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ANH POSITION PAPER

PROPOSED EUROPEAN MODEL FOR MPLs NOT FIT FOR PURPOSE

19 October 2007

EXECUTIVE SUMMARY

The European Commission (EC) is in the process of finalising approaches that allow the determination of Maximum Permitted Levels (MPLs) of vitamins and minerals for both food supplements and fortified foods. Although the EC has undertaken a public and stakeholder consultation, it appears that a significant number of flaws and inconsistencies are at risk of being built into the modelling process. The likelihood is that the proposed methodology will yield levels that cannot be matched against what is already known about nutrients and their interaction with humans.

This Position Paper clearly focuses on the weaknesses of the methodologies under consideration, explains why they are not fit for purpose, and provides commentary on the EC's Orientation Paper, dated July 2007.

The Paper goes on to demonstrate why existing risk management models under consideration need to be altered as they yield outputs that are both scientifically flawed and not biologically meaningful when validated against the results of food analyses and clinical data. The paper provides examples which show that determinations of MPLs, and even Upper Levels (ULs) from which they are derived, may be so low that they can easily be exceeded through the consumption of very small amounts of conventional foods. For example, the amount of beta-carotene in two cooked carrots would likely exceed the UL for beta-carotene, whilst just two brazil nuts would probably provide sufficient selenium to exceed both the UL as well as the MPL.

Most of the recent focus on methodologies for determining MPLs has been on the process which moderates the UL, but this Paper explains succinctly why even the starting point of MPL determinations, the UL, is seriously flawed scientifically. It is the use of multiple and additive safety and uncertainty factors that further compounds the unwarranted reduction of dosages. The resultant MPLs, should these be implemented in law, would curtail consumer choice to such an extent that many would be prevented from ingesting levels of vitamins and minerals required for optimal health.

This Position Paper includes a consideration of features that would be required for the development of a new, scientifically valid and proportionate risk management model. It is concluded that such a model would likely be best developed within an independent, academic setting rather than being subject to the often conflicting pressures of industrial stakeholders and political processes. The paper calls for a reconsideration by the EC of its approach to the determination of MPLs, which would otherwise be disproportionate in its effect and may in turn be subject to legal challenge.

Alliance for Natural Health
The Atrium, Curtis Road, Dorking, Surrey RH4 1XA, UK
e-mail: info@anhcampaign.org tel: +44 (0)1306 646600
www.anhcampaign.org

Background

In June 2006, the European Commission released a Discussion Paper for its consultation on the setting of maximum and minimum amounts of vitamins and minerals in foodstuffs. [1] Responses were provided by 13 Member States (two from Germany) and 34 stakeholders, including the Alliance for Natural Health (ANH).[1] In January 2007, Commissioner Kyprianou issued a short collective answer[1] to the consultation which stressed the fact that the Directorate General Health and Consumer Protection's intention is to ensure that the Food Supplements Directive (FSD) (Directive 2002/46/EC) ensures supplements are both safe to consumers, yet still offer wide consumer choice. Importantly, and, in some circles, controversially, the Commissioner also stressed that food supplements are not intended to have therapeutic effects.

In July 2007, the European Commission issued an Orientation Paper to selected parties[1], and its decision to not publicise this paper on its website has been criticised as it suggests a lack of openness and transparency.

Existing legal basis

The legal basis for the criteria required to establish maximum levels in food supplements is set out in Article 5 of the FSD, 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.
>
> When the maximum levels referred to in paragraph 1 are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

Similar criteria have been set for foods.

Although the criteria are clearly stipulated, the precise manner by which the criteria are to be used in the determination of maximum levels is not set in law.

There is a common tendency to assume that the Article 5 expression, "taking….into account" with reference to the criteria, means subtracting dietary intakes from upper safe levels to give the maximum permitted level (MPL). However, clearly, this widely accepted algorithm is not legally established.

Additionally, determinations of upper safe levels are often imprecise and overly cautious for particular nutrient forms, given there are flaws and inconsistencies in the underlying models used for determinations.

Flawed risk assessment models

The deficiencies of risk assessment models used for determinations of ULs (ULs) by authoritative bodies such as the EU Scientific Committee on Food (SCF) (subsumed by the European Food Safety Authority, which was in turn established in 2002) and the UK Expert Group on Vitamins and Minerals (EVM) have been communicated to the UK Food Standards Agency by the ANH as early as 2002.[1] Further consultation responses by the ANH to both the WHO/FAO[2] and the European Commission[3] further detailed the flaws and inconsistencies in proposed or utilised models.

Furthermore, these inconsistencies and flaws, as well as the misapplication of the precautionary principle, have also been extensively evaluated in the peer reviewed literature by Hanekamp & Bast.[4,5]

Some of the key limitations of common risk assessment determinations, as performed by the SCF, EVM and the US Institute of Medicine (IOM) are:

1. ***Selective (and therefore incomplete) use of relevant published scientific findings***, and lack of consideration of other relevant scientific or medical data, such as clinical data derived from years of practice of clinical nutrition. The avoidance of particular relevant studies and lack of inclusion of recent studies is a major reason for the low ULs for vitamins beta-carotene, B6, C and D and others[5].

