

Vitamin and mineral supplements: a risk management model



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Introduction

The fundamental principle of the European food supplement Directive and the founding principle of EU food law is to ensure consumer safety.

The establishment of safe supplements is foreseen in article 5 of the European Directive on food supplements which states:

1. *Maximum amounts of vitamins and minerals present in food supplements per daily portion of consumption as recommended by the manufacturer shall be set taking the following into account:*
 - (a) *upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups;*
 - (b) *intakes of vitamins and minerals from other dietary sources.*
2. *When setting the maximum levels referred to in paragraph 1, due account should also be taken of reference intakes of vitamins and minerals for the population.*

The setting of tolerable upper intake levels (UL) for vitamins and minerals has been undertaken by a number of bodies internationally including the EU Scientific Committee on Food (SCF), the Food and Nutrition Board of the US Institute of Medicine (FNB) and the UK Expert Group on Vitamins and Minerals (UK EVM). The task of setting 'maximum amounts of vitamins and minerals in food supplements' in the EU falls to the risk managers (European Commission and the Member States).

This discussion paper considers the first stage of the risk management process, namely evaluating the risk to the EU population of current and future intakes of nutrients.

The risk management methodology is divided into two major stages. Stage one considers the qualitative and quantitative categorisation of nutrients into three groups according to risk. Stage two then proposes a model of how to address each group.

Stage 1: Characterising the Safety of Vitamins & Minerals for Population Groups

The focus for the risk manager is not the risk characteristics of the individual nutrient. This is taken into account in the establishment of the UL during risk assessment. Rather the task of the risk manager is to assess how to manage the risk of population intakes exceeding the UL. For certain nutrients, the risk of exceeding the UL will be minimal. For other nutrients, intake from food in certain countries or population groups may be close to the UL. In accordance with the governing EU and international legal principle of proportionality, the risk manager is obliged to take risk management measures that reflect the relative risk of exceeding the UL for each nutrient. To do so he must therefore first evaluate the risk of any population group exceeding the UL associated with each nutrient.

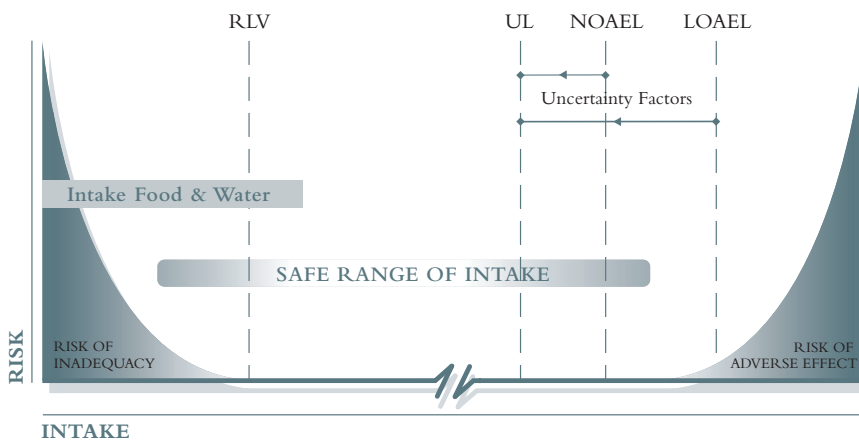
For the majority of micronutrients, the risk associated with exceeding the UL can be characterised *quantitatively*, taking into account individual ULs, Recommended Daily Allowances (RDAs) and intake. However, in some instances, there are insufficient data to establish a UL and a quantitative characterisation of risk is not possible. In the absence of relevant data, the risk manager must rely on *qualitative* judgements drawn from the risk assessment already undertaken.

I. QUANTITATIVE SAFETY CHARACTERISATION - FOR NUTRIENTS WITH A UL

Characterising the safety of nutrients for the population

In order to establish the risk to the population of exceeding the UL, the risk assessor has to draw together information on the range of safe intake with knowledge on existing patterns of intake. Markers for the upper end of this range, the Tolerable Upper Level of Intake (ULs), are in the process of being established by the SCF/EFSA. The recently established SCF Reference Labelling Values (RLV)¹ (Recommended Daily Allowance (RDA) for labelling purposes) could be considered as a marker for the lower end of this range of safe intake.²

Figure 1



1. Opinion of the Scientific Committee on Food on the revision of reference values for nutrition labelling. SCF/CS/NUT/GEN/18 Final, 6 March 2003
2. Strictly speaking, neither RDAs or ULs are 'end' markers or limits as they provide estimations for recommendations or guidelines and not, as is sometimes perceived, definitive cut-off points. Therefore, either intake above the UL or below the RDA is not in itself unsafe, but the risk increases the further intake goes beyond or below these levels.

