"Safe Upper Levels" for Nutritional Supplements: One Giant Step Backward

Alan R. Gaby, M.D.[1]

Introduction

In May, 2003, the Expert Group on Vitamins and Minerals (EVM), an advisory group originally commissioned in 1988 by the then Ministry of Agriculture Fisheries and Food, and subsequently reporting to the Food Standards Agency in England, published a report that set "Safe Upper Levels" (SULs) for the doses of most vitamin and mineral supplements. The establishment of SULs was based on a review of clinical and epidemiological evidence, as well as animal research and in vitro studies. For those nutrients for which the available evidence was judged insufficient to set an SUL, the EVM instead established "Guidance Levels", which were to be considered less reliable than SULs.

This writer's analysis of the EVM report reveals that the dose limits were set inappropriately low for many vitamins and minerals, well below doses which have been used by the public for decades with apparent safety. While the release of this 360-page document would be of little import, were it to be used solely as a manifesto for the pathologically risk-averse, preliminary indications are that it could be used very actively to support the arguments of those who are seeking to ban the over-the-counter sale of many currently available nutritional supplements. If the report is used that way, then the public health could be jeopardized.

On May 30, 2002, the European Union adopted Directive 2002/46/EC, which established a framework for setting maximum limits for vitamins and minerals in food supplements. The EVM report is seen by the UK government as the basis for its negotiating position in the process of setting these pan-European limits.

The apparent anti-nutritional-supplement, anti-self-care bias that permeated the process of setting safety levels is evident both in the way in which the SUL was defined and in the fact that the benefits of nutritional supplements were purposely ignored. The SUL was defined as the maximum dose of a particular nutrient "that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety." In other words, it is the highest dose that is unlikely to cause anyone any harm, ever, under any circumstance. Furthermore, the EVM was specifically instructed not to consider the benefits of any of the nutrients, and not to engage in risk/benefit analysis.[1]

There is little or no precedent in free societies for restricting access to products or activities to levels that are completely risk-free. Aspirin causes intestinal bleeding, water makes people drown, driving a car causes accidents, and free speech may offend the exquisitely offendable. Politicians and bureaucrats do not seek to ban aspirin or water or driving or free speech, because their benefits outweigh their risks. For vitamins and minerals, however, some authorities seem to believe that unique safety criteria are needed.

Moreover, the government's instructions to disregard the many documented benefits of nutritional supplements introduced a serious bias into the evaluation process. As the EVM acknowledged, determining safety limits involves an enormous degree of uncertainty and a fairly wide range of possible outcomes. The committee might have established higher safety limits than it did, had it been told to weigh benefits against risks. The government's instructions appeared to be an implicit directive to err on the side of excluding doses that are being used to prevent or treat

1. 301 Dorwood Dr., Carlisle, PA 17013

disease. And that is what the EVM did, often by making questionable interpretations of the data, and doing so in what appears to have been an arbitrary and inconsistent manner.

Riboflavin Guidance Level

A typical example of the EVM's dubious approach to establishing safety limits is its evaluation of riboflavin. The committee acknowledged that no toxic effects have been reported in animals given an acute oral dose of 10,000 mg/kg of body weight, or after long-term ingestion of 25 mg/kg/day (equivalent to 1,750 mg/day for a 70-kg human). Moreover, in a study of 28 patients taking riboflavin for migraine prophylaxis, a dose of 400 mg/day for 3 months did not cause any adverse effects. Despite a complete absence of side effects at any dose in either humans or animals, the EVM set the Guidance Level for riboflavin at 40 mg/day. That level was established by dividing the 400 mg/day used in the migraine study by an "uncertainty factor" of 10, to allow for variability in the susceptibility of human beings to adverse effects.

A more appropriate conclusion regarding riboflavin would have been that no adverse effects have been observed at any dose, and that there is no basis at this time for establishing an upper limit. If the EVM's recommendation is used to limit the potency of riboflavin tablets to 40 mg, then migraine sufferers will have to take 10 pills per day, in order to prevent migraine recurrences.[2]

Vitamin B_6 Safe Upper Level

Similar reasoning led to an SUL of 10 mg/day for vitamin B_6, even though this vitamin has been used with apparent safety, usually in doses of 50 to 200 mg/day, to treat carpal tunnel syndrome, premenstrual syndrome, asthma, and other common problems. The SUL for vitamin B_6 was derived from an animal study, in which a dose of 50 mg/kg of body weight/day (equivalent to 3,000 mg/day for a 60-kg person) resulted in neurotoxicity. The EVM reduced that dose progressively by invoking three separate "uncertainty factors:" 1) by a factor of 3, to extrapolate from the lowest-observed-adverse-effect-level (LOAEL) to a no-observed-adverse-effect-level (NOAEL); 2) by an additional factor of 10, to account for presumed inter-species differences; and 3) by a further factor of 10 to account for inter-individual variation in humans. Thus, the neurotoxic dose in animals was reduced by a factor of 300, to a level that excludes the widely used 50- and 100-mg tablets.

