the amount of vitamins and minerals in food supplements that could be taken daily by healthy adults and susceptible individuals over a lifetime. The EVM states that the levels in food supplements had been derived so that consumers could have confidence that harm should not ensue from daily intake up to that level. The SULs and GLs already build in significant safety margins with the use of uncertainty factors.

A key point of the EVM approach is that each assessment included total intake from food and, where appropriate, water. Thus, the SULs or GLs derived for supplements already take into consideration usage in fortified foods.

In addition, for many nutrients, particularly minerals used in food fortification the levels used are self-limiting for technical and organoleptical reasons.

A more scientific approach would be to 'categorise' the nutrients on a case-by-case basis. Taking appropriate measures for each of the groups seems a logical and practical method for risk management. The EHPM/ERNA model could be developed and refined to test the sensitivity and specificity for different scenarios and input variables.

The EHPM/ERNA categorisation is:

Group A No evidence of risk within ranges currently consumed; does not represent a risk to human health

Group B Low risk of exceeding the UL (from all sources)

Group C Potential risk of exceeding the UL.

On this basis only Group C which comprises relatively few nutrients may possibly need consideration of upper levels for both supplements and fortified foods.

It should also be borne in mind that the major trade associations of the UK food supplement industry have been operating with guidelines on safe upper levels for supplements for nearly 20 years. These guidelines have been consistent with the levels derived by the EVM.

In contrast, the other models included in the Annex to the consultation have significant limitations. For example, the ILSI model does not consider food supplement use and focuses only on food fortification, and the AFSSA model is based on arbitrary multiples of RDA rather than scientific risk assessment.

Evidence exists to show that vitamin and mineral intakes from foods and fortified foods grow in one Member State where fortification is freely practiced at about 1% per annum for vitamins and 0.7% for minerals[i].
Evidence also exists[ii] that fortification accounts for only 3% of an individual`s intake in Europe generally and only 10% in the case of extreme intakes, and is generally carried out at no more than 50% of an RDA per daily serving, often for organoleptic and nutritional rationale reasons .
It should be noted that if vitamin and mineral intakes from foods and fortified foods increase by 10% at mean intake level, this is unlikely to increase 97.5th percentile intake figures by as much as 10%, as the 10% growth is likely to be via new users rather than existing users.

i UK National Diet and Nutrition Surveys 1986/7 and 2001 comparisons
iiD.Godfrey, D.Tennant, and J.Davidson The Impact of fortified foods on total dietary consumption in Europe. Nutrition Bulletin 29 188-198

4. **The Commission would appreciate receiving available information on intakes of vitamins and minerals or indications of the best sources providing such data at EU level.**

Response
The UK also has some of the most comprehensive and detailed intake data from its NDNS covering the whole population from age 18 months upwards. The intake data include the 97.5 percentile intakes and also those significant proportions of the population that fail to achieve the Reference Nutrient Intake and the Lower RNI.

At the European level, the SENECA and other surveys can provide additional intake data. Sources of intake data include:
Gezondheidsraad Enkele belangrijke ontwikkelingen in de voedselconsumptie (2002), Turrini A, Saba A, Perrone D, Cialfa E & D'Amiels A (2001) Food consumption patterns in Italy.

The Irish Universities Nutrition Alliance (IUNA), the North-South Ireland Food Consumption Survey 2001, is a valuable reference point and should be considered.

5. **If such existing data refer only to the intake in some Member States, can they be used for the setting of legitimate and effective maximum levels of vitamins and minerals at European level? On the basis of what adjustments, if any?**

Response
The answer is yes. The use of the comprehensive intake from the UK NDNS and the Irish IUNA would be of use in the European context because the data reflects relatively liberal markets in terms of micronutrient usage. The EHPM/ERNA model, which is included in the Annex of the EU Discussion Paper, is based largely on UK data and changing patterns of consumption of foods and food supplements over time.

The EHPM/ERNA model also used the UK NDNS data for the development of intake models and future scenarios of intake from fortified foods.