2. ***Upper Levels are generally determined in the absence of adequate dose-response data*** (in humans), meaning ULs are based around No Observable Adverse Effect Levels which may be much lower than those which might first trigger adverse events, even in sensitive people.

3. ***Upper Levels are based on the most toxic form of a given nutrient group***. For example, the UL for iron is based on iron sulphate (used medically to treat anaemia) which causes gastrointestinal upset and is then applied to all iron forms including ferrous bisglycinate which has no side effects at considerably higher dose ranges. Another example which well illustrates the problem is that of vitamin D. The vitamin D UL of 25 mcg used in the EU (set by the SCF) is determined using older studies, on the basis of potential side effects of vitamin D2 [ergocalciferol], which is not produced in the body or consumed in foods, except yeasts, as well as by consideration of the very small proportion of people who have renal insufficiency or vitamin D hypersensitivity syndromes e.g. primary

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[1] Consultation response by the ANH to the Draft Report of the Expert Group on Vitamins and Minerals
(2002):
http://www.alliance-natural-health.org/_docs/ANHwebsiteDoc_11.pdf

[2] Consultation response by the ANH to the WHO/FAO nutrient risk assessment project (2004):
http://www.who.int/ipcs/highlights/alliancefornatlhealth.pdf

[3] Consultation response by the ANH to the European Commission's consultation (2006):
http://ec.europa.eu/food/food/labellingnutrition/supplements/documents/anh_en.pdf

[4] Hanekamp JC, Bast A. Food supplements and fortified foods: the EC's patriarchal precautionary perspectives on public health. *Env. Liability* 2006; 5: 181-191.

[5] Hanekamp JC, Bast A. Food supplements and European regulation within a precautionary context: a critique and implications for nutritional, toxicological and regulatory consistency. *Crit Rev Food Sci Nutr*. 2007; 47(3): 267-85.

hyperparathyroidism, granulomatus disease. This level is then applied to vitamin D3, which is both produced in the body following exposure to sunlight and consumed in foods such as oily fish. The 25 mcg level equates to around a quarter of the amount of vitamin D3 found in a healthy person, and one-tenth of the amount made in the body following around 30 minutes of full sunlight exposure. Using a more appropriate approach to the methodology of risk assessment in relation to vitamin D, as well as consideration of recent human trials, a recently published risk assessment of vitamin D yielded a much more reasonable level of 250 mcg[6], ten times the proposed SCF tolerable UL.

When determining ULs for normal, healthy populations, it is completely inappropriate to apply the level determined for one nutrient form on another which is known to be considerably safer, as well as to use incomplete data or data from diseased populations. This process results in ULs which are known to be lower than the amounts required for beneficial effects in the vast majority of healthy individuals.

4. ***The UL does not take into account the use-pattern of the nutrient***. For instance, for some sensitive individuals, a single 2000 mg dose of vitamin C may induce bowel upset, while probably no adult would respond adversely to this dosage being taken in four 500 mg divided doses.

5. ***Studies used to underpin the ULs are often marred by unrecognised confounding***, as usefully revealed by the German authors of a recent study of vitamin and mineral consumers in a very large German cohort study[32]. This problem of unrecognised confounding is considered in more detail below, in the section entitled *Using the four criteria to develop MPLs*.

6. ***Guidance levels and average intake levels are sometimes used as surrogates for scientifically determined upper safe levels***. In the case of many nutrients, there are inadequate human data (dose-response) to be able to calculate a scientifically meaningful UL. In such cases, guidance or average intake levels are established, but these are then inappropriately used as surrogates for the Safe Upper Level (SUL) when in many cases it is known that a 'true' 'highest safe level' would be considerably higher. Refer to Table 1 for some examples. Of the 30 nutrient group risk assessments conducted by the EVM in 2003, only 8 SULs were generated, as compared with 22 guidance levels.[7]

7. ***Risk assessment models used are not tested properly***. Any proper, scientific risk assessment methodology requires testing of the risk assessment model used. Testing typically involves comparing the model outputs with 'real' data, and in the field of nutritional interventions, the largest data set in which dose-responses are recorded can be found in the field of clinical nutrition (not in the published literature). When the SCF, EVM or IOM models used in risk assessment are tested in this way, they are clearly found to be wanting, given that they yield ULs that are within or even below the 'normal range' for given nutrient forms. In

[6] Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr*. 2007; 85(1): 6-18. Electronic PDF viewable at http://www.ajcn.org/cgi/reprint/85/1/6

[7] Expert Group on Vitamins and Minerals. *Safe ULs for Vitamins and Minerals*. London: Food Standards Agency. 360 pp.

many cases, even published literature relating to particular nutrient forms demonstrates that the UL for the corresponding nutrient groups is excessively precautionary. Some examples are given in Table 1.