The decision to base the SUL for vitamin B_6 on animal data (modified by a massive "uncertainty factor") was arbitrary, considering that toxicology data are available for humans.[3] A sensory neuropathy has been reported in some individuals taking large doses of vitamin B_6.[4,5] Most people who suffered this adverse effect were taking 2,000 mg/day or more of pyridoxine, although some were taking only 500 mg/day. There is a single case report of a neuropathy occurring in a person taking 200 mg/day of pyridoxine, but the reliability of that case report is unclear. The individual in question was never examined, but was merely interviewed by telephone after responding to a local television report that publicized pyridoxine-induced neuropathy.[6]

Because pyridoxine neurotoxicity has been known to the medical profession for 20 years, and because vitamin B_6 is being taken by millions of people, it is reasonable to assume that neurotoxicity at doses below 200 mg/day would have been reported by now, if it does occur at those doses. The fact that no such reports have appeared strongly suggests that vitamin B_6 does not damage the nervous system when taken at doses below 200 mg/day. As the EVM did with other nutrients for which a LOAEL is known for humans, it could have divided the vitamin B_6 LOAEL (200 mg/day) by 3 to obtain an SUL of 66.7 mg/day. Had the committee been allowed to evaluate both the benefits and risks of vitamin B_6, it probably would have established the SUL at that level, rather than the 10 mg/day it arrived at through serial decimation of the animal data.

Manganese Guidance Level

Chronic inhalation of high concentrations of airborne manganese, as might be encountered in mines or steel mills, has been reported to cause a neuropsychiatric syndrome that resembles Parkinson's disease. In contrast, manganese is considered one of the least toxic trace minerals when ingested orally, and reports of human toxicity from oral ingestion are "essentially nonexistent."[7] The neurotoxicity that occurs in miners and industrial workers may result from a combination of high concentrations of manganese in the air and, possibly, direct entry of nasally inhaled manganese into the brain (bypassing the blood-brain barrier).

In establishing a Guidance Level for manganese, the EVM cited a study by Kondakis et al., in which people exposed to high concentrations of manganese in their drinking water (1.8-2.3 mg/L) had more signs and symptoms of subtle neurological dysfunction than did a control group whose drinking water contained less manganese.[8] The committee acknowledged that another epidemiological study by Vieregge et al. showed no adverse effects among individuals whose drinking water contained up to 2.1 mg/L of manganese.[9] The EVM hypothesized that these studies may not really be contradictory, since the subjects in the Kondakis study were, on average, 10 years older than were those in the Vieregge study, and increasing age might theoretically render people more susceptible to manganese toxicity. Based on the results of these two studies, the EVM established a Guidance Level for supplemental manganese of 4 mg/day for the general population and 0.5 mg/day for elderly individuals.

There are serious problems with the EVM's analysis of the manganese research. First, the committee overlooked that fact that in the Kondakis study the people in the high-manganese group were older than were those in the control group (mean age, 67.6 vs. 65.6 years). Many of the neurological symptoms that were investigated in this study are nonspecific and presumably age related, including fatigue, muscle pain, irritability, insomnia, sleepiness, decreased libido, depression, slowness in rising from a chair, and memory disturbances. The fact that the older people had more symptoms than did the younger people is not surprising, and may have been totally unrelated to the manganese content of their drinking water.

Second, the EVM broke its own rules regarding the use of uncertainty factors, presumably to avoid being faced with an embarrassingly low Guidance Level for the general population. In setting the level at 4 mg/day, the committee stated: "No uncertainty factor is required as the NOAEL [obtained from the Vieregge study] is based on a large epidemiological study." As a point of information, the Nurses' Health Study was a large epidemiological study, enrolling more than 85,000 participants. The Beaver Dam Eye Study was a medium-sized epidemiological study, enrolling more than 3,000 participants. In contrast, in the Vieregge study, there were only 41 subjects in the high-manganese group, making it a very small epidemiological study. In its evaluation of the biotin, riboflavin, and pantothenic acid research, the EVM reduced the NOAEL by an uncertainty factor of 10, in part because only small numbers of subjects had been studied. Considering that more subjects were evaluated in the pantothenic acid research[10] (n=94) than in the Vieregge study (n=41), it would seem appropriate also to use an uncertainty factor the for manganese data. Applying an uncertainty factor of 10 to the Vieregge study would have produced an absurdly low Guidance Level of 0.4 mg/day for supplemental manganese, which is well below the amount present in a typical diet (approximately 4 mg/day) and which can be obtained by drinking several sips of tea. Parenthetically, in a study of 47,351 male health professionals, drinking large amounts

of tea (a major dietary source of manganese) was associated with a reduced risk of Parkinson's disease, not an increased risk.[11] In changing its methodology to avoid reaching an indefensible conclusion, the EVM revealed the arbitrary and inconsistent nature of its evaluation process.

