ANH
Alliance for Natural Health

Response by the

Expert Committee of the Alliance for Natural Health

regarding

the Draft Report of the Expert Group on Vitamins and Minerals (EVM)

(released August 2002)

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EXECUTIVE SUMMARY

1. This report represents the response of the Expert Committee of the Alliance for Natural Health[1] (ANH) to the Expert Group on Minerals and Vitamins (EVM) Draft Report *Safe Upper Levels of Vitamins and Minerals* released in August 2002.

2. The report contains a general critique of the risk assessment methodology employed by the EVM as well as more detailed examination of the sections concerning Vitamin B6, β-carotene, Vitamin D and Vitamin C. Recommendations to the EVM / FSA are also provided.

3. Serious omissions and errors of interpretation have been made and these, in the view of the ANH Expert Committee, are so substantial as to invalidate the risk assessment and conclusions drawn by the EVM.

4. General methodological problems include failure to:
    - Include relevant published studies;
    - Refer to adverse event data;
    - Consult adequately with experts in nutritional medicine;
    - Appropriately interpret animal studies;
    - Consider the effects of combinations of nutrients;
    - Take adequately into account variations in susceptibility across different population sub-groups;
    - Consider the effects of declining nutritional quality of diets;
    - Consider the effects of increased exposure to environmental toxins which should be counteracted by increased antioxidant intakes.

5. With regard to the EVM's risk assessment of Vitamin B6, the EVM has ignored key data and continued to misrepresent other data, some of it widely discredited, in order to justify an Upper Safe Level (USL) of 10 mg / day. The EVM also does not appear to have adequately responded to the recommendations made in 1998 by the Select Committee on Agriculture.

6. The EVM's review of β-carotene ignored key data and drew on studies, which are open to a range of interpretations, on particularly vulnerable groups (notably smokers and asbestos workers) to formulate a USL for the entire population. A better approach for public health would be to recommend contraindications on labels for specified vulnerable groups.

7. There are very serious flaws in the EVM risk assessment of Vitamin D which could have serious consequences on susceptible groups, especially non-white members of the population, and the young and elderly, particularly in winter.

[1] Refer to www.alliance-natural-health.org for background information.

8. In undertaking the risk assessment of Vitamin C, the EVM has ignored a very substantial literature on 'high dose' usage, alone and in combination with other nutrients. The EVM specifies side effects associated with intakes of the vitamin exceeding 1 g / day which are not substantiated with evidence.

9. There is a clear conflict of interests in the membership of the EVM, with 58% of the members declaring pharmaceutical interests.

10. Recommendations are provided by the ANH Expert Committee (Section 4.3) which include the need for development of new models of nutrient safety and optimum nutrient intake and supplementation, taking into account all relevant data and knowledge.

1. INTRODUCTION

This report reflects the views of key members of the Expert Committee of the Alliance for Natural Health (ANH), and represents the ANH's response to the consultation requested by the Expert Group on Vitamins and Minerals (EVM) following release in August 2002 of their draft report entitled *Safe Upper Levels for Vitamins and Minerals*.

The remit of the EVM was to review "relevant evidence" on 32 micronutrients used in dietary supplements and fortified foods and determine, where evidence was considered adequate, Upper Safe Levels (USLs). Where evidence was not considered adequate, the case for 23 of the 32 micronutrients evaluated by the EVM, guidance levels have been suggested.

A further remit of the EVM was to only consider those "supplements sold under food law". Accordingly, again as stated by the EVM, "the non-nutritional efficacy of vitamins and minerals has not been considered since such effects would be classified as medicinal and would be within the remit of the Medicines Control Agency".

Given the diversity of scientific views on the subject, in addition to varying political, economic and commercial pressures, there are very substantial variations between what dosages of specific vitamins are considered appropriate for products sold under food law compared with those sold under medicinal law in different EU members states. As a result, the ANH argues that the restrictive remit of the EVM excluded a very important body of data that is critical in developing scientifically valid upper safe or guidance levels for nutrients.

This report does not set out to be an exhaustive analysis of every aspect of the EVM report. Instead it provides a general critique of the overall methodology employed by the EVM (Section 2), while it also offers, by example, a more in depth and specific evaluation of the EVM assessment of four key nutrients, namely Vitamin B6, β-carotene, Vitamin D and Vitamin C (Section 3). The final section (Section 4) includes the ANH's Conclusions and Recommendations.

2. GENERAL CRITIQUE

2.1 Approaches to determination of Upper Safe Levels

The science used to determine recommended, optimum or upper safe levels of nutrients is evolving rapidly and there is a diversity of views on the methodology that should be used to make these determinations or estimates.

Eminent scientists and nutritionists have supported a view that optimum micronutrient levels are likely, for many groups, to vastly exceed those standards set by RDAs (Recommended Daily [or Dietary] Allowance). This latter view was famously publicly postulated by the eminent scientist, Dr Linus Pauling, nearly 30 years ago. Dr Pauling, in his testimonial to a US Congressional Committee in 1977 (Pauling, 1979) said that RDAs were:

> "...only the estimated amount that for most people would prevent death or serious illness from overt vitamin deficiency. Values of the daily intake of the various vitamins that lead to the best of health for most people may well be several times as great, for the various vitamins, as the values of the RDA. The proposed regulation restricting the sale of vitamins, through classifying them as drugs, could lead to great damage to the health of the American people, by interfering with their obtaining vitamins in the optimum amounts, such as to lead to the best of health."

Today, very low micronutrient levels typical of RDAs (superseded in the USA by Dietary Reference Intakes [DRIs]) are still widely advocated by highly influential bodies such as the Food Standards Agency (UK) and the US National Academy of Sciences (NAS).

In 1999, the NAS published a report, *A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients* (NAS, 1999), which details a risk assessment approach that is responsible for the development of excessively low micronutrient levels stipulated by DRIs. This methodology, essentially very similar to that employed by the EVM, is in the view of the Expert Committee of the ANH, both out-of-date and fundamentally flawed. A summary of the reasons for this are given in Section 2.2 of this report, while more detailed examination of the EVM's flawed approach is given in relation to four micronutrients appraised in Section 3.

Most recently, there has been considerable debate in the Codex Alimentarius Commission which is charged with setting global food standards, guidelines and related texts under the Joint FAO/WHO Food Standards Programme. During a meeting (24th Session of the Codex Committee on Nutrition and Special Dietary uses, 4-8 November 2002, Berlin) the relative merits of RDA-based and risk-based approaches for evaluation of upper levels of nutrients were discussed. Although consensus could not be achieved, it was apparent during these discussions that 'scientifically-based risk-based approaches' to the development of upper levels, although still fraught with problems, are gaining favour over the now out-dated RDA-based approach.

It is of interest that one of the Observer's on the EVM, Dr Derek Shrimpton, indicated with supporting evidence as early as 1995 that there is no correlation between

micronutrient safety and arbitrary multiples of the RDA, stating that 5 of the 13 vitamins are "considered safe at virtually any level" (Shrimpton, 1995).

2.1.1 Identification of Risk

There is a wealth of scientific research to demonstrate that the micronutrient dosages typical of stipulated RDAs are many times (sometimes several orders of magnitude) less than the optimum dosages for individual nutrients.

RDA values are completely independent of USLs. Although there is a wealth of published scientific evidence that micronutrient levels well above the RDA are not only safe but also beneficial (e.g. for Vitamin C, see Klenner 1974 and review by Bendich & Langseth 1995; for β-carotene, see Jialal & Grundy 1993), the most powerful scientifically valid evidence for safety of supplement dosages substantially above-RDAs comes from peer-reviewed studies on 'high dose' supplementation which have been ignored by the EVM.