Table 1. Examples of nutrient forms for which ULs are not relevant to particular vitamin or mineral forms

Vitamin/mineral form	SCF UL (nutrient group) [EVM: Guidance Level]	Selection of evidence demonstrating that the UL is not relevant to the particular nutrient form
Vitamin D3	25 mcg (vitamin D)	Hathcock *et al* (2007)[10]; Veith (2006)[8]; Bernardi *et al* (2002)[9]
Mixed, natural carotenoid complex	Not set (iron) [EVM: 7 mg, non-smokers; 0 mg, smokers]	Bulux *et al* 1998[10]; Nishino *et al* (2005)[11]; Tang *et al* 2005[12]; Zhao *et al* (2006)[13]
Vitamin B6 (pyridoxine)	25 mg (vitamin B6)	Pietz *et al* (1993)[14]; Vaasdev *et al* (1999)[15]
Gamma-tocopherol	300 mg (vitamin E)	Stone & Papas (1997)[16]; Pryor (2000)[17]; Yu *et al* (2005)[18]
Ester-C	Not set [EVM: 1000 mg]	Gruenwald *et al* (2006)[19]; Bush & Verlanqieri (1987)[20]

[8] Vieth R. What is the optimal vitamin D status for health? *Progress in Biophysics and Molecular Biology*, 2006; 92(1):26-32. Review.

[9] Bernardi RJ, Johnson CS, Modzelewski RA, Trump DL. Antiproliferative Effects of 1{alpha},25-Dihydroxyvitamin D3 and Vitamin D Analogs on Tumor-Derived Endothelial Cells. *Endocrinology*. 2002; 143(7) 2508-2514.

[10] Bulux J, Quan de Serrano J, Perez R, Rivera C, Solomons NW. The plasma beta-carotene response to a single meal of carrots in Guatemalan schoolchildren. *Int J Food Sci Nutr,* 1998; 49(3): 173-9.

[11] Nishino H, Murakoshi M, Mou XY, Wada S, Masuda M, Ohsaka Y, Satomi Y, Jinno K. Cancer prevention by phytochemicals. *Oncology*, 2005; 69 Suppl 1: 38-40.

[12]Tang G, Qin J, Dolnikowski GG, Russell RM, Grusak MA. Spinach or carrots can supply significant amounts of vitamin A as assessed by feeding with intrinsically deuterated vegetables. *Am J Clin Nutr*, 2005; 82(4): 821-8.

[13] Zhao X, Aldini G, Johnson EJ, Rasmussen H, Kraemer K, Woolf H, Musaeus N, Krinsky NI, Russell RM, Yeum KJ. Modification of lymphocyte DNA damage by carotenoid supplementation in postmenopausal women. *American Journal of Clinical Nutrition*, 2006; 83(1): 163-9.

[14] Pietz J, Benninger C, Schafer H, Sontheimer D, Mittermaier G, Rating D. Treatment of infantile spasms with high-dosage vitamin B6. *Epilepsia*, 1993; 34(4): 757-63.

[15] Vaasdev S, Ford CA, Parai S, Longerich L, Gadag V. Dietary vitamin B6 supplementation attenuates hypertension in spontaneously hypertensive rats. *Molecular and Cellular Biochemistry.* 1999; 200(1-2): 155-162(8).

[16] Stone WL, Papas AM. Tocopherols and the etiology of colon cancer. *Journal of the National Cancer Institute*, 1997; 89: 1006-1014. Review.

[17] Pryor WA. Vitamin E and heart disease: basic science to clinical intervention trials. *Free Radical Biology & Medicine*, 2000; 1;28(1):141-64. Review.

[18] Yu FL, Gapor A, Bender W. Evidence for the preventive effect of the polyunsaturated phytol side chain in tocotrienols on 17 beta-estradiol epoxidation. *Cancer Detect Prev,* 2005;29(4): 383-8

Iron bisglycinate	Not set [EVM: 17 mg]	Szarfarc *et al* (2001)[21]; Bovell-Benjamin *et al* (2000)[22]; Jeppsen & Borzelleca 1999[23]
Magnesium pidolate	250 mg (magnesium)	Paolisso *et al* 1992[24]; McGuire *et al* 2000[25]

European Commission's Orientation Paper

The following section provides a discussion of the four key criteria outlined in Article 5 of the FSD which need to be accounted for in the determination of MPLs and which have been considered in the Commission's Orientation Paper.

Criterion 1: the Upper Safe Level

Given the established criteria, the starting point for determination of Maximum Permitted Levels (MPLs) is the Upper Safe Level (USL) as derived by risk assessment. The European Commission has listed those ULs derived by the SCF, the EVM and the IOM (see Annex of this document).
The Commission encouragingly appears to support a 'better regulation' approach which ensures that MPLs are not set for vitamins or minerals where there are "no evident safety concerns" and it lists those vitamins for which there is "general agreement" for which the setting of MPLs could be waived:

- Vitamin B1 (thiamin)
- Vitamin B2 (riboflavin)
- Vitamin B5 (pantothenic acid)
- Vitamin B12
- Biotin

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[19] Gruenwald J, Graubaum HJ, Busch R, Bentley C. Safety and tolerance of Ester-C compared with regular ascorbic acid. *Advances in Therapy*, 2006; 23(1): 171-8.

[20] Bush MJ, Verlanqieri AJ. An acute study on the relative gastro-intestinal absorption of a novel form of calcium ascorbate. *Research Communications in Chemical Pathology and Pharmacology.* 1987; 57(1): 137-40.