Traditionally, RDAs/RLVs have indicated the amount of a nutrient needed to prevent deficiency diseases in the vast majority of a population group. Increasingly, scientific bodies are reviewing RDAs to also take into account the impact of inadequate intake on a range of specific health indicators. Individuals who chronically consume vitamins and minerals below the RDAs are at risk of inadequate intakes of these nutrients. While a RDA cannot be used in risk assessment to establish upper safe levels of intake, by delimiting a lower safe level, the RDAs can be used as an *indicator* to help establish the extent of the range of safe intake and may therefore help the risk manager to classify the relative safety of each nutrient for the population. In other words, where the UL and the RDA are closer together the safe range of intake is relatively small. Where they are farther apart the safe range of intake is relatively large. The RDA should therefore always be taken into account in establishing the breadth of the range of safe intake or risk characterisation.

As illustrated in figure 1, the UL and RDA/RLV (RDA for labelling purpose) alone indicate the range of safe intake for all sources of the nutrient (foods including fortified foods and food supplements). For the purposes of assessing the specific risk in relation to consumption of food supplements, the risk manager will need to consider those in the population at the greatest risk of exceeding the UL (and therefore, at least theoretically, those most vulnerable in relation to food supplement intake.) Data demonstrating the highest intake from dietary sources 'namely at the 97.5th percentile' help characterise the risk of exceeding the UL. Individual intake studies cannot completely reflect real population patterns, but taken as whole, they provide a useful picture of European intake patterns. The 97.5th percentile intake data used here represents an average of male adult intake (the population group generally with the highest nutrient intake) - labelled Mean Highest Intake (MHI) - from studies undertaken in Ireland, Italy, Netherlands and the UK.

As the UL represents a total figure for all sources, potential intake from water (IW) should also be taken into account, although this data tends to be scarce. The relative potential of higher intake groups exceeding the UL can be characterised as follows:

$$\text{Population Safety Index (PSI)} = \frac{UL - (MHI + IW)}{RLV}$$

As dietary intake develops over time, and as monitoring of dietary intake becomes more efficient, this risk characterisation can be recalculated to assess whether the risk of exceeding the UL has changed. Using ULs set by the EU SCF (or US FNB where the SCF has not yet completed risk assessment), SCF Reference Labelling Values and European intake data for food and water (see Annex I for details), the following quantitative risk characterisation can be established:

Table 1

Nutrient	PSI = $\frac{UL - (MHI + IW)}{RLV}$
Nicotinamide	52.8
Vitamin E	23.2
Vitamin C	22.0
Vitamin B6	21.9
Vitamin D	8.1
Molybdenum	7.4
Selenium	3.6
Phosphorus	2.1
Iron	1.5
Iodine	1.1
Copper	0.8
Calcium	0.6
Zinc	0.4
Vitamin A (Preformed retinol)	-1.2

Categorising Risk

Having characterised, through the PSI, the safety of each vitamin and mineral, the risk manager must decide at what point the PSI necessitates risk management measures. The risk manager must assess to what extent additional nutrient intake from supplements may potentially lead to a total intake in any population group exceeding the UL.

The most comprehensive data (from the UK and Germany) on nutrient intake patterns from supplements indicate that supplements contribute a maximum of 141% (in the case of vitamin C) of the RLV to total nutrient intake.² (See Annex II)

As a result, it is reasonable to conclude that where the PSI of a nutrient is higher than 1.5 'i.e. where the difference between the current highest intake from food and the UL is more than 150% x RLV' the chance of exceeding the UL through supplementation is extremely low. Some risk management measures may be appropriate to ensure that exceeding the UL, even if unlikely, does not occur, and that the risk manager is aware of the limited nature of the risk.

Where the PSI is 1.5 or below, i.e. where the difference between the current highest intake from food and the UL is less than 150% x RLV, supplementation may potentially lead to intakes that approach the UL. A specific risk management strategy that minimises the chance of exceeding the UL will therefore need to be developed for these nutrients on a case-by-case basis.

