

UPPER SAFETY LIMITS FOR VITAMINS — WHY HAVE DIFFERENT AUTHORITIES SET DIFFERENT GUIDANCE?

In this article, Pamela Mason explains how upper safety limits for vitamins and minerals are set and why they may differ depending on which authority has set them

The publication of the United Kingdom's Expert Vitamin and Mineral (EVM) group report¹ on safe upper levels for vitamins and minerals has stimulated a great deal of debate. This is partly because the levels the EVM group has set differ from those set by other authorities in Europe and the United States (see Table 1).

In some cases, the differences are quite large. For vitamin A, the guidance level for total intake in the UK is a maximum of 1,500µg retinol equivalents per day, while the level set by authorities in the European Union (EU) and the US is 3,000µg. In the UK, the guidance level for the upper intake of vitamin C from supplements is 1,000mg while in the US, the upper intake level from all sources (food and supplements) is 2,000mg. For beta-carotene, the EVM group has set a safe upper level of 7mg from supplements, while neither the authorities in the EU nor the US thought there were sufficient data to set a figure. This was not because they were happy that beta-carotene is safe at high intakes: indeed, the US advised that the general population should obtain its beta-carotene from fruits and vegetables, not from supplements.

None of these levels is yet enshrined in law — they are guidelines only — but lack of agreement is potentially confusing for pharmacists and other health professionals, as well as for supplement users. Manufacturers are also concerned because of the potential for the hindrance of free circulation of products within the EU and from other countries. The Council for Responsible Nutrition (CRN) in the US (a trade association) has called for clarification and has suggested that the World Health Organization sets harmonised levels that supersede those in existence already.

During the next couple of years, the European Commission is due to set maximum limits — not for vitamin and mineral intake per se, but for permissible levels of vitamins and minerals in supplements, and these levels will eventually be spliced into the European Directive on Food Supplements. (In its current form, this directive will be implemented into UK law on 31 July 2003). How much the EC will be influenced by the EVM report is unclear, but the UK Food Standards Agency (FSA) will be sending a copy of the report to Brussels.

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WHICH AUTHORITIES HAVE SET UPPER SAFE LEVELS?

Concern about overdosing on vitamins is as old as their discovery during the early part of the 20th century. Fat-soluble vitamins, for example, have long been known to cause toxicity in high doses. However, it is the much publicised benefits of taking vitamin supplements, the sheer choice of products on the market, together with the knowledge that up to half the population in Western countries take them that has fuelled the added safety concerns of more recent years.

The supplement industry has been working with the concept of upper safety limits for 18 years, and in October 1997, the European Federation of Health Product Manufacturers (EHPM) association and the Council for Responsible Nutrition established safe upper levels for 25 vitamins and minerals.² The approach they used was to base the upper level well below that at which a significant adverse effect had been reported in the literature. The author of the report reviewed the literature, identified levels of intake which were associated with adverse effects (where adverse effects had been noted), and set safe upper levels for both long-term and short-term consumption. The CRN/EHPM levels shown in Table 1 are those which were set for long-term consumption and they relate to intakes from supplements alone, not total intake. It is important to be aware that these figures, like the upper safety limits set by the other authorities in Table 1, are not recommendations for intake, but guidelines for maximum daily doses of nutrients.

At about the same time, the Food and Nutrition Board (FNB) of the US National Academy of Sciences³⁻⁶ also began to set upper safety limits for vitamins and minerals and, in 2000, the European Commission's Scientific Committee on Food (SCF)⁷ followed suit. So far the SCF has considered 21 nutrients, and guidance on some (eg, vitamin C and iron) is still to come. The report from the UK's EVM group is the most recent, although other authorities, for example, in Scandinavia, are working on the same issue.

HOW ARE THE FIGURES SET?

Basically, the EVM group, the SCF and the FNB all used similar methodology to set their upper safety limits. This involved four main stages:

- Hazard identification
- Hazard characterisation

- Exposure assessment
- Risk characterisation

Hazard identification Essentially, hazard identification means identification of the known or potential adverse effects of a nutrient. The literature was reviewed for studies — human, animal and *in vitro* — that had considered safety in relation to vitamins and minerals. All three authorities found this difficult, not only because of a lack of good quality nutrition trials but also because most studies of vitamins and minerals to date have tended to investigate potential benefits rather than adverse effects. Randomised controlled trials in humans were used as evidence where possible, but failing that, less robust human studies or studies in animals and test tubes were used. None of the authorities used systematic review type methodology.