[21] Szarfarc SC, de Cassana LM, Fujimori E, Guerra-Shinohara EM, de Oliveira IM. Relative effectiveness of iron bis-glycinate chelate (Ferrochel) and ferrous sulphate in the control of iron deficiency in pregnant women. *Archivos Latinoamericanos de Nutricion,* 2001; 51(1 Suppl 1): 42-7.

[22] Bovell-Benjamin AC, Viteri FE, Allen LH. Iron absorption from ferrous bisglycinate and ferric trisglycinate in whole maize is regulated by iron status. *American Journal of Clinical Nutrition*, 2000; 71(6): 1563-9.

[23] Jeppsen RB, Borzelleca JF. Safety evaluation of ferrous bisglycinate chelate. *Journal of Food Chemistry and Toxicology.*, 1999; 37(7): 723-31.

[24] Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesauro P, Varricchio M, D'Onofrio F. Daily magnesium supplements improve glucose handling in elderly subjects. *American Journal of Nutrition*, 1992; 55: 1161-1167.

[25] McGuire JK, Kulkarni MS, Baden HP. Fatal hypermagnesemia in a child treated with megavitamin/megamineral therapy. *Pediatrics*, 2000: 105 (2): art e.

The Commission has also included chromium (III) and vitamin K in this list, however these were appended with question marks, presumably because there is more resistance to including these in any waiver.

Criterion 2: Intake data

The European Commission indicates that it is not in a position to use data generated by EFSA as EFSA is still considering how to deal with this issue and "*would not be able to provide help for some years to come*". The Commission conclude that in the absence of such data, the most comprehensive national data available, which is derived from the UK and Ireland, should be used.

Criterion 3: Population reference intakes

The third variable required to be "taken into account" are population reference intakes, normally considered as Recommended Daily Allowances (RDAs), which are intended to indicate the minimum intakes required to avoid specific deficiency diseases. The RDAs have no bearing on safety and hence have been the subject of challenges by the European Commission over certain governments using the RDAs as the basis to classify vitamins and minerals as medicinal products, hence imposing barriers to free movement of goods in the EU given the more liberal policies of other Member States. The Commission cites two European Court of Justice cases (C-387/99 and C-150/00). The first of these, *Commission vs Germany*, supported by Denmark, challenged the practice of classifying as medicinal any products containing dosages of vitamins and minerals (except vitamins A and D) in excess of three times the daily level set by the Deutsche Gesellschaft für Ernährung (German Food Association). The Court found in favour of the Commission, given that such products were lawfully marketed in other Member States, that there was no adequate basis for suggesting lack of safety and that the German restriction would impose and obstruct the free of movement of goods (under Article 28 of the EC Treaty). In the second case, *Commission vs Austria*, supported by Denmark and Finland, the Commission again challenged medicinal classification for vitamin and mineral products, except those containing vitamins A, D, K and the mineral chromium, when they contained more than the RDA. Once again the Commission won, Austria being accused by the Court of having "failed to fulfil its obligations under Article 28 EC".

It is thus essential that the RDAs are not in anyway used to influence any decision on risk or safety, while the inference is that any determination of MPL that emerged below the RDA might need to be re-considered given that it might interfere with consumers' ability to ingest sufficient vitamins or minerals to guard against deficiency diseases.

It must be added that many of the RDAs (or IOM Dietary Reference Intakes [DRIs]) have not been updated with recent science, while the determination of others have included methodological weaknesses. There is also a common failure for RDAs to take into account particular health markers that have been more recently established as being associated with nutrients, e.g. immune markers for vitamin C, cardiovascular markers for various B vitamins including folate, and low plasma levels of 1,25-dihydroxyvitamin D which has been shown to be a risk factor for certain cancers.

The Commission contemplates the use of RDA/PRIs "to categorise nutrients on the basis of their risk of exceeding upper intake levels". This may in fact be an ambiguous interpretation of the Population Safety Index (PSI) as determined by

EHPM/ERNA which utilises the labelling RDA as a denominator.[26] However, in reality the failure of RDA/PRIs to properly represent the daily dosages required to offset a much broader range of diseases or risk factors, rather than the classical diseases with which they were originally associated (e.g. scurvy for vitamin C, beriberi for vitamin B1, pellagra for vitamin B3, rickets for vitamin D, etc.), means that they are of little value in determining risk or MPLs. Their only possible value is highlighting higher potential risk where the gap between the RDA/PRI and the UL is narrow, which is the key purpose of the PSI.

Finally, RDA/PRIs have been set thus far for only 12 vitamins and 6 minerals, leaving a large number, particularly of minerals, without any RDA/PRI value. Thirteen vitamins and 15 minerals are listed in Annex I of the FSD, and an additional 10 minerals[27] are presently mandated under the derogation scheme of the Directive (total = 25 minerals). This means that there are presently RDA/PRI values for only 24% of mineral groups presently allowed under the FSD.

Criterion 4: Population groups

The Commission summarises some of the difficulties of taking additional account of requirements of particular population groups (e.g. diabetics, other diseased groups, pregnant/breastfeeding women, elderly, children, smokers, other high risk groups, etc.) and argues that these groups have already been considered in the determination of ULs.