According to this classification, nutrients would be categorised as follows:

Table 2

Low risk of exceeding the UL		Potential risk at excessive intakes	
Nutrient	PSI	Nutrient	PSI
Nicotinamide	52.8	Iron	1.5
Vitamin E	23.2	Iodine	1.1
Vitamin C	22.0	Copper	0.8
Vitamin B ₆	21.9	Calcium	0.6
Vitamin D	8.1	Zinc	0.4
Molybdenum	7.4	Vitamin A (Preformed retinol)	-1.2
Selenium	3.6		
Phosphorus	2.1		

2. Supplement use may vary across countries and over time, but it is unlikely that intake will on average exceed those for vitamin C (one of the most popular supplements) in those countries with the highest use of food supplements.

Magnesium and Folic Acid

The UL established by the SCF for **magnesium** of 250mg/day is a UL for supplementation and does not include intake from normal food and beverages, so a PSI cannot be obtained in the same way as for other nutrients with a UL. Provided supplementation is managed so as to remain within this level, there is no risk of adverse effects.

As is the case for magnesium, for **folic acid** the SCF established a UL for supplementation rather than total intake from all sources. Excessive intake of folic acid may, particularly in the elderly, mask vitamin B₁₂ deficiency and therefore the progression of neurological symptoms. A UL for supplementation for folic acid of 1000µg was established by the SCF. There is a low risk of the combined intake of folic acid exceeding the UL from both supplements and fortified foods as currently sold in the EU of exceeding the UL.

II. QUALITATIVE RISK CHARACTERISATION OF NUTRIENTS WITHOUT A UL

Where risk cannot be characterised in quantitative terms due to the absence of an established UL, the risk manager must draw conclusions, on the basis of the available risk assessments, on the implications of the inability of risk assessors to set a UL. The SCF Opinions on vitamins and minerals provide extensive reviews of each nutrient, through which the risk manager has an indication of the nature of the adverse effects associated with each nutrient and potential risks in relation to existing patterns of intake.

In summary, for those vitamins and minerals for which no UL is available:

Table 3

Nutrient	Qualitative risk characterisation
Biotin	The SCF (2001) concluded that the risk of human toxicity from the usual dietary intake of biotin and from biotin supplements appears to be low. The SCF had insufficient data to draw any conclusions concerning the safety of very high-level supplements. Although it was not possible to derive a numerical UL for biotin owing to lack of quantitative data, existing evidence from observational studies indicates that current levels of intake of biotin from all sources do not represent a health risk for the general population.
Chromium*	No adverse effects have been convincingly associated with excess intake of chromium from food or food supplements. Overall, there are insufficient data from human or animal studies to derive a safe upper level for chromium. The oral toxicity of the poorly absorbed trivalent chromium appears to be low.
Pantothenic acid	Owing to the low toxicity of pantothenic acid and the lack of systematic oral dose response intake studies, no LOAEL and NOAEL can be established and hence no numerical UL can be derived. The SCF (2002) concluded that evidence from clinical studies using high doses of pantothenic acid (10–20 grams/day) indicates that intakes considerably in excess of current levels of intake from all sources do not represent a health risk for the general population.

* No SCF Opinion available, based on reports by the US FNB and UK EVM

Table 3 cont.

Nutrient	Qualitative risk characterisation
Riboflavin	<p>No study has reported significant adverse effects in humans of excess riboflavin consumption from food or food supplements. Although the SCF (2000) could not derive a UL for riboflavin from the limited evidence, it concluded that current levels of intake of riboflavin from all sources do not represent a risk to human health.</p>
Thiamin	<p>Systematic data on adverse effects with oral intake of vitamin B₁ in humans are very limited. However, from the available literature it can be concluded that vitamin B₁ orally ingested has a very low risk of adverse effects. The US FNB (1998) concluded that no UL could be derived if based on inadequate data. The SCF (1993) mentioned no evidence of adverse effect at oral intakes up to 500 mg/day for one month. Previous evaluations of micronutrient safety classified vitamin B₁ as a nutrient with no adverse effects. The SCF (2001) concluded that it is not possible to derive a numerical UL for vitamin B₁. However, existing evidence from clinical studies as well as the long history of therapeutic use, at levels up to 200 mg/day for months, indicate that current levels of intake from vitamin B₁ from all sources do not represent a health risk for the general population.</p>
Vitamin B ₁₂	<p>There are no adverse effects known for vitamin B₁₂ from foods or from food supplements. There are no clearly defined adverse effects produced by vitamin B₁₂ that can be used to define a LOAEL or NOAEL, which can be used as a basis for deriving a UL. The SCF (2000) concluded that there is no evidence that the current levels of intake from food and food supplements represent a health risk. Adverse effects have not been reported in the treatment of patients with compromised B₁₂ absorption who received amounts up to 1000 µg/day orally for prolonged periods.</p>

Table 3 cont.