Hazard characterisation When any adverse effects had been identified, the relationship between the dose of the nutrient and the adverse effect(s) was evaluated. Following the dose-response assessment, the safe upper level was set. This involved the determination of three factors:

NOAEL NOAEL is the "no observed adverse effect level", ie the highest intake of a nutrient at which no adverse effects have been observed. For example, the US set a NOAEL of 200mg for vitamin B₆ because according to its interpretation of the literature, this is the highest intake of vitamin B₆ where no peripheral neuritis has been observed.

LOAEL LOAEL is the "lowest observed adverse effect level", ie the lowest intake of a nutrient at which an adverse effect has been demonstrated. For example, the UK set a LOAEL of 20mg for beta-carotene because it considered this to be the lowest intake of beta-carotene where an increased risk of cancer has been observed in smokers.

Uncertainty factor An uncertainty factor is the uncertainty associated with, for example, extrapolating data from:

- Animals to humans (a large uncertainty factor is applied if it is believed that animal data underpredict average human responses to a nutrient)
- Studies involving few subjects to the whole population
- Subsections of the population (eg, individuals with a disease or in a particular age group) to the general, healthy population

TABLE 1: GUIDANCE ON DAILY INTAKES OF VITAMINS AND MINERALS FOR ADULTS

Vitamin/mineral	*EU RDA	†EVM (UK)	‡EHPM/CRN	§FNB (US)	¶SCF (EU)
Vitamin A (retinol equivalent) (µg)	800	1,500 (G, T)	2,300	3,000	3,000
Betacarotene (mg)		7 (U, S)	20	-	-
Vitamin D (cholecalciferol) (µg)	5	25 (G, S)	10	50	50
Vitamin E (tocopherol) (mg)	10	540 (U, S) (800 IU)	800	1,000	300
Vitamin K (µg)		1,000 (G, S)		-	
Vitamin B ₁ (thiamine) (mg)	1.4	100 (G, S)	100	-	-
Vitamin B ₂ (riboflavine) (mg)	1.6	100 (G, S); 43 (G, T)	200	-	-
Vitamin B ₆ (pyridoxine) (mg)	2	10 (U, S)	100	100	25
Vitamin B ₁₂ (cobalamin) (µg)	1	2,000 (G, S)	3,000	-	-
Niacin (mg)	18		150	35	
Nicotinamide (mg)		500 (G, S); 560 (G, T)	900		900
Nicotinic acid (mg)		17 (G, S)	10		10
Folic acid (µg)	200	1,000 (G, S); 1,500 (G, T)	400	1,000	1,000
Biotin (µg)	150	900 (G, S); 970 (G, T)	2,500	-	-
Pantothenic acid (mg)	6	200 (G, S); 210 (G, T)	1,000	-	-
Vitamin C (ascorbic acid) (mg)	60	1,000 (G, S)	2,000	2,000	
Calcium (mg)	800	1,500 (G, S)	1,500	2,500	2,500
Magnesium (mg)	300	400 (G, S)	300	350	250
Phosphorus (mg)	800	250 (G, S); 2,400 (G, T)	1,500	4,000	
Iron (mg)	14	17 (G, S)	15	45	
Zinc (mg)	15	25 (U, S); 42 (U, T)	15	40	25
Copper (mg)		1 (U, S); 10 (U, T)	5	10	5
Manganese (mg)		0.5-4 (G, S); 8.7-12.2 (G, T)	15	11	-
Iodine (µg)	150	500 (G, S); 940 (G, T)	500	1,100	600
Selenium (µg)		350 (U, S); 450 (U, T)	200	400	300
Chromium (µg) (trivalent)		10,000 (G, T)	200		-
Molybdenum (µg)		-	200	2,000	-
Boron (mg)		6 (U, S); 9.6 (U, T)	20		
Silicon (mg)		700 (U, S); 760 (U, T)			