This is correct, and hence means that the ULs in many cases cannot be applied to healthy populations, as amply demonstrated in the case of beta-carotene where the UL is largely the consequence of two trials which evaluated the effects of intervention with high doses of synthetic beta-carotene on heavy smokers or asbestos workers[5].

Using the four criteria to determine MPLs

Having considered the criteria, the Commission states, "*the total intakes from the overall food supply do not pose risks for public health, that is, they should be safety based*". It goes on to argue that, in determining the MPLs, intakes from both food supplements and fortified foods should be taken into account.

Any method of determining MPLs which involves addition of highest mean intakes of both food supplements and fortified foods, when subtracted from the ULs, which, for reasons given above, may be questionable, is highly likely to yield levels that are overly cautious. While this might be reasonable for environmental chemicals, pollutants and other contaminants, in the case of nutrients which are both necessary and beneficial to health, such an approach is grossly inappropriate.

In essence, the Commission's proposed approach suggests the following:

[26] The PSI = Upper Level – (Mean Highest Intake from food + intake from water) / EU labelling RDA; European Federation Association of Health Product Manufacturers (EHPM) and Responsible Nutrition Alliance (ERNA). *Vitamin and Mineral Supplements: a risk management model.* EHPM/ERNA. November 2004. 23 pp.

[27] Derogated minerals (under Article 4(6) of Directive 2002/46/EC on food supplements, presently includes sulphur, boron, silicon, lithium, vanadium, strontium, silver, gold, nickel and tin.

MPL = UL – Highest Mean Intake (from food, fortified foods *and* water)

This is an extraordinarily precautionary model as, in order to protect consumers from potentially excessive intakes, safety factors are included multiple times. These are as follows:

1. The UL generally does not reflect a true 'highest safe level' given the absence of adequate dose-response data in humans and other limitations (outlined above). Instead, ULs tend to be based around No Observable Adverse Effect Levels (NOAELs) which in many cases may be well beneath the level that would first trigger any negative effects, even in more sensitive individuals;
2. The UL incorporates an uncertainty factor to cater for lack of reliability of scientific data on which it is based;
3. The Mean Highest Intake from foods value will be based on average consumption patterns derived from national dietary surveys (e.g. UK, Ireland, Germany) which already include consumption of fortified foods
4. The inference made by the Commission is that a Highest Mean Intake level for fortified foods will be added to the value from the normal diet (which already includes fortified foods) and, in addition, intakes from drinking water may be further added (as per the EHPM/ERNA model).

The Commission's proposed approach has no adequate scientific basis. There is no evidence that those who consume the largest amounts of supplements also consume the largest amounts of fortified foods. In fact, scientific evidence suggests that consumption of vitamins, minerals and other supplements is specifically associated with healthy lifestyle traits, which in turn, includes an increased tendency to avoid smoking and consume healthy (whole) foods rather than less healthy food groups, such as fortified, processed foods[28]. High consumption rates of healthy, whole, home prepared foods, by definition, implies low (or even negligible) consumption of fortified foods.

In a recently published comprehensive study of the EPIC-Heidelberg cohort (1994-1998) in Germany, including 13,615 women aged 35-65 and 11,929 men aged 40-65, it was found that vitamin and/or mineral supplements were consumed regularly by 40% of women and 33% of men.[32] This study revealed, among other findings, the following associations for consumers of vitamin and minerals supplements:

- Supplement consumers had a lower tendency for obesity
- Supplement consumers tended to be more physically active
- Supplement consumers had a lower tendency to be smokers
- Supplement consumers tended to be more educated (and more health conscious)
- Supplement consumers tended to consume healthier whole food groups
- Supplement consumers tended to consume fewer unhealthy, processed food groups

[28] Reinert A, Rohrmann S, Becker N, Linseisen J. Lifestyle and diet in people using dietary supplements: a German cohort study. *Eur J Nutr*. 2007; 46(3): 165-73. Epub 2007 Mar 21.

The authors conclude, "*…data of our study indicate that the use of vitamin and mineral supplements in EPIC-Heidelberg is related to a more health conscious behaviour and can be regarded as one marker of a health conscious lifestyle.* ***Studies on the protective effect of nutrients (including supplementation) on cancer and chronic disease risk should always be aware of this source of confounding****.*" [our emphasis].

The authors have therefore revealed an important source of confounding in several of the studies used to underpin very low UL determinations.

Putting this into perspective, the negative findings of recent beta-carotene and vitamin E studies (and subsequent meta-analyses[29,30]), which have generated media headlines the world over, could be attributed to this confounding. Stated simply, if your study design takes a diseased or highly susceptible population (e.g. heavy smokers and asbestos workers in the case of key beta-carotene studies[31,32,33]; high cancer or cardiovascular disease risk in the case of key vitamin E studies[33,34,35,36,37]) and you then apply an intervention with high doses of isolated, synthetic forms of vitamins, negative outcomes may just as easily be associated with unhealthy lifestyle traits (including low supplementation), which in turn could have increased their risk of death. As such, the authors' conclusions that the supplement interventions were likely to have triggered the increased risk of death may be flawed, as the risk of unhealthy lifestyles in earlier life is clearly an important factor which has not been accounted for.