6. **Should the intake from different population groups be taken into account in the setting of maximum levels of vitamins and minerals?**

Response
Yes, it could be appropriate to have maximum levels set for two groups—adults including young adults, and children between 4 and 10 years of age.

The risk assessment process already recognises that there may be sensitive groups, e.g. children, certain adult individuals, the elderly, women during pregnancy or lactation. There can be a range of sensitivities to adverse effects that are influenced by such things as body weight and lean body mass.

The derivation of SULs for the essential nutrients is based on the principle that the most sensitive members of the general population must be protected from the adverse effects of high nutrient intakes. Some highly sensitive subpopulations can have responses (in terms of incidence, severity or both) to the substance of interest, and these responses may differ at different life stages and physiological states.

The extent to which SULs for a subpopulation are considered separately from the general population is an area of scientific judgement, and the nutrients are usually assessed on a case-by-case basis.

The only logical sub-population that could be considered is that of children aged between 4 years and 10 years. However, data across the EU are too sparse to be definitive at the present time, and it may be more prudent to defer a decision until more conclusive data become available.

Whilst infants and young children are defined in EU food law there is no equivalent definition for a child of 4 years and upwards and member states have variable upper age limits. It is suggested that the range for a child, other than a young child, should be 4 to 10 years.

7. **Taking into account all the above-mentioned considerations, how far should PRIs/RDAs be taken into account when setting maximum levels for vitamins and minerals?**

Response

The setting of maximum levels should be based on scientific risk assessment. The use of arbitrary multiples or fractions of RDAs/PRIs to set ULs is no longer acceptable from the scientific risk assessment point of view or as an objective approach to risk management.

However, RDAs can be used as an indicator to help establish the extent of the range of safe intake and could form an approach to help categorise the relative safety of each nutrient. If the UL and RDA are close together, the safe range of intake is relatively small, whereas if the UL and RDA are further apart, the safe range of intake is relatively large. The approach to use the RDA as an 'indicator' was included in the EHPM/ERNA model to develop a Population Safety Index (PSI).

8. **Should the minimum amount of a vitamin or a mineral in a food to which these nutrients are added be the same as the significant amount required to be present for a claim and/or declaration of the nutrient in nutrition labelling?**

Response
For claims for nutrients in conventional and fortified foods, there is a need for consistency across several legislative instruments, namely the Nutrition Labelling Directive (under review), the addition of vitamins and minerals and certain other substances in food, and the legislation on nutrition and health claims made on foods. Claims on fortified foods tend to reflect the criteria for 'source of' and 'high in' the specified nutrient. It seems appropriate to maintain consistency for the 15% RDA per specified recommended daily intake for supplements as the basis for a 'significant amount' and the minimum to make a claim on a food.

Allowance should be made for the combined use of vitamin A (as retinol) and beta carotene where the total of the two has normally to be declared as µg RE. In such a case the total should be a minimum of 15%. It is also important that the minimum level relates to the total content in the food. For example a supplement containing wheat germ oil will contain a natural source of vitamin E in addition to any added amounts.

9. **Should different minimum amounts be set for certain nutrients in specific foods or categories of foods? If yes, on what basis? Should minimum amounts for vitamins and minerals in food supplements also be linked to the significant amounts that should be present for labelling purposes or should they be set in a different way?**

At present there are no legal minima for micronutrients in food supplements as the Nutrition Labelling Directive 90/496/EEC exempts food supplements. It is believed that there is a need for minimum amounts both for nutritional purposes and to prevent misleading products being placed on the market.

For vitamins and minerals the most logical route would be to set the minima at the proportion of the RDA (RLV) required for a claim of a 'source' of a vitamin and mineral as specified in the proposed Regulation on Nutrition and Health Claims for Foods (but related to recommended daily intake of the supplement instead of a weight or volume of product).