In addition to this are the extremely low numbers of reported adverse events related to vitamin and mineral supplementation. In the UK, the Medical Toxicology Unit studies (see Shaw 1996) represent a very valuable database of adverse events for pharmaceutical products and dietary supplements and this resource was not referred to by the EVM.

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.

The US FDA has on file (data collected over a 20 year period) approximately 2,500 adverse event reports (AERs), including 79 deaths, that may be related to dietary supplements (see news report on: www.cnn.com/HEALTH/9802/22/supplement.safety/).

At the time of writing, these data are not presently accessible as they have been temporarily withdrawn from the FDA website (see http://vm.cfsan.fda.gov/~dms/aems.html). Forty four of the 79 reported deaths were apparently attributable to ephedrine-containing products (FDA 1997).

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 2001 inclusive are accessible from http://www.aapcc.org/annual.htm). These data show clearly that pharmaceutical products present by far the greatest risk of poisoning, as supported by Lazarou *et al* 1998, see below).

Keeping the figures for dietary supplement adverse events in perspective are comparable figures for adverse events and deaths caused by foods and pharmaceutical drugs.

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 (Mead *et al* 1999).

Properly prescribed and administered prescription and over-the-counter drugs are estimated in the USA to cause annually 2.2 million serious adverse events, and some 106,000 deaths (Lazarou *et al* 1998).

The concept of risk evaluation and setting of USLs for vitamins and minerals presupposes that these nutrients taken as supplements or in fortified foods are inherently toxic at levels ingested by the population and are responsible for significant adverse events. As shown above, this is simply not borne out by available data.

2.2 Specific comments on EVM methodology

The EVM report contains so many oversights in key areas that it is the opinion of the Expert Committee of the ANH that the proposed USLs and guidance levels should not be accepted in their present form. Specific problems associated with the EVM risk assessments are elaborated in the case of three micronutrients in Section 3.

The EVM approach to risk assessment was considered deficient in at least nine major areas. These are considered below.

a) **Absent data**. The EVM has ignored a very substantial literature including high quality, peer-reviewed studies on 'high dose' supplementation. Some of this literature was specifically omitted as a result of the EVM's remit, but these omissions were not justified in the text of the EVM report. In addition, key data and research have been omitted, deliberately or through ignorance, from the risk assessments.

b) **Adverse event databases**. The EVM has ignored consideration and analysis of adverse events reports associated with dietary supplements (including the UK Medical Toxicology Unit database) which in total are the result of many decades of usage by 20-50% of the population in most western countries.

c) **Specialist consultation**. The EVM has failed to consult with acknowledged, medically qualified doctors and expert practitioners of nutritional medicine who cumulatively have many decades of experience in nutritional therapies and use of so-called 'high dose' supplements. Specialists in nutritional medicine are also conspicuously absent from the membership of the EVM, which is clearly geared towards pharmaceutical interests (see Annex 5 of EVM report, pp. 262-366).

d) **Animal studies**. The EVM has relied excessively on animal studies which are fraught with difficulties when extrapolating to humans. These studies provide much less meaningful data than studies and experience in the field of nutritional medicine and evaluations of population-wide supplement use and adverse event reports (see separate submission by Dr Paula Baillie-Hamilton). Where animal studies have been relied upon in the risk assessment, incorrect assumptions have often been made (e.g., Vitamin B6).

e) **Nutrient combinations**. Studies including combinations of micronutrients (e.g. Vitamins B6, B12 and folic acid, or Vitamins A, C and E) were not adequately considered.

f) **Variation in susceptibility**. Variations for different human groups, e.g. sex, gender, habits, diet were not sufficiently taken into account (Kelley & Bendich 1996; Fairfield & Fletcher 2002).

g) **Declining nutritional quality**. The EVM did not take into account the declining nutritional quality of western diets (refer to substantial losses of vitamins and minerals via USDA food tables over 110 year period: http://www.nal.usda.gov/fnic/foodcomp/Bulletins/timeline.htm).

h) **Environmental toxins**. The EVM did not consider the need for increasing levels of antioxidant vitamins and other co-factors to counteract the effects of increasing population exposures to environmental toxins and other xenobiotics (see separate submission by Dr Paula Baillie-Hamilton).

3. CRITIQUE OF INDIVIDUAL NUTRIENT ASSESSMENTS BY THE EVM

This section deals specifically with four nutrients considered by the EVM, namely Vitamin B6, β-carotene, Vitamin D and Vitamin C.

3.1 Vitamin B6

The EVM indicates that vitamin B6 (pyridoxine) is "claimed to alleviate symptoms of premenstrual syndrome, pregnancy sickness, carpal tunnel syndrome, hyperhomocystinaemia (a risk factor for cardiovascular disease) and neuropathies".

Other diseases or symptoms typical of B6 deficiency were ignored, including hyperactivity in children (200 mg/day: Coleman *et al* 1979), epilepsy in infants (50-100 mg/day: Coker 1992; Crowell & Roach 1983), diabetic neuropathy (200 mg/day: Patel *et al* 1991), autism (30 mg/kg body wt or more: Martineau *et al* 1985; Rimland *et al* 1978), and asthma (100 mg/day in children: Collipp *et al* 1975). These studies, as indicated in Section 2.2a), provide very useful human data on higher B6 dose rates that were ignored by the EVM.

Furthermore, apart from the brief indication of B6's possible role in hyperhomocystinaemia, the EVM fail to mention the rapidly growing body of work that suggests that B6, in combination with other nutrients such as folate and B12, might be pivotal in the treatment of heart disease which is in itself a symptom of micronutrient deficiency (e.g. Chao *et al* 1999; Chambers *et al* 2000; Undas *et al* 1999).

3.1.1 Previous assessments of USLs

It is remarkable that the first report from the Department of Health's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment concluded that an upper safe level of vitamin B6 should be set at 10 milligrams, then, when the fundamental errors in their mathematics were pointed out to them, their revised report (released in June 1997) adjusted the safety factors in order to arrive at the same level of 10 milligrams.

The EVM report has reviewed yet again the same data and added in a further safety factor to arrive at the same result again.

It is also interesting to note that the Select Committee on Agriculture published on 23 June 1998 a "damning report" on the Government's intention to limit the level of consumption of vitamin B6 to a daily dose of 10 mg vitamin. The following extracts are taken from the report:

> "The Government should withdraw its proposed draft regulations to limit the level of vitamin B6 per daily dose to 10 milligrams".
>
> "It is our view that the doubts concerning the Dalton and Dalton study are so serious that it is scientifically unjustifiable to use them as the basis for establishing a lowest observed adverse effect level in relation to Vitamin B6 intake."

The Government's response to this stated:

> "We do not consider that there is a basis for a voluntary limit of 100 milligrams per day dose".

The response concluded that a decision should be deferred until after the EVM had produced its report, and stated:

> "In the meantime, the Government's advice to consumers is that their daily intake of vitamin B6 from supplements sold under food law should not exceed more than 10 milligrams per day other than on professional advice".

The Expert Committee of the ANH contends that the EVM appears to have misrepresented available data and ignored other data in order to argue its case for a USL of 10 mg /day. The ANH very strongly contests the risk assessment undertaken by the EVM and would welcome the opportunity of submitting an alternative risk assessment to the EVM.

3.1.2 Safety factors

As suggested above, it seems that there has been a consistent desire by the UK government (and some other authorities) to find a USL of 10 mg/day. The obvious conclusion to draw from this is that there is a clear vested interest in setting the upper limit at 10 milligrams rather than 100 milligrams. Possible reasons for this were set out in a letter by Dr Damien Downing in the Lancet (May, 1998).