Niacin (nicotinic acid) Guidance Level

Large doses of niacin (such as 3,000 mg/day) can cause hepatotoxicity and other significant side effects. The EVM focused its evaluation, however, on the niacin-induced skin flush, which occurs at much lower doses. The niacin flush is a sensation of warmth on the skin, often associated with itching, burning, or irritation that occurs after the ingestion of niacin and disappears relatively quickly. It appears to be mediated in part by the release of prostaglandins. The niacin flush is not considered a toxic effect per se, and there is no evidence that it causes any harm. People who do not like the flush are free not to take niacin supplements or products that contain niacin. For those who are unaware that niacin causes a flush, an appropriate warning label on the bottle would provide adequate protection.

Granting, for the sake of argument, that the niacin flush is an adverse effect from which the public should be protected, the EVM's Guidance Level still is illogical. The committee noted that flushing is consistently observed at a dose 50 mg/day, which it established as the LOAEL. That dose was reduced by an uncertainty factor of 3, in order to extrapolate the LOAEL to a NOAEL. Thus, the Guidance Level was set at 17 mg/day, which approximates the RDA for the vitamin. The EVM also noted, however, that flushing has been reported at doses as low as 10 mg, so the true LOAEL is 10 mg/day. Applying the same uncertainty factor of 3 to the true LOAEL would have yielded a Guidance Level of a paltry 3.3 mg/day, which probably is not enough to prevent an anorexic person from developing pellagra. As with manganese, the EVM applied its methodology in an arbitrary and inconsistent manner, so as to avoid being faced with an embarrassing result.

Vitamin C Guidance Level

The EVM concluded that vitamin C does not cause significant adverse effects, although gastrointestinal (GI) side effects may occur with high doses. The committee therefore set a Guidance Level based on a NOAEL for GI side effects. It is true that taking too much vitamin C, just like eating too many apples, may cause abdominal pain or diarrhea. The dose at which vitamin C causes GI side effects varies widely from person to person, but can easily be determined by each individual. Moreover, these side effects can be eliminated by reducing the dose. Most people who take vitamin C supplements know how much they can tolerate; for those who do not, a simple warning on bottles of vitamin C would appear to provide the public all the protection it needs. Considering the many health benefits of vitamin C, attempting to dumb down the dose to a level that will prevent the last stomachache in Europe is not a worthwhile goal. However, as mentioned previously, the EVM was instructed to ignore the benefits of vitamin C.

Granting, for the sake of argument, that there is value in setting a Guidance Level for GI side effects, the EVM did a rather poor job of setting that level. The committee established the LOAEL at 3,000 mg/day, based on a study of a small number of normal volunteers.[12] An uncertainty factor of 3 was used to extrapolate from the LOAEL to a NOAEL, resulting in a Guidance Level of 1,000 mg/day. However, anyone practising nutritional medicine knows that some patients experience abdominal pain or diarrhea at vitamin C doses of 1,000 mg/day or less, and the EVM did acknowledge that GI side effects have been reported at doses of 1,000 mg.

It is disingenuous to set a NOAEL and then to concede that effects do occur at the no-effect level. To be consistent with the methodology it used for other nutrients, the committee should have set the LOAEL at 1,000 mg/day, and reduced it by a factor of 3 to arrive at a NOAEL of 333 mg/day. The EVM was no doubt aware of the credibility problems it would have faced, had it suggested that half the world is currently overdosing on vitamin C. To resolve its dilemma, the committee used a scientifically unjustifiable route to arrive at a seemingly politically expedient outcome.

Conclusion

These and other examples from the report demonstrate that the EVM applied its methodology in an arbitrary and inconsistent manner, in arriving at "safety" recommendations that are excessively and inappropriately restrictive. While the directive to evaluate only the risks, and to ignore the benefits, of nutritional supplements created a rigged game, the members of the EVM appeared to be willing participants in that game.

If the EVM report is used to relegate currently available nutritional supplements to prescription-only status, then millions of people would be harmed, and very few would benefit. It would be of little consolation that the higher doses of vitamins and minerals could still be obtained with a doctor's prescription, because most doctors know less about nutrition than do many of their patients. Moreover, the overburdened health-care system is in no position to take on the job of gatekeeper of the vitamin cabinet; nor is there any need for it to do so.

Ironically, as flawed as the EVM report is, its recommendations may ultimately prove to be "as good as it gets" in Europe. Other European countries are recommending that maximum permitted levels be directly linked to multiples of the RDA, which could result in limits for some nutrients being set substantially lower than those suggested in the EVM report.

While some nutritional supplements can cause adverse effects in certain clinical situations or at certain doses, appropriate warning labels on vitamin and mineral products would provide ample protection against most of those risks.

References

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