Brief commentary on the Annex: examples of models

1. The French Agency of Food Safety (AFSSA)

In this model for food supplements, for those nutrients for which a risk of exceeding the safety limit exists (vitamin C, magnesium, vitamin D, B9, calcium, iron and iodine), the maximum content was limited to 1 RDA; for those where the risk is low (B_1, B_2, B_3, B_8, B_{12}) the maximum content was limited to 3 x RDA. Clearly, these levels are not based on scientific risk assessments. However, a categorisation approach was used that was based on risks of deficiencies or inadequacy of intakes.

2. Danish Institute of Food and Veterinary Research

This model focuses on a safe strategy for the addition of vitamins and minerals to foods and develops an Acceptable Level of Addition (ALA) for each nutrient per energy portion of the food. The 'space' for food fortification is derived from the equation **MA = UL – (CI_{95} + SI)**, where MA is the maximal allowance for intake from fortified food; UL is the upper safe level established by SCF. CI_{95} is the current 95 percentile dietary intake from a regular diet; SI is the supplemental intake based on a combined multivitamin-mineral tablet (levels not stated in consultation document). Although the model includes fortified foods and food supplements, the contribution from supplements is relatively low.

3. BfR German derivation of maximum levels of vitamins and minerals added to foods based on risk assessment (Grossklaus *et al.*)

This model categorises nutrients both according to risk of adverse effects: 'high' (vitamins A, D, copper, iron and zinc), 'moderate' (vitamins E, K, C, B_6, magnesium and molybdenum, and 'low' (vitamins B_1, B_2, B_{12}, chromium), and to risk of deficiency: (1) highest—folate, iodide, vitamin D; (2) vitamin K, biotin, fluoride, zinc and selenium; (3) vitamins B_1 and B_2, copper; (4) vitamins B_6, B_{12}, sodium, chloride and phosphorus. Several equations are presented:

R = UL –DINF, where R = amount available for addition to supplements (R_S) and fortified foods (R_F), and DINF is the current estimated 95 percentile or 97 percentile intakes of a micronutrient from non-fortified foods (i.e. Dietary Intake from Non-Fortified foods).

When **$R = R_S + R_F$,**

Maximum Level for Supplements, ML_S, = $\underline{R_S}$ MEF

and

Maximum level for Fortified Foods, $ML_F = \underline{R_F}$ MEF

Where **MEF** is a **m**ulti-**e**xposure **f**actor depending on the number of portions consumed.
The model has several limitations, not least that the setting of MEFs is fairly arbitrary. Moreover, the model is stated **not** to be suitable for several key nutrients! These include vitamin A, beta-carotene, vitamins B_1, B_2, B_{12}, C and K, sodium, chloride, phosphorus, biotin, pantothenic acid, nicotinamide, iron, fluoride, selenium, molybdenum, manganese and chromium.

The maximum levels are not stated and the methodology is complex and arbitrary.

4. ILSI Europe. Vitamins and minerals: a model for safe addition to foods (Flynn *et al.* 2003)

This model bases the nutrient contribution on the energy contributions from 100 kcal servings of foods. The model does not take into account contributions from food supplements and hence has major limitations. However, the model provides a useful categorisation of micronutrients into three groups: (1) least risk (vitamins B_2, B_{12}, C and E, pantothenic acid, niacin and thiamin); (2) medium risk (vitamins B_6, D, folic acid, biotin, copper, iodine and selenium, and (3) higher risk (iron, zinc, calcium, phosphorus and magnesium. A special fourth category is made for preformed retinol (vitamin A).

5. EHPM/ERNA Risk Management Model

The EHPM/ERNA discussion Paper sets out a methodology for characterising the safety of vitamins and minerals both quantitatively when there is a UL and qualitatively for nutrients without a UL. The result is a categorisation of the nutrients into three groups according to risk.

The three groups are: -

A. No evidence of risk within ranges currently consumed; do not represent a risk to human health. Vitamins B_1, B_2, biotin, B_{12}, pantothenic acid, vitamin K, trivalent chromium.