Indeed, if the safety factor of 300 proposed in the EVM report were applied to most pharmaceutical drugs on the market, it would not be possible for them to be taken at anything approaching an effective therapeutic dose. The EVM report states that:

> "these uncertainty factors are appropriate because the LOAEL in the dog related to a sub-chronic study and therefore may have underestimated the toxicity during chronic exposure. The need for an inter-species factor is supported by the fact that the LOAEL dose in dogs is an equivalent to an intake of 3000 milligrams per day in humans, which would produce severe toxicity, suggesting that humans might be more sensitive than dogs".

Yet the EVM's "overall database" on intakes of this level in humans amounts to two subjects in the study by Berger *et al* (1992), who developed numbness and pins and needles in the toes. This severely restricted data set hardly allows the assertion that this dose "would produce" anything, and the symptoms of peripheral paraesthesia described do not amount to severe toxicity. The report glosses over this, as did several earlier reviews, by taking symptoms (peripheral paraesthesia) which can be early indicators of peripheral neuropathy, but which are clearly reversible on terminating B6 treatment, and conflating them into a positive diagnosis of peripheral neuropathy.

3.1.3 No valid evidence for human toxicity at 100 mg/day or below

The only published data showing toxicity at less than 200 mg daily is the study of Dalton & Dalton (1987). The EVM states in its report that this study is flawed, yet it proceeds to use it in the risk assessment, stating:

"In the absence of better data it is not possible to dismiss this investigation".

It further states that the Dalton and Dalton study, together with that by Parry and Bredesen (1985):

> "are consistent with the overall database, which clearly indicates that a duration of exposure as well as dose is important".

This argument is cyclical, as these two studies in fact amount to practically the entire database on longer term administration of B6. Moreover, they are not compatible with each other, as the Dalton paper appears to show toxicity at levels about an order of magnitude lower than the other study, and the symptomology is quite different.

The Dalton & Dalton study is inconsistent with the known facts regarding pyridoxine-related peripheral neuropathy, and indeed peripheral neuropathy in general. It is also a questionable study in a number of ways, as follows:

a) The study contained no control group for comparison. Those subjects referred to as controls are in fact subjects in whom the intervention (B6 supplementation) failed to produce the effect under study (neurological symptoms). A true control group would have comprised subjects with PMS who were not taking B6, and the study would have reported on the incidence of symptoms in this group *vs* those who were taking B6.

b) The clinical picture described is clearly dissimilar to that reported by other studies (Schaumburg *et al* 1983, Parry & Bredesen 1985; Berger *et al* 1992) in humans in several respects:

- paraesthesia is reported as 3 times more common in the upper limbs, in direct contrast to other studies;
- the paraesthesia is not “glove and stocking”, in at least the case report subject;
- tendon reflexes are preserved;
- hyperaesthesia is not reported in other studies;
- bone pain is not reported in other studies;
- muscular weakness is not reported in other studies — except when pre-existing (Parry & Bredesen 1985);
- muscular fasciculation is not reported in other studies.

c) No electrophysiological testing was performed in the study. This would have allowed comparison with the findings in other reports of B6-induced neuropathy. In its absence it is impossible to establish whether the syndrome described is the same as that reported elsewhere — particularly important in view of the divergence of the clinical pictures.

d) In contrast to all other studies, there is no dose-response relationship. In particular:

- frequency of occurrence of symptoms does not correlate directly with dose ingested;
- severity of symptoms does not correlate directly with dose ingested;
- time to onset of symptoms does not correlate inversely with dose ingested.

e) Although the EVM cites 50 mg per day as the lowest dose at which symptoms have been reported (and that in the Dalton & Dalton study alone), the lowest dose category reported in the paper is actually "< 50 mg", although no doses are given for this or any other category. Moreover, the relative risk of developing symptoms at this level is very close to that at the highest dose level (38% vs 41%), with wide variation in the intervening groups. This makes the paper's hypothesis essentially not credible.

f) All subjects had presented with PMS, which is recognized to cause a variety of diffuse, non-specific symptoms. Because there is no true control group, the prevalence of the symptoms reported on in subjects not taking B6 is unknown. It is therefore not possible to say that the symptoms described were due to B6 and not to PMS.

g) Since PMS is reported elsewhere to respond markedly to placebo — 70% improvement in one study (Williams *et al* 1985), it is possible that the improvement on B6 withdrawal is entirely due to placebo effect.

h) Fifteen years on, the study still awaits replication, or any other confirmation.

Given the above inadequacies of the Dalton & Dalton paper, ANH submits that it does not amount to a basis for formulating public policy. It is relevant to point out that another study carried out to test the hypothesis forwarded by the Dalton & Dalton (1987) study showed very clearly that the Dalton findings were both highly questionable and the symptoms reported were much more likely to be the result of factors independent of B6 intake (e.g., PMS) (Gaby 1997).

A rather better data set is available in the form of the Medical Toxicology Unit monitoring exercise (Shaw *et al* 1996), in which evidence of toxicity from traditional remedies and food supplements was sought over a period of 8 years. In this time, no case of peripheral neuropathy linked to vitamin B6 was noted. Since the surveillance could be said to involve the whole population, and since the number of supplements sold and consumed in the UK that contain 50 mg or more of B6 is virtually incalculable but certainly greatly exceeds 100,000 one-month courses per annum, this represents in excess of 6,000 man-years of supplementation at this level with no case of toxicity reported. This large survey, therefore, supports the null hypothesis — the view that B6 in doses of the order of 50 mg per day does not produce toxicity.

3.1.4 Absent data

There are a number of important studies that have been omitted from the literature review by the EVM.

Particularly noteworthy is the omission of the highly significant Medical Toxicology Unit review in the UK (Shaw *et al* 1996) and an important study on toxicity of B6 in humans, the 1983 *New England Journal of Medicine* report of seven cases of B6 toxicity (Schaumburg *et al* 1983), in which no subjects experienced symptoms at doses below 2,000 mg/day.

Furthermore, other studies have been omitted from the review (several are cited above; see also citations in Downing 1998).

3.2 β-carotene

Supplementation with relatively high doses (20-180 mg/day) of β-carotene is well understood as it has long been used to treat patients with erythropoietic photoporphyria. These treatments have shown no evidence of toxicity and they do not result in abnormally elevated blood vitamin A.

3.2.1 Study selection and interpretation

The EVM arrived at a USL for this nutrient by primary reference to one large-scale intervention study, the Alpha-Tocopherol and Beta-Carotene Prevention Study (ATBC 1994), and secondary reference to two other intervention studies, namely the β-carotene and Retinol Efficacy Trial (CARET) (Omenn *et al* 1996) and the US Physicians' Health Study (PHS) (Hennekens *et al* 1996).

The first two studies gave supplements of β-carotene, together with either vitamin A or vitamin E, to subjects considered to be at high risk of developing lung cancer. Subjects were either smokers, heavy smokers who had recently quit, or asbestos-exposed workers. Both studies identified an increase in the diagnosis rate of lung cancer in the group with highest beta-carotene intake. There was no evidence of increased incidence of other forms of cancer related to β-carotene supplementation.

The third (PHS) study, also a large-scale study, involving 22,071 subjects, tested the effect of β-carotene with and without aspirin on the incidence of cardiovascular disease and lung cancer. The subjects in this study were more representative of the normal population, with only 11% smokers. The dose rate for β-carotene in the PHS study was 2.5 times greater than in the ATBC study and 1.7 times greater than in the CARET Trial. The duration of β-carotene administration in the PHS study was also greater (11-12 years) than the other two studies (6 years median for the ATBC Study and 4 years mean for the CARET Trial, after it was cut short two years early).

