Bundesinstitut für Risikobewertung (BfR)

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

BfR opinion from November 13th 2002

On 2 October 2002 the United Kingdom at a meeting of the Standing Committee on the Food Chain and Animal Health, Section General Food Law, indicated that its national Expert Group had submitted its draft report on vitamins and minerals on 29 August 2002. It contains upper levels of various standards for safe total intake ("safe upper levels"). The United Kingdom has requested an opinion on this draft report which can also be accessed on the Internet on:
http://www.food.gov.uk/science/ouradvisors/vitandmin/evmreport.

With the publication of this draft report another body has turned its attention to this subject. The terms of reference and the methods are clearly formulated. The draft reports published are transparent and well-structured.

Attention is drawn to the fact that the standing expert body for food Issues of the European Commission (Scientific Committee on Food - SCF) is also working on the laying down of upper levels for the total intake of vitamins and minerals. The first of these upper levels (UL) have already been defined and published as opinions of the SCF.[1]

The activities of various international expert bodies underline the urgent need to solve the existing problems in this area.

For some time now, BfR (and before BgVV) has been examining this subject albeit with the difference that maximum levels for the admixture of a vitamin or mineral to supplements (individual products) are derived. As far as we know no other body has endeavoured to do this[2].

On the EVM approach:

The EVM Expert Group elaborates upper levels for the total intake of vitamins and minerals from all sources whereby, in some cases, it is unclear to what extent the one or the other intake source has been taken into account. From the difference between the dietary vitamin and mineral intake and the derived upper level, EVM estimates the possible additional safe intake through the total consumption of supplements and gives corresponding upper levels for this. By contrast, the proposals of BfR only refer to maximum levels for the use of minerals in individual food supplements, i.e. to individual products. That is why the work results of EVM cannot be compared with the derivations of BfR.

Depending on the availability of reliable qualitative and quantitative data on adverse reactions, which have occurred with various doses of micronutrients, EVM derives the recommendation of **Safe Upper Levels (SULs)**.

In the case of inadequate data for the derivation of an SUL, another concept is introduced, a far more uncertain **guidance value.** This value indicates, in the opinion of the EVM experts, the level at which no harmful effects are to be expected from life-long intake.

When deriving upper levels, EVM in principle embarks on two courses depending on the respective data situation: either "total intake" or "supplemental intake":

In the first case a safe upper level (SUL) can be derived on the basis of the available data for total intake from all sources (SUL-total intake, e.g. 10 mg/day for copper). Dietary intake and intake from other known sources is deducted from this upper level (in the case of copper 5 mg/day). The

[1] http://europa.eu.int/comm/food/fs/sc/scf/index_en.html
[2] Regelungs- und Höchstmengenvorschläge zum Schutz des Verbrauchers vor Überdosierung beim Verzehr von Nahrungsergänzungsmitteln (NEM) und angereicherten Lebensmitteln mit Vitaminen und Mineralstoffen (Teil I; Mineralstoffe), http://www.bgvv.de/sixcms_upload/media/70/mineralstoffe.pdf

difference to the upper level (in the opinion of EVM) is the available scope for additional intake through food supplements and/or from new sources of fortification, i.e. in the case of copper 5 mg/day for additional intake from food supplements and fortified foods.

In the second case, it is only possible, on account of the data situation, to derive an SUL for intake with supplements (SUL-supplemental intake, e.g. 25 mg/day for zinc) and not a "SUL-total intake". EVM believes that by adding up the normal dietary intake of vitamins and minerals and intake from other known sources, it is possible to estimate a total safe upper level (SUL-total, in the case of zinc: 25mg/day + max. intake of 17.2 mg = 42.2 mg) and, once again, a scope can be given for the additional intake from food supplements and fortified foods.
It should be noted that EVM, unlike BfR, does not derive any maximum levels for the admixture of a vitamin or mineral substance to supplements (individual products) but does give the remaining scope for total intake from supplements from the above-mentioned calculation of difference.

Methods and results

Like other bodies, EVM also uses the relevant scientific literature for its assessment which could be taken into account here up to September 2001. It either undertakes the risk assessment itself or has it done by external contractors.

An assessment was undertaken of vitamins and minerals which are either essential or present in food supplements with the exception of germanium which is neither essential nor available on the British market. It can, however, be obtained from other sources as a supplement. For the purposes of risk assessment, data from clinical trials and from animal experiments were used, with priority being given to data from humans.

For most vitamins and minerals exposure data are based on individual consumption data from the National Diet and Nutrition Survey of 1986/87. In the case of trace elements and vitamin K, data from the Total Diet Study were used, an ongoing study in which the average UK diet is analysed. The potential exposure to micronutrients from supplements was estimated using information from the OTC Directory 2001-20002.

In principle, the database which can be used to assess the safety in use of vitamins and minerals, is full of gaps. There is a particular lack of well-designed comparative human studies of reasonable size, significant duration and different levels of intake in order to permit statements about long-term tolerance. Furthermore, there are very few data in particular about vulnerable groups in the population such as children or older people. It should be stressed in particular that many of the clinical studies used for risk assessment were not designed to detect adverse effects but rather to detect potentially beneficial effects of vitamins and minerals and only permit limited statements about adverse effects, if at all. For most vitamins and minerals the Group was unable to derive safe upper levels; where possible, in these cases, guidance levels were given instead. These guidance levels should not be placed on a par with SULs as they draw on a far more restricted database. For some substances, recourse had to be made to animal experiments and the data extrapolated to humans using empirical uncertainty factors. For some substances there were not even enough data for that (germanium, vanadium and sodium chloride); two minerals could not be considered in detail (sulphur, fluoride).