*EU RDA=The recommended daily allowance considered sufficient to prevent deficiency in most individuals in the population. The RDA is used on the labels of dietary supplements. The EU has not set RDAs for some nutrients; †EVM (UK Expert Vitamin and Mineral Group upper safety limits)=These refer to the maximum amount of a vitamin or mineral that can be taken each day as a long-term supplement (U=safe upper level set by the EVM group, G=guidance only, S=intakes from supplements only, T=total intake from all sources including food and supplements); ‡EHPM/CRN=Upper safe levels defined by the European Federation of Health Product Manufacturers Associations and the UK Council for Responsible Nutrition as daily intakes from supplements which could be consumed on a long term basis. The upper safe levels are made on the assumption that a typical European diet is con-

sumed. These figures are not recommended intakes, but levels of consumption which it would be unwise to exceed; §FNB=Tolerable upper intake levels defined by the Food and Nutrition Board of the US National Academy of Sciences as the highest total level of a nutrient (diet plus supplements) which could be consumed safely on a daily basis, that is unlikely to cause adverse health effects to almost all individuals in the general population; ¶SCF (EU)=Tolerable upper intake levels defined by the European Commission's Scientific Committee on Food as the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans; NB: hyphens (-) in the columns indicate that the nutrient has been considered but no levels set. Where there is a complete blank, the nutrient has not been considered (but may be in the future).

- Acute or short-term exposure to a nutrient to chronic or long-term exposure (ie, a judgement as to whether or not chronic intake is likely to lead to adverse effects at lower doses than those observed with acute intakes)

In addition, inter-individual response to nutrients can vary considerably. So, if the authority considered that the scientific evidence indicated minimal population variability in response to consumption of a nutrient, the uncertainty factor applied was small, and vice-versa. Moreover, if the evidence base was considered to be poor, in particular if it was too poor to set a NOAEL, a LOAEL was sometimes set instead. A LOAEL is thought to be a less robust figure than a NOAEL, and an additional uncertainty factor was usually applied to take account of the uncertainty in deriving an safe upper level from a LOAEL.

Following the determination of the NOAEL or LOAEL or both, and the uncertainty factor, the following equation was used to set the safe upper level:

$$\text{Safe upper level} = \frac{\text{NOAEL (or LOAEL)}}{\text{Uncertainty factor}}$$

In some instances, however, neither a NOAEL nor a LOAEL was identified and

the upper safety limit was set from levels noted in the literature. For example, the EVM group did not set either a NOAEL or a LOAEL for magnesium. Studies reporting mild diarrhoea in a small percentage of healthy subjects at doses of 384-470mg a day were used as evidence to set a guidance upper level of 400mg/day supplemental magnesium.

Exposure assessment Exposure assessment involved evaluating the usual daily nutrient intake among members of the population. National dietary surveys and similar data were used for this purpose.

Characterisation of risk Characterisation of risk included a description of the scientific uncertainties and calculation of the margin between the recommended dietary allowance (RDA) or actual intake and the upper safe level. Sub-populations with distinct sensitivities to certain nutrients (eg, patients with haemochromatosis may be sensitive to high intakes of vitamin C) were also considered.

WHY THE DIFFERENT FIGURES?

Although the methodology used by the three authorities to set the upper safety limits is essentially the same, there are differ-

ences in the figures for several reasons. First, in some cases, the authorities used different research studies to set the NOAELs, LOAELs and upper safety limits. In some cases, this happened simply because of the time the reports were published and the appearance of new research in the literature. For example, the upper safe level for vitamin A set in the UK is lower than that set in the EU and the US because of recent studies that have shown a link between high vitamin A intakes and risk of fracture. These studies had not been published when the EU and the US set their upper safety limits. However, in other cases, cultural differences may have played a role. For example, although the US FNB evaluated both US and European data, it tended to place slightly more emphasis on North American studies.

Secondly, the three authorities frequently set different NOAELs and LOAELs (see Table 2). To complicate matters further, the three authorities were sometimes in disagreement on whether to set a NOAEL or a LOAEL or none at all (see Table 2). With vitamin B₆, for example, the EVM group concluded that the available human data were inadequate and set a LOAEL of 50mg/kg body weight/day based on what it considered to be the most appropriate of the studies performed in animals under controlled conditions. By contrast,