Bearing this in mind, and unmentioned by the EVM, it was of particular interest that the PHS study showed no significant effect of β-carotene on any type of cancer, cardiovascular events, stroke or death from all causes.

The EVM inappropriately dismiss the importance of this study, stating:

> "...as current smokers comprised only 11% of the total study population the PHS trial had limited capacity to detect adverse effects in this subgroup (in contrast with ATBC where 100% of the study population were smokers, and CARET, which included only current or recently-quit heavy smokers and individuals with previous high-level asbestos exposure)."

3.2.2 Specific comments relating to the ATBC Study and CARET Trial

In respect of the ATBC Study and the CARET Trial, the EVM report states:

> "Epidemiological studies have suggested an association between supplementation with β-carotene and an increase in lung cancers in smokers and in individuals who have been heavily exposed to asbestos."

There are important misrepresentations in this statement, as shown below:

a) the studies are described as being epidemiological, implying that they were looking at a baseline or background levels of supplementation in the population; in fact, both studies were active interventions with relatively high dose supplements.

b) the supplementation continued for six years and four years respectively in the two studies. Given that, in the ATBC study the subjects had been smokers for an average of 36 years, at a rate of over 20 cigarettes daily, it is evident that the changes leading to the initiation of cancer will have happened before supplementation started. It is possible to infer from the studies that β-carotene, as used, does not cure or retard cancer once begun; but certainly not that it encourages cancer.

c) the EVM report ignores the reported finding that, in the ATBC study, those subjects with the highest blood levels of β-carotene (and of vitamin E) at the start of the study had the lowest risk of developing cancer. This is the true epidemiological finding.

d) the following statement in the ATBC study is also ignored:

> "In light of the totality of the data available on the relationship between the intake of antioxidant vitamins and a corresponding reduction in cancer, an adverse effect of β-carotene seems unlikely and may well be, in spite of formal statistical significance, due to chance."

Once again, as with vitamin B6, EVM group have selected a study of highly questionable significance to be their key document. There are a number of other points on which these studies and their interpretation can be criticized, but these are of limited relevance here. Some of these points are considered in a review by Hughes (1999), ignored by the EVM.

Using two studies which show the possibility of increased susceptibility to lung cancer among *high risk individuals* in order to develop USLs for the entire population is flawed. The EVM conceded that:

> “Observational studies in humans have shown that high intake of β-carotene-containing foods in the diet, as well as higher serum β-carotene levels, are associated with reduced risk of chronic diseases, such as coronary heart disease and cancer.”

Surely the EVM, even with its misinterpretation of the ATBC Study and CARET Trial, would have been more prudent to recommend inclusion of a contraindication on the label that warned smokers and asbestos workers of possible risks associated with β-carotene supplementation. This would allow the majority of the population to derive the clear benefits of β-carotene supplementation, particularly when in conjunction with other antioxidants such as Vitamins C and E.

Finally, it is surprising that the EVM omit a number of key studies and reviews, yet cite 7 studies which are Roche Internal Research Reports.

3.2.3 Absent data

As with other micronutrients considered by the EVM, important human studies have been omitted by the EVM. One recent example is the Age-Related Eye Disease Study (AREDS 2001) involving 3640 participants, ages 55-80, with an average

follow-up of 6.3 years. The authors found no statistically significant serious adverse effects associated with any of the formulations used, as well as beneficial effects on visual acuity of the antioxidant supplements (including 15 mg /day β-carotene) combined with zinc.

Another study by Jialal & Grundy (1993) (β-carotene 30 mg/day) also showed no adverse effects.

3.3 Vitamin D

3.3.1 General comments

There are such serious inaccuracies and omissions in the EVM's section on vitamin D that it is clear that the necessary expertise was not available to the group. One acknowledged expert in the field commented that this section "would not be acceptable for publication in any reputable journal." The result is a set of recommendations that are out of date, and if implemented would be overtly harmful to the health of large sectors of the population.

3.3.2 Chemistry and geochemistry

The report fails to distinguish vitamin D2 from D3, in a manner that implies lack of comprehension of the distinction, and that has grave consequences for the report's conclusions. Specifically, the report states:

a) "Two nutritionally significant compounds are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol)."

   Vitamin D3 is the naturally occurring form in food and in human chemistry; vitamin D2 is a synthetic product, which only occurs naturally in yeasts. Metabolites of vitamin D2 are not present in the human diet and are never detectable in the circulation unless the synthetic product, ergocalciferol (vitamin D2) is administered. Put simply, vitamin D3 is a nutrient and vitamin D2 is a drug. Failure to distinguish between them reinforces the fundamentally flawed approach to assessment of toxicity that is discussed above (Section 2.).

b) "Vitamin D2 and D3 are assumed to have equal levels of efficacy and toxicity in humans."

   The assumption of equal efficacy is gravely outmoded, being based on research performed prior to 1938 (Park 1940). More recent studies, ignored by the report, indicate that vitamin D3 is in fact about 4 times as effective as D2 (Trang *et al* 1988). Regarding toxicity, see Section 3.3.2 c) below.

c) "Data on the comparative toxicity of vitamin D2 and D3 in humans are lacking."

This statement is plainly inaccurate; all the published iatrogenic toxicity data implicate vitamin D2, and there is no recorded case of iatrogenic toxicity of D3 (Vieth 1999). The only known cases of vitamin D3 toxicity have been as the result of industrial accidents involving exposures to vitamin D that were at least two orders of magnitude greater than could possibly occur nutritionally (Blank *et al* 1995), and four times greater than can be obtained from sunlight exposure. Consequently, to approach vitamins D2 and D3 as being equivalent in this respect ignores the currently available data, and again emphasizes the fundamental flaws in the EVM approach.

3.3.3 Study selection and interpretation

The EVM report ignores much of the more recent evidence on vitamin D, and bases its conclusions instead on older studies, or on "assumptions" for which no studies are cited, but which on examination are found to be based on very old and superseded research. Reference to contemporary research would have led to the following conclusions, not drawn in the report:

a) Human requirements for vitamin D3 are significantly higher than formerly believed.

Several studies have demonstrated that ultraviolet light exposure of the full skin surface of an adult for a day is equivalent to a vitamin D consumption of about 250 mcg (10,000 IU). There is no evidence that this is in any way harmful. In this context the current RDAs, and the EVMs guidance, are so small as to be irrelevant. Indeed, there is evidence that RDA-level intakes or supplementation have no effect on serum vitamin D levels or on the prevalence of deficiency (Vieth 2001a; Lehtonen-Veromaa 1999). Recommendations for intake could more logically be based on what appears to be a physiological (in that it is readily obtainable from casual sun exposure) plasma level of 25(OH)D of 100 nmol/L. Dose-response curves on this basis indicate that a more appropriate adult RDA would be 4000 IU, ten times the current recommendation. The extensive literature on this is summarized in (Vieth 2001).

b) Vitamin D3 is much less toxic than formerly believed.

The EVM report cites the 1984 Narang paper; it states that in this study 30 subjects received varying doses of vitamin D, but omits to make it clear that the highest intake group (0.095mg or 3800 IU), the only one to experience a rise in serum calcium beyond the normal range, comprised only 6 subjects. Since the study considered patients with tuberculosis, a recognised factor that increases sensitivity to vitamin D, it should not have been included in the consideration in any case. The report then cites the Vieth paper (Vieth *et al* 2001) and misrepresents its findings, referring to a rise in urinary calcium which was not, in fact, observed. It does not cite 2 other papers in which subjects received 4000 IU and 50,000 IU (short-term) without adverse effects (Tjellesen *et al* 1986; Barger-Lux *et al* 1998).