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[29] Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005; 142(1): 37-46.

[30] Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet*. 2004; 364(9441): 1219-28. Review.

[31] Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (1994) The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330: 1029-1035.

[32] Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammer S (1996) Effects of a combination of beta-carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 334: 1150-1155.

[33] Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of longterm supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996; 334: 1145-49.

[34] Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet*. 1996; 347: 781-6.

[35] Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000; 342: 154-60.

[36] AREDS Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. *Arch Ophthalmol.* 2001; 119: 1439-52.

[37] MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002; 360: 23-33.

Why the existing risk management model is not fit for purpose – and should be changed

A quasi-scientific process known as 'risk assessment' creates the UL, while a 'risk management' process moderates the UL to yield the MPL. Any staged process which has multiple margins or errors in it will end up being at significant variance from its intended form. This problem is particularly true of the proposed models for determining MPLs, which include multiple errors and safety margins. It is clear that the models are erroneous when the model outputs (MPLs) are compared with known responses to a wide range of vitamin and mineral dosages, the most comprehensive knowledge base probably being from the field of clinical nutrition.

Using the Commission's proposed approach, which is essentially similar to that used by the Bundesinstitut für Risikobewertung (BfR) (Federal Institute for Risk Assessment) in Germany, extremely low MPLs are revealed.

Some of the results emerging from the BfR's 2005 risk assessments are shown in Table 2.

Table 2. Some proposed maximum daily levels for food supplements, as determined by the BfR[38]

Vitamins		Minerals	
Vitamin	**Max daily dose**	**Mineral**	**Max daily dose**
Beta-carotene	2 mg	Magnesium	250 mg
Vitamin B1	4 mg	Iron	0
Vitamin B6	5.4 mg	Zinc	2.25 mg
Niacin (B3)	17 mg	Selenium	25-30 mcg
Vitamin C	225 mg	Copper	0
Vitamin D	5 mcg	Chromium	80 mcg
Vitamin E	15 mg	Manganese	0

The failure of such methodologies can readily be seen following testing of the model outputs against real data. It is evident that these levels are so low that they would often prevent consumers from exerting free choice and consuming levels within a known, healthy intake range.

For example, the USDA National Nutrient Database for Standard Reference[39] shows that a single boiled, cooked and drained carrot contains 7835 IU of beta-carotene, which is equivalent to 4.7 mg. Given that the UL (EVM) is within the same order of magnitude (7 mg), it implies that the amount of beta-carotene present in two carrots (9.4 mg), should it be present in a supplement, may pose a risk to health. This is very well known to not be the case. A single brazil nut kernel, typically weighing around 5 g, contains around 36 mcg/g of selenium[40]. This means that one fifth of a Brazil nut contains in excess of the BfR's

[38] Domke A, Großklaus R, Niemann B, Przyrembel H, Richter K, Schmidt E, Weißenborn A, Wörner B, Ziegenhagen R. *Use of Vitamins in Foods: Toxicological and nutritional-physiological aspects*. BfR, Berlin. 222 pp.

[39] http://www.nal.usda.gov/fnic/foodcomp/search

[40] Moodley R, Kindness A, Jonnalagadda SB. Elemental composition and chemical characteristics of five edible nuts (almond, Brazil, pecan, macadamia and walnut) consumed in Southern Africa. *J Environ Sci Health B.* 2007; 42(5): 585-91.

proposed MPL, but it also means that the SCF's UL of 300 mcg, represents the amount of selenium that may be ingested in 1.8 brazil nuts.

An example of how food fortification could negatively influence MPLs can be shown with folate or folic acid. Although the SCF has determined a UL for folate of 1000 mcg, which appears reasonable, this actually equates to approximately 3.8 cups of spinach (the USDA database[43] indicates that one cup of cooked spinach yields 263 mcg folate), or roughly a typical portion of spinach (unlikely to be consumed on a daily basis). However, given that the Highest Mean Intake for folate in foods has been determined in the UK as 359 mcg for men[41], if a high intake from fortified foods is also included given mandatory folic acid fortification, it is conceivable that MPLs in supplements would be extremely low, well below the typical 400-800 mcg daily levels common in existing products. Additionally, the levels would be applied to all forms of folate, including the monoglutamate, synthetic form, folic acid, as well as the food forms, such as 5-formyl tetrahydrofolate and 5-methyltetrahydrofolate, which have significantly different risk and benefit profiles.

These examples demonstrate the scientific irrationality of the proposed methods for determining MPLs. They also allow us to draw possible inferences about how the European Commission, and Member State governments, are reacting over risk assessment and management approaches to vitamins and minerals:

- Given that likely MPLs, and even sometimes the ULs, are often within the ranges of vitamin and mineral intakes from food, regulators must recognise that there is a difference in the risk of nutrients present in foods, compared with those used in food supplements or fortified foods;

- If this difference is recognised, why are regulators not considering imposing different levels for different forms of vitamins and minerals, given that some are food forms, while others are synthetic forms, either nature-identical or nature-near-identical (e.g. different isomeric forms or mixtures)?;