After detailed assessment of the available data for each individual micronutrient and risk assessment based thereon, **Safe Upper Levels** (SULs) were established for 9 of the 34 substances (**vitamin B6, ß-carotene, vitamin E, boron, copper, nickel, selenium, zinc, silicon** and **guidance values** for the other 22.

Upper Levels of other Expert Committees

With regard to the daily intake of vitamins and minerals, upper levels have already been elaborated[3] by various state and non-state committees using different methods and procedures. Besides the EU Scientific Committee on Food (SCF), other bodies like the Nordic Council of Ministers (Food) and the US Food and Nutrition Board (FNB) have recently derived safe upper levels for the

[3] EXPERT GROUP ON VITAMINS AND MINERALS PAPER FOR DISCUSSION 7 May 1999:VITAMINS AND MINERALS – PREVIOUS METHODS OF ASSESSMENT EVM/99/13/P ;http://archive.food.gov.uk/dept_health/pdf/evmpdf/evm13fin.pdf

individual substances. In English-speaking countries these upper levels are called "Upper Safe Intake Level" or as used in the SCF, "Tolerable Upper Intake Level (UL)".

As a consequence of the parallel assessment and elaboration of upper levels for total safe intake of vitamins and minerals in the form of Safe Upper Levels or Tolerable Upper Intake Levels and various maximum levels like, in this case the so-called guidance levels, there will probably be conflicts when different ULs are derived. Furthermore, the many different values, which are to be used as the basis for action options, will not contribute to the harmonisation of different national decisions.

By way of example, here are two substances with deviating assessment results:

- Manganese: SCF: no UL can be derived; EVN: *For guidance purposes, it is reasonable to assume that in the general population, an intake of up to 4mg manganese/day in addition to the diet would be unlikely to produce adverse effects.*

  Using the same data, SCF reaches the conclusion that because of the narrow limits between the oral test concentration with adverse effects in humans and because of the estimated intake from food as a consequence of the neurotoxicity and the potentially higher sensitivity of some groups in the population, there should be no exposure to manganese in addition to intake from the normal diet, particularly as there is no evidence of a health benefit.[4]

- Magnesium: FNB: UL350 mg[5]; SCF: UL: 250 mg[6]; EVM: Guidance: 400 mg[7].

  Whereas in the SCF expert report of 11 October 2001 based on 20 clinical studies, an LOAEL and a NOAEL are derived for magnesium in conjunction with diarrhoea, EVM is of the opinion that the database is too narrow for the laying down of a Safe Upper Level and falls back on the (lowest) magnesium dose of 360 – 470 mg/day for the derivation of its guidance value at which mild diarrhoea occurred in the studies it took into account (n=7).

Within the framework of the necessary harmonisation, we believe it would be beneficial if all EU Member States were to consider the UL values of SCF as binding.

It should also be borne in mind that assessments were undertaken for a number of trace elements for which, up to now, no physiological function could be detected in humans and which, in conformity with Annex I of the EU Directive 202/46/EC of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, should not, in our opinion, be used in food supplements like: boron, silicon, tin, germanium and vanadium. Furthermore, the database was considered to inadequate in the case of germanium and vanadium to be able to derive a safe upper level or a guidance value.

Guidance values in the case of an inadequate database

Given the lack of toxicological data, EVM frequently falls back in its risk assessment on therapeutic studies with a limited number of patients with specific diseases who have taken corresponding therapeutic doses over a limited period of time which are far higher than the amounts contained in food supplements. The extrapolation of the “safe“ maximum levels obtained in this way, for which

[4] SCF/CS/NUT/UPPLEV/21 FINAL, 28.Nov 2000, Opinion of the Scientific Committee on Food on Tolerable Upper Intake Level of Manganese
[5] referred to food supplements
[6] referred to food supplements
[7] p.297: For Guidance purposes only, 400mg/day supplemental magnesium would not be expected to result in any significant adverse effects.

no adverse effects were observed, to a healthy population and lifelong intake appears questionable to us in some cases.

By way of example, the following substances are mentioned:

Vitamin K: guidance value: 1 mg, thiamine: guidance value: 103 mg, riboflavin: guidance value: 100 mg, vitamin $B_{12:}$ guidance value: 1 mg.
In particular, the last value seems to us to merit criticism for several reasons. Firstly, the value was, partly derived from a therapeutic study in patients with pernicious anaemia whose resorption of vitamin B_{12} was considerably reduced because of the missing intrinsic factor. Secondly, in healthy humans rising intake leads to a reduction in the resorption rate. Hence, in our opinion, the use of the therapeutic dose of 1 mg is not suitable as a guidance value for supplements.

In the opinion of BfR the precautionary principle should be applied in cases in which there are insufficient data and gaps in knowledge. In this context, recommendations for the laying down of maximum levels should be oriented towards nutritional needs particularly as for healthy people there is no evidence of an (additional) benefit from higher daily intake amounts. Under no circumstances, however, should therapeutic doses be administered as they are reserved for the medicinal products. The safety level for food supplements must be higher in theopinion of BfR. According to the opinion represented here, it is a contradiction of the consumption designation of a food supplement if the product contains far higher amounts of nutrients than those which would normally be consumed through daily diet[8].

The problem of the growing practice of the fortification of foods for general consumption with vitamins and minerals is not taken into account in the Draft EVM Expert Report of EVM. Nor does it address questions about whether fortification is reasonable, up to which level it should be tolerated in order to avoid overdoses or adverse interactions.

Since BfR risk assessments, particularly for vitamin supplements, have not yet been completed, BfR refrains from giving a more detailed opinion at this point.

[8] Grossklaus R, BgVV, Bewertung von Nahrungsergänzungsmitteln aus der Sicht des Lebensmittel- und Bedarfsgegenständegesetzes, Ernährungs-Umschau 2000; 47:132-141