The key study on which the EVM report bases its guidance level is the Johnson study (Johnson *et al* 1980), in which 2 out of 63 elderly patients

given 2000 IU developed hypercalcaemia. However it is well known that elderly patients often have reduced renal function, and therefore tolerate less of most drugs and many nutrients, and recommendations already reflect this. Moreover this dose is a trivial fraction of the dose obtainable from sunlight, and substantially smaller than that found to be safe in several other studies.

While it might be reasonable to recommend a lower USL for the elderly, to impose this restriction on the entire population is unnecessary and potentially dangerous.

3.3.4 Concluding comments

The USL recommended by the report will not be adequate for Asian or black people, who will be discriminated against, and unable to obtain adequate vitamin D for health. Indeed, large numbers of the young and the elderly population (both white and non-white) are known to be deficient in vitamin D during the winter, and they will also suffer from this recommendation. Apart from the role of vitamin D in calcium metabolism, it is now well known (and acknowledged briefly by the report) that it has importance for a range of other health problems, including diabetes mellitus, several cancers, multiple sclerosis, hypertension, and resistance to respiratory infection. The EVM report's recommendations would have deleterious effects on these diseases in the community; this is therefore another instance of a fundamentally flawed approach to nutrient safety. In the instance of vitamin D this has been compounded by either ignorance or negligence concerning the basic facts. As a result, the document upholds the most conservative of past recommendations, with no regard for the available evidence.

3.4 Vitamin C

Many widely discussed putative adverse effects of vitamin C (as well as vitamin E and trivalent chromium) have little factual basis (Hathcock 1997). A large literature on Vitamin C supplementation has developed, much of it involving gram dosages substantially over the European RDA.

As indicated by Garewal & Diplock (1995) with reference to antioxidant vitamins:

> "..... it is important that such agents be virtually free of toxicity. The agents of most interest are alpha-tocopherol (vitamin E), ascorbic acid (vitamin C) and beta-carotene. When used for disease prevention, the doses given are several-fold greater than the Recommended Dietary Allowance (RDA), the latter being based on amounts necessary for the prevention of classic deficiency conditions recognised decades ago. Alpha-Tocopherol, ascorbic acid and beta-carotene are remarkably well tolerated and free from toxicity."

Despite a plethora of data from studies within the last 20 years, and the four year time period the EVM has had to compile its report, only seven references were used to inform its opinion on Vitamin C. Additionally, two limited, old studies (Cameron & Campbell 1974 & Stein *et al* 1976) were the key studies used to determine the guidance level of 1000 g/day.

The EVM addressed certain safety issues in the report and these are commented on in Sections 3.4.1 - 3.4.5 below.

3.4.1 Urinary oxalate and urinary stones

The two main references relied upon by the Expert Committee are Urivetsky *et al* (1992) and Wandzilak *et al* (1992), with a mention of two papers by Levine *et al* (1996, 1999). Of these Wandzilak *et al* reach a negative conclusion about any hazard from doses of Vitamin C up to 10,000 mg per day, while Urivetsky *et al* were working specifically with patients with calcium oxalate stones. The EVM has not quoted the important paper by Rivers (1989). This is a review of safety in which it is reported that ingestion of 5 and 10 g per day of ascorbic acid had only a marginal effect on urinary oxalate and that the variations observed were within the range experienced with individuals who do not consume a supplement of Vitamin C. The paper by Rivers appears to be among the most significant in the field and yet was omitted by the EVM.

This paper also reports that gram doses of Vitamin C were found to be beneficial for the prevention and treatment of several disorders and although large doses may be contra-indicated in cases of renal insufficiency, it was concluded that adverse health effects are not induced in healthy persons by ingesting large doses of ascorbic acid.

This, and the paper by Wandzilak *et al* (1992) are quoted by Murray (1996). Murray states that numerous studies demonstrate that in persons not on haemodialysis or suffering from recurrent kidney stones, severe kidney disease, or gout, high-dosage Vitamin C therapy does not cause kidney stones. Vitamin C administration of up to 10 g per day has not shown any effect on urinary oxalate levels.

It should be pointed out that even if there had been any clear effect upon urinary oxalate in normal people, there is a lack of any evidence that links either urinary oxalate or Vitamin C intake with the incidence of urinary stones. Therefore the suspicion about this that has been sometimes mooted is extremely tendentious and quite unsuitable to be relied upon to deny the public or the patients of nutritional practitioners the right to use Vitamin C at levels above 1 g. Basically it is no more than an unsupported suggestion.

The suggestion of an adverse effect upon those with renal disease, actual nephrolithiasis or just a tendency to high urinary oxalate, may be slightly more plausible, but remains tendentious because no such adverse effect has been demonstrated. A label warning could be made, but it remains unclear whether it is justified.

3.4.2 Effects on Vitamin B12 status

There is no support for the suggestion that Vitamin C impairs the body status of Vitamin B12. The EVM has quoted no references specifically on this. Herbert *et al* (1978) found that when 18 males aged 23 to 62 years were given 2 g of Vitamin C daily for 29 months, plasma Vitamin B12 was only reduced after years and then it was reversible.

There seems to be no justifiable reason for concern on the B12 issue.

3.4.3 'Rebound scurvy'

The EVM refers to 'rebound scurvy' but does not cite references. Murray (1996) in his review writes as follows:

> "Some researchers report that abrupt cessation of high-dosage Vitamin C intake leads to rebound scurvy or in pregnant women the presence of rebound scurvy after birth of their babies. However, other studies do not support the existence of rebound scurvy with sudden cessation or after pregnancy. While the existence of rebound scurvy is controversial (some experts question its existence), it is better to favour the side of caution. So, if you have been taking high dosages of Vitamin C (e.g., greater than 500 milligrams per day), reduce your dosage gradually."

Once again there seems to be a complete lack of any literature to support the reality of this alleged hazard. It would therefore be inappropriate to rely upon unsupported supposition as the basis for a restriction on the permitted intake of a vitamin that large numbers of people wish to use at levels greater than 1 g per day. Advice (on product labels) to come off high doses progressively might be prudent but would still be based only upon supposition.

3.4.4 Metabolic acidosis and changes in prothrombin activity

The EVM refers to these but presents no evidence about them. In the absence of any evidence, no weight should be attached to these unsupported suggestions.

3.4.5 Studies investigating administration of Vitamin C at daily levels above 1 g

There are many studies that have been conducted to investigate the possible benefits of Vitamin C intakes above 1 g. Many of these have produced clearly positive and beneficial results.

The EVM, owing to the unwarranted limitation of their brief, have specifically excluded consideration of such studies. The decision to exclude these studies is deplorable and cannot be justified scientifically if the objective is to use available and relevant studies to develop USLs following risk assessment.

Nonetheless, the fact that so many studies have been carried out to investigate benefits at high intakes without revealing side effects other than occasional temporary gastrointestinal ones, amounts to real evidence in favour of the safety of these intakes.