- However, if the difference is not recognised, why, we argue slightly facetiously, are regulators not insisting on warning labels being applied to common foodstuffs where there is a risk that excessive intakes may impose risk? Should packets of carrots containing two or more carrots or two or more brazil nuts carry health warnings over excess consumption? Should vegetable juicing be regulated? Surely not, given that there is no evidence that intakes of food forms are unsafe;

- Another possible inference is that the whole process of delivery of MPLs is a system being driven ultimately by political or economic processes, rather than scientific ones? Such an inference is perhaps plausible, given the Commission's statement in its Orientation Paper: "*This will imply that decisions which will have to be based not only on scientific grounds but will have to take into account also current market practices. Further discussion with industrial stakeholders will be needed in order to identify these practices and at the same time protect consumers' health.*"

- Our question is which stakeholders will hold more sway in decision-making? The large pharmaceutical suppliers of synthetic vitamins and largely inorganic mineral salts, or the more innovative food supplement

[41] National Diet & Nutrition Survey (NDNS) 2000/1, Food Standards Agency, UK.

manufacturers that specialise in delivering food forms of nutrients? Time will no doubt provide the answer, but there is a real risk that the final decision will be one which acts disproportionately on the smaller, specialised suppliers and manufacturers that have greater interests in food forms of nutrients.

Vitamin and mineral intakes regarded by most governments as adequate today, increasingly appear to be insufficient, particularly in relation to specific vitamins and minerals (e.g. vitamin C, D3, magnesium, etc.). This point has been previously made in the Common Position of the proposed regulation of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to foods: "*progress in scientific knowledge indicates that intakes of some nutrients for maintaining optimal health and well-being could be higher than those currently recommended*."[42]

So, although food fortification is one strategy which helps to ensure certain consumers (those who elect to consume fortified foods) ingest sufficient vitamins and minerals, it must be recognised that food supplementation is an alternative strategy, in which the consumer is allowed to exercise free choice in what supplementary nutrients are consumed. In determining risk, it is neither logical, nor is there any adequate supporting evidence, to combine intakes from conventional foods and fortified foods and subtracting this statistic from ULs when determining MPLs of vitamins and minerals for food supplements.

Requirements of a scientifically rational, new risk management model

We summarise below the main features required for a scientifically rational risk management model.

1. ***Identification of those vitamin and mineral forms where intake from food supplements (or fortified foods) may expose humans to significant health risks.*** An approach of this type, although applied to nutrient groups not forms, has already been developed in the EHPM/ERNA model, however, the PSI relies on two statistics, the UL and the RDA/PRI, that we regard as being flawed or faulty. Accordingly, we argue that another method is required which is based on more robust scientific principles, and takes into account differences in safety profile between different nutrient forms.

2. ***In cases where this potential risk has been established, the risk should be characterised, both in terms of its severity (e.g. low, moderate, high) and its reversibility or otherwise***. Presently the models identify risk and treat all forms of risk in the same way. There are no graded risk management approaches which take into account different forms of risk. The norm in food regulation, is that low risks are managed through provision of warning labels, bans are applied only to high risks. Imposing bans on low or mild risk scenarios (where the risk is fully reversible) must be considered a disproportionate risk management approach.

3. ***Risk assessment approaches, for the reasons given above, must include assessment of all relevant data and must be applied to individual nutrient forms, rather than nutrient groups, owing to differences in safety/risk profile between different members of the same nutrient group.***

[42] Common Position on proposed regulation of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to foods, dated 4 November 2005. http://register.consilium.europa.eu/pdf/en/05/st09/st09857.en05.pdf

This point was recognised at the EFSA colloquium on risk/benefit assessment of nutrients, held in Tabiano, Italy in July 2006.[43] Although this increases considerably the number of risk assessments required, it ensures that risk management policies are proportionate and scientifically based. The workload can be distributed by ensuring that determinations for the highest risk nutrients (with the narrowest margins between the beneficial range and potential adverse effect levels) are prioritised.

4. *Development of a proportionate, graded risk management approach* which applies more stringent measures to higher risk nutrient form/dosage combinations, and, at the other extreme, does not require that any risk management measures are applied to those nutrients for which the risk is low or negligible. A model which has elements of grading has been proposed via the EHPM/ERNA model and has been seemingly endorsed in the Commission's Orientation Paper. However, there should be at least three gradations in risk management policy, namely:

    - No measures for lowest risk category
    - Warning labels for intermediate risk category
    - Restrictions (bans) on dosage of particular nutrient forms, based on scientifically valid risk assessment and management determinations

    Such gradations are common place in existing food law in the EU. There are a wide range of foods which are known to induce adverse effects in certain population groups (e.g. dairy products in those that are lactase deficient, peanuts in allergy sufferers, wheat products in those that are gluten intolerant) and it would be legally inconsistent, on the basis of precedent, to regulate food supplements, which are a category of food, in a substantially different way.

    Trigger points for each of these risk management measures, and any others that are considered appropriate, need to be clearly defined.

Conclusion

The view of the ANH is that the existing proposals for MPLs are gravely at risk of acting as a disproportionate risk management measure, which could seriously interfere with consumer freedom of choice and prevent people from ingesting levels of particular vitamins and minerals that are well known to be beneficial.