B Low risk of exceeding the UL. Vitamins B_6, C, D, E, folic acid, nicotinamide, P, Mg, Mo, Se

C Potential risk at excessive intakes. Vitamins A (preformed retinol), beta-carotene, Ca, Cu, F, I, Fe, Mn, Zn

The Paper develops a new index of safety called the 'Population Safety Index (PSI), which is calculated as follows:

$$PSI = \frac{UL - (MHI + IW)}{RLV}$$

Where the UL is set by the EU SCF (or US FNB where an SCF value was not available); MHI is the 97.5 percentile average intake of an adult male (the population group generally considered to have the highest nutrient intake from food); IW represents intake from water, where appropriate; RLV is the new 'RDA' set out by the SCF in 2003 as an indicator of the lower end of the range of safe intake.

The method also embraces potential changes to dietary patterns by comparing changes already evident from the UK NDNS between 1986/7 and 2000/2001. The EHPM/ERNA model estimated a 50% increase in intake of vitamins and an increase of 10% for minerals from conventional foods and fortified foods.

The rationale for the selection of the 50% increase in vitamins and the 10% for minerals is given in the discussion paper. In essence, this was based on changes in micronutrient intake between the 1986/87 UK Adult Survey and the 2000/01 NDNS survey. To quote from the paper 'Although only in the cases of two vitamins, namely C and B_6 did the intake increase by more than 20%, to take into account potential changes in dietary patterns the risk manager may be justified in introducing a precautionary risk management factor of 150% increase in dietary intake (from foods and fortified foods). In contrast, the experience in the UK showed that for many mineral elements (e.g. magnesium (–4%), copper (–9%), zinc (–6%) and iodine (–9%)), mean intakes had declined over a 15-year period, and only phosphorus (+3%), potassium (5%) and calcium (+8%) had increased. Only the intake of calcium increased beyond 5%. Given that, for technical and taste reasons, mineral fortification is self-limiting, a precautionary risk management factor of 110% was set for future additional fortification of minerals.

The Maximum Supplement Level (MSL) was determined as follows for the Group B nutrients

For vitamins MSL = UL – (MHI x 150%)

For minerals MSL = UL – (MHI x 110%)

Group C nutrients were considered on a case-by-case assessment taking into account risk of excess and risk of deficiency of the nutrient concerned. Preformed retinol was identified as a special case that would need further detailed examination.

The EHPM/ERNA model has merit but needs to be further refined with more intake data from different population groups and a more detailed process for identifying and supporting Group C. However, the model does take into account fortified foods and makes provision for possible future situations. The model focuses on adult males, but the principles could be applied to, and tested on, any population group, including children.

Finally, CRN agrees with the following statements in the EU Discussion Paper.

- Paragraphs 13 and 14 highlights the fact that it is increasingly difficult to develop accurate assessments of the patterns of overall diets and the contribution from conventional foods, fortified foods and food supplements, since these vary across the regions of the EU, between population groups and over time. Hence, more research is needed

- Paragraph 14 identifies that changing culinary and social habits may lead to low intakes for some nutrients and that with the popularity of fortified foods and food supplements, there is a need to ensure that the potential cumulative effect should not threaten to undermine the high level of human health, which is the main policy objective. Consumer protection is of paramount importance.
- Paragraph 14, however, reiterates the point that optimal health may depend on higher levels of nutrients than those recommended today on the basis of avoiding deficiencies, particularly of trace elements.
- Paragraph 15 states that the application of divergent maximum permitted levels of nutrients causes serious problems to the free circulation of products in the European market.
- Paragraphs 17 and 18 state that the upper safe levels should take into account the upper safe levels set by scientific risk assessment, intakes of nutrients from all dietary sources and their reference intakes for the population.
- Paragraphs 21 and 22 state that the basic food law principles are for the laws to be proportionate to ensure a high level of protection of public health and to avoid undue constraints for businesses and over-regulation.
- Paragraph 27 states that the setting of maximum levels in food supplements and fortified food is inevitably interrelated and hence, they have to be considered together.

[i] UK National Diet and Nutrition Surveys 1986/7 and 2001 comparisons

[ii] D.Godfrey, D.Tennant, and J.Davidson The Impact of fortified foods on total dietary consumption in Europe. Nutrition Bulletin 29 188-198