There are thought to be hundreds of such studies and the following list comprises only a few examples of them:

a) Kataoka *et al* (1993)

Abstract
Intermittent high doses of 1.5 – 3 g were given to patients for 3-5 days followed by a 2 day abstinence over a period of 2-14 months following treatment for HTLV-I associated myelopathy. Clinical outcomes were excellent and there was no reported toxicity.

b) Mai *et al* (1990)

Abstract
Patients who were given 2 g Vitamin C daily along with Vitamin E and selenium had a positive clinical outcome and side effects were rare.

c) Bendich & Langseth (1995)

Abstract
The safety of high dose Vitamin C was confirmed in eight placebo controlled double blind trials in which up to 10 g Vitamin C was ingested for up to 3 years, outcomes showed lowered incidences of CVD LDL oxidation, blood pressure and mortality with no toxicity reported.

d) Meyers *et al* (1990)

Abstract
The Department of Internal Medicine at Kansas University found that ascorbic acid reactions are rare at dosages less than 4 g / day and feel that antioxidant vitamins are safe although one should use prudence in persons with liver disease or renal dysfunction.

e) Diplock (1995) and Hathcock (1997)

Combined abstract
According to a study published in the American Journal of Clinical Nutrition, widely discussed putative adverse effects of Vitamins, C E and Trivalent Chromium have little factual basis (Hathcock 1998). The US and Canada have already published a new standard for the tolerable upper intake level (UL) at 2g Vitamin C per day. A previous study published in the same journal (Diplock, 1995) reported a consensus of opinion that adverse effects do not occur in healthy subjects ingesting large amounts of Vitamin C.

f) Cameron & Campbell (1974), a paper quoted by the EVM.

3.4.6 Expert conclusions on USL of Vitamin C

Taking into account the many decades of combined experience of members of the Expert Committee of the ANH in the practice of Nutritional Medicine, along with literature studies, the ANH Expert Committee is fully convinced that 4g per day of Vitamin C is safe and is often effective for a list of worthwhile clinical purposes. The only side effect noted at such dose rates is temporary stomach acidity, with the usual associated symptoms. This applies only to a few cases at this particular intake. These can be managed by reduction of intake in those particular cases or by substitution of free ascorbic acid, either in whole or in part, with an ascorbic acid salt, such as sodium, magnesium or potassium ascorbate. Naturally such action requires that the right to use these salts should also be retained.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 General Conclusions

The concept of using risk assessment to develop USLs or guidance levels is reasonable, although, as recommended by the Select Committee on Agriculture, there should be sufficient evidence to justify such a regulatory approach if this is to be adopted. As indicated below, the Expert Committee of the EVM consider that such evidence is still wanting. However, a risk assessment approach is in principle favoured substantially over a 'multiple of the RDA' approach, the latter having absolutely no credible scientific basis. The following five overall conclusions are drawn in relation to the EVM draft report:

a) **Draft EVM report is fundamentally flawed**. Following the review of the EVM draft by the ANH Expert Committee, it is considered that the report is sufficiently flawed scientifically that all of its risk analyses, guidance and other recommendations should be regarded as questionable and therefore cannot be supported. The errors and omissions are sufficiently grave that it would not be possible to rectify the draft report without a very substantial revision.

b) **Inappropriate risk assessment model used**. The risk assessment approach used by the EVM is modelled closely on the US National Academy of Sciences (NAS) Risk Assessment Model, which was based on models developed originally to assess the health hazards of toxic chemicals in the environment. Such xenobiotics are likely to have significant negative effects on humans as well as other biological organisms. Extrapolation from animal or *in vitro* systems to humans is fraught with difficulties. The question should be asked: is a model based on inherently toxic substances relevant to the evaluation of nutrients that are essential to optimal human health and are components of a natural, healthy diet?

c) **Failure to justify approach**. The EVM has not justified either i) why studies on use of 'therapeutic' dosages of nutrients were specifically excluded from the review and risk assessment, and ii) why a framework to evaluate the necessity for regulation of dietary supplements, as proposed by the Select Committee on Agriculture in 1999, was not proposed.

d) **Absent data**. Critical to the development of USLs or guidance levels, is the consideration of adequate data for the risk assessment process. These data should be in the form of published peer-reviewed studies (not exclusively experimental studies) as well as adverse event data. The exclusion of UK adverse event data in relation to dietary supplements from the survey by the Medical Toxicology Unit (Shaw *et al* 1996) is a glaring omission.

e) **Conflicts of interest**. Five out of 12 (58%) of the Members of the EVM declared interests in the pharmaceutical industry, while no Member had exclusive interests in the non-pharmaceutical sector of the dietary supplement industry (see pp. 362-364 of the EVM report). This imbalance has clearly led to bias and is likely to be a major factor in the omission of key data. The problems associated with such bias in regulatory matters in Europe are discussed in a recent edition of the *British Medical Journal* (Abraham 2002; Bardelay & Kopp, 2002).

4.2 Specific conclusions relating to Vitamin B6

There is no evidence that the EVM has responded appropriately to recommendations made by the Select Committee on Agriculture. On 15 April 1999, the following question and answer was given in the UK Parliament[2]:

> **"Q: Dr. Iddon.** To ask the Minister of Agriculture, Fisheries and Food what steps he is taking to ensure that his ad hoc expert advisory group on vitamins and minerals takes note of the recommendations of the Agriculture Committee's report on vitamin B6 in relation to *(a)* the quality of scientific advice and *(b)* the use of safety factors. [79484]
>
> **A: Mr. Rooker.** Members of the Expert Group on Vitamins and Minerals are aware of the conclusions and recommendations of the Agriculture Select Committee's report on vitamin B6 and will take these into account in carrying out its remit. The Group will, as a matter of course, give consideration to the use of safety factors and the quality of the available scientific evidence, and I am satisfied they are capable of reaching their own conclusions on these matters."

Although there is no doubt that the EVM has reached its "own conclusions", the scientific quality of the EVM's conclusions on B6 (and other nutrients) are frequently dubious and appear to be based on very limited, selective data which 'fit' the generally low USLs proposed or suggested.

Specifically in relation to B6, the Select Committee on Agriculture made the following key recommendations[3]:

- "in relation to dietary supplements, the Government should withdraw its proposed draft regulations to limit the level of vitamin B6 per daily dose to 10 mg" (paragraph 23).

- "the Government should seek to introduce a voluntary limit, pending the report of the Expert Group on Vitamins and Minerals, with the industry, of 100 mg per daily dose. All dietary supplements containing vitamin B6 should display a clear warning that intakes above this level may carry health risks, particularly when taken over an extended period. No legislation should be considered until the Expert Group has reported" (paragraph 24).

In addition, the Select Committee recommended[2]:

- "We would ... urge that the Expert Group on Vitamins and Minerals be asked to produce recommendations for a framework for deciding whether regulation of dietary supplements is necessary at all, or whether consumer advice is sufficient" (paragraph 19).

- "It is our view that the doubts concerning the 1987 Dalton and Dalton study are so serious that it is scientifically unjustifiable to use them as the basis for

[2] http://www.parliament.the-stationery-office.co.uk/pa/cm199899/cmhansrd/vo990415/text/90415w05.htm
[3] http://www.parliament.uk/commons/selcom78/agripnts.htm

establishing a lowest observed adverse effect level in relation to vitamin B6 intake" (paragraph 20).

- "The evidence on the efficacy of vitamin B6 is inconclusive, and many consumers may experience a placebo effect rather than any actual health benefit. Nevertheless, such people are perfectly entitled to make such choices for themselves, so long as they are provided with sufficient information to avoid the potential health risks of high levels of intake, and so long as dietary supplements do not make medicinal claims. ... We trust that the unfortunate row which has taken place over vitamin B6 will act as a constant reminder to [the Expert Group on Vitamins and Minerals] of the need to base its recommendations and advice on sound and substantiated scientific knowledge, and adherence to a clear definition of the role and limits of Government intervention in this area as it recommends and Parliament agrees" (paragraph 25).