TABLE 2: EXAMPLES OF NOAELS, LOAELS, UNCERTAINTY FACTORS AND UPPER SAFE LEVELS

Vitamin or mineral	NOAEL/ LOAEL	Uncertainty factor	Upper safety limit
<i>Vitamin A (retinol equivalent (µg))</i>			
UK *EVM	None set	None set	1,500
EU †SCF	None set	None set	3,000
US ‡FNB	§NOAEL=4,500	1.5	3,000
<i>Betacarotene (mg)</i>			
UK EVM	¶LOAEL=20	3	7
EU SCF	None set	None set	None set
US FNB	None set	None set	None set
<i>Vitamin D (µg)</i>			
UK EVM	None set	None set	25
EU SCF	NOAEL=100	2.0	50
US FNB	NOAEL=60	1.2	50
<i>Vitamin B₆ (mg)</i>			
UK EVM	LOAEL=50mg/kg/d	300	10
EU SCF	LOAEL=100	4.0	25
US FNB	NOAEL=200	2.0	100
<i>Vitamin C (mg)</i>			
UK EVM	LOAEL=3,000–4,000	3.0	1,000
EU SCF		To be announced	
US FNB	LOAEL=3,000	1.5	2,000
<i>Calcium (mg)</i>			
UK EVM	None set	None set	1,500
EU SCF	None set	None set	2,500
US FNB	LOAEL=5,000	2.0	2,500
<i>Magnesium (mg)</i>			
UK EVM	None set	None set	400
EU SCF	NOAEL=250	1.0	250
US FNB	LOAEL=360	1.0	360
<i>Selenium (µg)</i>			
UK EVM	LOAEL=910	2.0	450
EU SCF	NOAEL=850	3.0	300
US FNB	NOAEL=800	2.0	400
<i>Iron (mg)</i>			
UK EVM	LOAEL=50–220	3.0	17
EU SCF		To be announced	
US FNB	LOAEL=70	1.5	45
<i>Zinc (mg)</i>			
UK EVM	LOAEL=50	2.0	25
EU SCF	NOAEL=50	2.0	25
US FNB	LOAEL=60	1.5	40

*EVM=Expert Vitamin and Mineral group; †SCF=Scientific Committee on Food; ‡FNB=Food and Nutrition Board; §NOAEL=No observed adverse effect level; ¶LOAEL=Lowest observed adverse effect level

both the EU and the US used human data, however, the EU set a LOAEL of 100mg, while the US set a NOAEL of 200mg.

Thirdly, and often as a result of the basis for setting the NOAEL or LOAEL, uncertainty factors varied, often quite dramatically (Table 2). Thus, for vitamin B₆, the UK EVM

group applied an uncertainty factor of 300 partly because it used animal data to identify the LOAEL and also because it set a LOAEL rather than a NOAEL. The uncertainty factor was calculated by multiplying three (for extrapolating a LOAEL to a NOAEL) by 10 (to take account of inter-species variation) and

by 10 again (to account for inter-individual variation). The UK safe upper level is therefore 10mg daily. The EU and US uncertainty factors are four and two respectively, which are lower than the UK value because human data were used. Moreover, the EU applied an uncertainty factor of 4 because of the need to extrapolate a LOAEL to a NOAEL, while the US had set a NOAEL so only applied an uncertainty factor of half that amount.

Fourthly, both the EU and the US upper safety limits relate to total intake from food and dietary supplements, while the UK EVM group has, in many cases, set levels for supplements and total intake separately. Moreover, the EVM group has distinguished between nutrients for which it considered there was sufficient evidence to set a safe upper level and those where it considered evidence was less robust and set guidance levels only.

CONCLUSION

Several authorities around the world have set upper safety limits for vitamins and minerals. That some of the figures vary quite widely is confusing. The basic methodology used by the EVM group in the UK, the SCF in the EU and the FNB in the US is essentially the same. The figures vary because different studies were sometimes used as evidence, and there were differences in the NOAELs, LOAELs and uncertainty factors used to set the upper safety limits. In addition, some levels relate to supplements alone and some to total intake from both food and supplements. Harmonisation of levels, particularly at European level, would do much to reduce confusion for health professionals, the general public and manufacturers alike.

Until the EU has set maximum levels of vitamins and minerals in dietary supplements, pharmacists should use the UK EVM levels as guidance in advising customers. However, they should be aware that these levels may change as new research is published and the EU generates its own figures. For people who wish to take a supplement, the value and safety of a multivitamin containing no more than the RDA of a range of nutrients should be emphasised.

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