There are many problems associated with existing and proposed methodologies, many of which have been discussed in this paper. They multiply out safety and uncertainty factors, so that final MPLs are likely to be overly cautious and will not stand up to scrutiny against real data (e.g. dosages consumed in foods, or those that have been monitored medically over decades by clinical nutritionists). Data which are used to determine MPLs may not be relevant to given nutrient forms or delivery systems, or determinations may be made on such limited data that extrapolations to humans are scientifically meaningless.

[43] European Food Safety Authority (EFSA). *Risk-Benfit Analysis of Foods: Methods and Approaches. EFSA Scientific Colloquium Summary Report, 13-14 July 2007, Parma, Italy*. EFSA: Parma, July 2007. p. 141.

We strongly recommend that the European Commission considers very seriously the development of a more appropriate model, which we believe would be better developed within an independent, university setting, rather than by stakeholders or the European Commission itself. It is clear that elements of the proposed model have been severely influenced by certain industrial stakeholders, and such influence appears to have taken the intended risk management process some distance from its intended purpose, namely the protection of consumers.

Owing to the complexities of nutrients (risk vs benefit; two-tailed risk, risk of excess and risk of inadequacy), it is evident that a more appropriate solution could be developed which would avoid the inevitable consequences of a disproportionate measure, namely legal challenge. Given that EFSA has already commenced work in this field, through its hosting of the *6th Scientific Colloquium on Risk-Benefit Analysis of Foods*[47], we strongly urge the Commission to delay imposition of its proposed measure until a more proportionate and scientifically valid approach to risk management has been developed.

Alliance for Natural Health
19 October 2007

About the Alliance for Natural Health (ANH)

The ANH is a UK-based, internationally-active, non-governmental organization working to positively shape regulatory and scientific frameworks affecting natural health. As an alliance, the ANH brings together scientists, medical doctors, integrative practitioners, lawyers and consumers, as well as suppliers of food and dietary supplements, globally as a means of working towards the development of sustainable approaches to healthcare. The ANH has been extensively involved in inputs to European Member State governments, the European Commission and the European Food Safety Authority (EFSA) with regard to the EU Nutrition & Health Claims Regulation which came into force across Europe on 1 July 2007.

www.anhcampaign.org

ANNEX: ULs (UL) as determined by the Scientific Committee on Food (SCF) / European Food Safety Authority (EFSA), the UK Expert Group on Vitamins and Minerals (EVM) and the US Institute of Medicine (IOM)

Annex 1
UL established by SCF/EFSA, EVM and IOL

	SCF/EFSA (UL)	IOM (UL)	EVM (SUL or GL[14])
Biotin (µg)	-	-	900 (GL in addition to foods)
Folate (Folic acid) (µg)	1000	1000	1000 (GL in addition to foods)
Nicotinic acid (mg)	10	35 (niacin)	17 (GL for supplements only)
Nicotinamide (mg)	900	35 (niacin)	560 (GL)
Pantothenic acid (mg)	-	-	200 (GL in addition to food)
Vitamin B2 (mg)	-	-	40 (GL in addition to food)
Vitamin B1 (mg)	-	-	100 (GL in addition to food)
Vitamin B6 (mg)	25	100	10 (SUL in addition to food)
Vitamin B12 (µg)	-	-	2000 (GL in addition to food)
Vitamin C (mg)	-	2000	-
Vitamin A (retinol) (µg RE)	3000 (does not apply to postmenopausal women)	3000	1500 (GL)
β-carotene (mg)	-	25 (for smokers)	7 (SUL for supplements only)
Vitamin D (µg)	50	50	25 (GL in addition to food)
Vitamin E (mg)	300	1000	800 IU (SUL in addition to food)
Vitamin K (µg)	-	-	1000 (GL in addition to food)
Sodium (mg)	-	-	-
Chloride (mg)	-	-	-
Potassium (mg)	-	-	3700 (GL in addition to food)
Calcium (mg)	2500	2500	1500 (GL in addition to food)
Phosphorus (mg)	-	4000	250 (GL in addition to food)
Magnesium (mg)	250 (for supplements only)	350	400 (GL in addition to food)
Iron (mg)	-	45	17 (GL in addition to food)
Zinc (mg)	25	40	25 (SUL in addition to food)
Copper (mg)	5 (not applicable during pregnancy or lactation)	10	10 (SUL)
Iodine (µg)	600	1100	500 (GL in addition to food)
Selenium (µg)	300	400	450 (SUL)
Manganese (mg)	-	11	12.2 (GL)
Chromium (mg)	-	-	10 (GL)
Molybdenum (µg)	600	2000	-
Fluoride (mg)	7 (for children above 8 years and adults)	10	-
Boron (sodium borate and boric acid) (mg)	10	20	9.6 (SUL)
Nickel (µg)	-	1000	-
Tin (mg)	-	-	13 (GL)
Vanadium (mg)	-	1.8	-
Silicon (mg)	-	-	1500 (SUL supplemental silica equivalent to 700 mg of elemental silicon)

[14] SUL: Safe Upper Levels
GL: Guidance levels. GL are determined when the database is insufficient to establish an upper intake level or when, no adverse effect has been identified.
EVM has calculated also a GL for cobalt: 1.4 mg