- "We recommend that, to assist in avoiding any repeat of the vitamin B6 controversy, consumer and industry interests should be able to nominate one or two independent scientific experts in nutrition and toxicology for appointment as full members of the [Expert Group on Vitamins and Minerals]" (paragraph 26).

In relation to Vitamin B6, the ANH Expert Committee conclude the following:

a) There is no evidence that the EVM have produced, as recommended by the Select Committee (paragraph 19), an adequate framework which evaluates whether regulation of dietary supplements is necessary, or whether consumer advice is sufficient;

b) Quite remarkably, the EVM have continued to use the Dalton & Dalton (1987) study to justify their very low USL of 10 mg per daily dose, despite its flaws being recognised by the EVM in their report;

c) The independent scientific experts on the EVM were given Observer status rather than full membership of the EVM and so were able to provide very little effective input and decision-making. One of these Observers (Dr Marilyn Glenville, upon approach by the ANH) informed the ANH that the EVM failed to consider a number of studies presented because they were not experimental in nature. Surprisingly, the EVM decided to include the Dalton & Dalton (1987) study which is both non-experimental and has been very widely discredited on the grounds of methodological errors.

d) There is no valid scientific basis for a USL below 50 mg per daily dose. We would endorse a limit of 100 mg per day on B6 supplements (the USL in healthy individuals being substantially higher than this), and/or a label warning against prolonged self-administration without medical advice.

e) The ANH Expert Committee would welcome the opportunity of submitting an alternative risk assessment on B6 to the EVM.

4.3 Recommendations

Based on the ANH Expert Committee's critique of the EVM Draft Report, the following recommendations are made:

- The analyses and conclusions of the EVM report are so questionable that **it is imperative that the recommended upper or guidance levels are not translated into UK law**.

- The EVM needs to **'go back to the drawing board' and review all data on adverse events and safety of micronutrients**.

- **The EVM membership should be expanded so that at least 50% of its members are acknowledged experts in nutritional medicine**, with no interests in the pharmaceutical industry.

- The risk assessments **should take better account of differences in susceptibility in population sub-groups** (e.g., age, gender, genetic, habit, lifestyle, diet-related factors).

- **Adverse event and non-experimental data should be preferred** over extrapolations from animal and *in vitro* studies.

- **Contraindications for particularly susceptible, minority sub-groups** (e.g., smokers taking β-carotene supplements) **should be stated on labels**, so that higher nutrient dosages remain available to the majority.

- **The effects of short-term use of high dose supplements should be considered quite separately from long-term usage.** Where appropriate, the potential adverse effects of long-term usage should be stated on product labels.

- **The existing models for risk assessment of nutrients are in urgent need of review**. In relation to the Food Supplements Directive, under which vitamin and mineral products in Europe in the future will be controlled, a negative rather than positive list should be prepared. The mode of action of each substance should be considered and all relevant data should be taken into account, including, particularly where research data are limited, adverse event data from countries where use-patterns are more or less equivalent. A new paradigm for risk assessment of nutrients should consequently be developed which is not based on that of inherently toxic substances.

- **New models are required for nutrient supplementation where all relevant evidence is considered and risk: benefit analyses are undertaken**. Such models should take into account the declining nutrient status of diets and increased exposures to environmental toxins. They should allow for optimum supplementation regimes for diverse population groups. They would need to consider the likely impact on health resulting from both the availability and non-availability of 'higher dose' supplements.

  The health risks and benefits of supplementation should be compared directly with pharmaceutical 'standards'. If 'higher dose' supplements are not re-classified as medicines, they will be more freely available to the public and can be administered as part of a preventative health management programme.

  A very substantial literature is developing on the benefits of supplementation. For example, Ames *et al* (2002) demonstrate some of the mechanisms by which high dose supplementation might ameliorate genetic polymorphisms resulting in problems as diverse as cancer, cardiovascular disease, haemolytic anaemia, Alzheimer's Disease, migraine and rages.

REFERENCES

Abraham JW (2002) Making regulation responsive to commercial interests: streamlining drug industry watchdogs. *British Medical Journal* 325: 1164.

Age-Related Eye Disease Study Research Group (2001) A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss. *Arch Ophthalmol* 119:1417-1436.

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. *New England Journal of Medicine* 330: 1029-1035.

Ames BN, Elson-Schwab I, Silver EA (2002) High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K_m): relevance to genetic disease and polymorphisms. *American Journal of Clinical Nutrition*, Vol. 75, No. 4, 616-658.

Bardelay D, Kopp C (2002) Commentary: Concern over drug industry's influence on regulatory policy in Europe. *British Medical Association* 325:1167-1168.

Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF (1998) Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. *Osteoporos Int* 8: 222-30.

Bendich A, Langseth L (1995) The health effects of vitamin C supplementation: a review. *J. Am. Coll. Nutr.* 14 (2):124-36.

Berger AR, Schaumburg HH, Schroeder C, Apfel S, Reynolds R (1992) Dose response, coasting, and differential fiber vulnerability in human toxic neuropathy. *Neurology* 42: 1367-1370.

Berger AR, Schaumburg HH, Schroeder C., Apfel S, Reynolds R (1992) Dose response, coasting, and differential fibre vulnerability in human toxic neuropathy: a prospective study of pyridoxine neurotoxicity. *Neurology* 42: 1367-1370.

Blank S, Scanlon KS, Sinks TH, Lett S, Falk H. (1995) An outbreak of hypervitaminosis D associated with the overfortication of milk from a home-delivery dairy. *Am J Public Health* 85: 656–9.

Cameron, E, Campbell, A (1974) The ortho-molecular treatment of cancer. Clinical trial of high dose ascorbic acid supplements in advanced human cancer. *Chemical and Biological Interactions* 9: 285-315.

Chambers JC, Ueland PM, Obeid OA, Wrigley J, Refsum H, Kooner JS (2000) Improved vascular endothelial function after oral B vitamins : An effect mediated through reduced concentrations of free plasma homocysteine. *Circulation* 102: 2479-83.

Chao CL, Chien KL, Lee YT. Effect of short-term vitamin (folic acid, vitamins B6 and B12) administration on endothelial dysfunction induced by post-methionine load hyperhomocysteinemia. *Am J Cardiol* 1999;84:1359-61.

Coker SB (1992) Postneonatal vitamin B6-dependent seizures. *Pediatr* 90: 221-3.

Coleman M, Steinberg G, Tippett J *et al* (1979) A preliminary study of the effect of pyridoxine administration ina group of hyperkinetic children: a double-blind crossover comparison with methylphenidate. *Biol Psychiatr* 14: 741-751.

Crowell GP, Roach ES (1983) Pyridoxine-dependent seizures. *Am Family Phys* 27: 183-6.

Diplock AT (1995) Safety of Antioxidant Vitamins and Beta-carotene, *American Journal of Clinical Nutrition* Dec 62 (6 Suppl): 1510S-1516S.

Downing D (1998) Pyridoxine in the UK. *Journal of Nutritional and Environmental Medicine* 1: 3-6.

Ervin RB, Wright JD, Kennedy-Stephenson J (1999) *Use of dietary supplements in the United States, 1988-94*. National Center for Health Statistics, Vital Health Stat 11 (244).

Fairfield KM, Fletcher RH (2002) Vitamins for chronic disease prevention in adults: scientific review. JAMA, June 19, 2002; 287(23): 3116-26.

FDA (Food & Drug Administration) (1997) Dietary Supplements Containing Ephedrine Alkaloids. Federal Register: June 4, 1997 (Volume 62, Number 107) (available on http://vm.cfsan.fda.gov/~lrd/fr97064a.html).

Foote JA, Giuliano AR, Harris RB (2000) Older adults need guidance to meet nutritional recommendations. *J Am Coll Nutr* : 19:628-640.

Gaby AR (1997) The safety of Vitamin B6. *Journal of Nutritional and Environmental Medicine* 7: 385-386.

Garewal HS, Diplock AT (1995) How ‘safe’ are antioxidant vitamins? *Drug Saf* 13: 8-14.

Glerup H, Mikkelsen K, Poulsen L *et al*. (2000) Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med* 247: 260–8.

Hathcock JN (1997) Vitamins and minerals: efficacy and safety. *American Journal of Clinical Nutrition* Aug 66 (2): 427-37.

Hennekens CH, Buring JE, Manson J-A E, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R (1996) Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *New England Journal of Medicine* 334: 1145-1149.

Herbert, V, Jacob, E, Wong, KTJ, Scott, J & Pfeffer, RD (1978) Low serum Vitamin B12 levels in patients receiving ascorbic acid in megadoses: studies concerning the effect of ascorbate on radioisotope Vitamin B12 assay. *American Journal of Clinical Nutrition* 31: 253-258.

Hughes, DA (1999) Effects of carotenoids on human immune function. *Proc Nutr Soc*. 58 (3): 713-718.

Jialal I, Grundy SM (1993) Effect of combined supplementation with alpha-tocopherol, ascorbate, and beta carotene on low-density lipoprotein oxidation. *Circulation* 88 (6):2780-2786.

Johnson, K.R., Jobber, J., Stonawski, B.J. (1980) Prophylactic vitamin D in the elderly. *Age and Ageing* 9: 121-7

Kataoka A, Imai H, Inayoshi S, Tsuda T (1993) Intermittent high-dose Vitamin C therapy in patients with HTLV-I-associated myelopathy, *Rinsho Shinkeigaku Mar* 33 (3): 282-8.

Kelley DS, Bendich A (1996) Essential nutrients and immunologic functions. *American Journal of Clinical Nutrition*, Vol 63, 994S-996S.

Klenner FR (1974) Significance of high daily intake of ascorbic acid in preventive medicine. *J Int Acad Prev Med* 1: 45-49.

Lazarou, J, Pomeranz, BH, Corey, PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *Journal of the American Medical Association*: 279:1200-1205.

Lehtonen-Veromaa M, Mottonen T, Irjala K *et al*. (1999) Vitamin D intake is low and hypovitaminosis D common in healthy 9- to 15-year old Finnish girls. *Eur J Clin Nutr* 53: 746–51.

Levine, M, Conry-Cantilena C, Wang, Y. *et al* (1996). Vitamin C pharmacokinetics in healthy volunteers. *Proceedings of the National Academy of Sciences* 93: 3704-3709.

Levine, M., Rumsey, SC. Daruwala, R. Park, JB. Wang, Y (1999) Criteria and Recommendations for Vitamin C Intake. *Journal of the American Medical Association* 281: 1415-1423.

Mai J, Sorensen PS, Hansen JC (1990) High dose antioxidant supplementation to MS patients. Effects on glutathione peroxidase, clinical safety, and absorption of selenium. *Biol Trace Elem Res* Feb 24 (2): 109-17.

Martineau J, Barthelemy C, Garreau B, Lelord G (1985) Vitamin B6, magnesium and combined B6-Mg therapeutic effects in childhood autism. *Biol Psychiatr* 20: 467-78.

Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, Griffin PM & Tauxe RV (1999) Food-Related Illness and Death in the United States. *Emerging Infectious Diseases* 5 (5).

Meyers DG, Maloley PA, Weeks D (1996) Safety of antioxidant vitamins, *Archives of Internal Medicine* 156 (9): 925-35.

Murray, M.T. 1996 *Encyclopaedia of Nutritional Supplements*, Prima Publishing.

National Academy of Sciences (1999) *Dietary Reference Intakes: A Risk Assessment Model for Developing Upper Intake Levels for Nutrients*. National Academy Press.

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. *New England Journal Medicine* 334: 1150-1155.

Park (1940) The therapy of rickets. *J Am Medic Assoc* 115: 370-9.

Parry G.J, Bredesen DE (1985) Sensory neuropathy with low-dose pyridoxine. *Neurology* 35: 1466-1468.

Patel V, Chaudhuri R, Wong J *et al* (1991) A trial of pyridoxine in the treatment of diabetic mononeuropathy: a double-blind, placebo controlled, crossover study. *Diabetes* 40 (Suppl 1): 511A [abstr no. 2039].

Pauling, L. (1979) *Linus Pauling before Congress*, In Williams, Roger J. & Kalita, Dwight K. (Eds.) *A Physician's Handbook on Orthomolecular Medicine*. Keats Health Science Books, New Canaan, CT.

Rivers JM (1989) Safety of high-level Vitamin C ingestion. *J Vit. & Nutrit Res*. Suppl 30: 95-102.

Schaumburg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ (1983) Sensory neuropathy from pyridoxine abuse. *New England Journal of Medicine* 309: 445-448.

Serenius F, Elidrissy AT, Dandona P. (1984) Vitamin D nutrition in pregnant women at term and in newly born babies in Saudi Arabia. J Clin Pathol 37: 444–7.

Shaw D, Kolev S, Leon C (1996) *Toxicological problems resulting from exposure to traditional medicines and food supplements. Traditional Remedies Surveillance Project, Medical Toxicology Unit*, Guy's and St Thomas' Hospital Trust, London.

Shrimpton DH (1995) *Essential Nutrients in Supplements*. European Federation of Associations of Health Product Manufacturers: 1-32.

Stein HB *et al* (1976) Ascorbic acid-induced uricosuria: a consequence of megavitamin therapy. *Annals of Internal Medicine* 84: 385-388.

Tjellesen L, Hummer L, Christiansen C, Rodbro P. (1986) Different metabolism of vitamin D2/D3 in epileptic patients treated with phenobarbitone/phenytoin. *Bone* 7:337-42.

Trang H, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. (1998) Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. *Am J Clin Nutr* 68: 854–8.

Undas A, Domagala TB, Jankowski M, Szczeklik A (1999) Treatment of hyperhomocysteinemia with folic acid and vitamins B12 and B6 attenuates thrombin generation. *Thromb Res* 95(6): :281-8.

Urivetsky M, Kessaris D., Smith AD (1992) Ascorbic acid overdosing: a risk for calcium oxalate nephrolithiasis. *Journal of Urology* 147:1215-1218.

Vieth R (1999) Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 69: 842-56.

Vieth R (2001) Vitamin D Nutrition and its Potential Health Benefits for Bone, Cancer and Other Conditions. *J Nutr Env Med* 11: 275–291.

Vieth, R., Chan P-CR, MacFarlane GD (2001a) Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 73: 288-94.

Vieth R, Cole DE, Hawker G, Trang H, Rubin LA. (2001b) Wintertime vitamin D insufficiency is common in young Canadian women, and their vitamin D intake does not prevent it. *Eur J Clin Nutr* 55:1091-7.

Wandzilak, T.R. *et al* (1994) Effect of high dose Vitamin C on urinary oxalate levels. *Journal of Urology* 151: 834-837.

Williams MJ, Harris RI, Dean BC (1985) Controlled trial of pyridoxine in the Premenstrual Syndrome. *J Int Med Res* 13: 174-9.