Nutrient	Qualitative risk characterisation
Vitamin K*	<p>Vitamin K₁ (phylloquinone), which is the form occurring naturally in food, is not associated with adverse effects in animal and human studies. A quantitative risk assessment cannot be carried out and a UL cannot be derived.</p> <p>However, no adverse effects have been reported with high intakes of vitamin K.</p>
Vitamin C	<p>Because of limited data, a tolerable upper intake level was not established by the EFSA (Ardal 2004). In contrast, the US FNB found that the data are conclusive enough to set a UL of 2000mg/day.</p> <p>Knowing that mild acute gastrointestinal intolerance e.g. flatulence and diarrhoea are the most clearly defined adverse effects at high intakes of 3-4g/day of vitamin C it seems to be appropriate to use the US FNB Upper Level for calculating a PSI (Table 2) and a MSL according to group B nutrients (Tables 4 and 7).</p>
Manganese	<p>Subgroups of the population of potential concern are elderly people, individuals with iron-deficiency anaemia and people with liver disease. The risk of an adverse effect resulting from excess intake of manganese from food and food supplements appears to be low.</p>

* No SCF Opinion available, based on reports by the US FNB and UK EVM

Qualitative assessment of SCF Opinions (and other authoritative reports) show no adverse effects in healthy individuals associated with high intakes of biotin, chromium, pantothenic acid, riboflavin, thiamin, vitamin B₁₂ and vitamin K. Assessment of manganese demonstrates potential concerns at higher levels of intake and risks have been associated with higher intake of beta-carotene in individuals who are heavy smokers (See Annex 3 for qualitative risk characterisation for manganese and beta-carotene).

CONCLUSION OF CATEGORISATION OF VITAMINS AND MINERALS

On the basis of the evaluations above, taking into consideration qualitative (where no UL is available) and quantitative risk characterisations using the PSI (population safety index, see definition page 7), three categories of vitamins and minerals emerge.

Table 4

A. No evidence of risk within ranges currently consumed; does not represent a risk to human health	B. Low risk of exceeding the UL	C. Potential risk at excessive intakes
Vitamin B ₁	Vitamin B ₆	Vitamin A
Vitamin B ₂	Vitamin C	Beta-carotene (smokers)
Biotin	Vitamin D	Calcium
Vitamin B ₁₂	Vitamin E	Copper
Pantothenic acid	Folic Acid	Fluoride**
Vitamin K	Nicotinamide	Iodine
*Chromium	Phosphorus	Iron
	Magnesium	Manganese
	Molybdenum	Zinc
	Selenium	

* The classification is based on those sources currently approved in Annex II of Directive 2002/46/EC and 2001/15/EC.

** Intake data for fluoride were not available in the UK NDNS study, so is provisionally placed in Group C. US FNB reported potential risk of fluorosis in children. The final categorisation would depend on relevant intake data.

Having established categories of vitamins and minerals according to risk, the risk manager must then develop risk management strategies that proportionately reflect the risk associated with each group.

Stage 2: Setting Maximum Supplement Levels (MSL)

An approach should be developed by the risk manager that reflects the relative risk associated with each risk category of nutrients.

Group A - No evidence of risk within ranges currently consumed; does not represent a risk to human health

In the case of nutrients in Group A, no adverse effects have been observed. Where risk assessment has established that current intake from foods, fortified foods and supplements poses no significant risk, there is no rationale for applying any risk management measure.

In this context, setting an MSL cannot on the basis of the science available be considered a necessary risk management measure. Moreover, quantitative restrictions on vitamin and mineral content which are not based on risk assessment would be in breach of EU and international trade law. The individual company should therefore be responsible for establishing appropriate levels for the content of vitamin B₁, B₂, B₁₂, biotin, pantothenic acid, vitamin K and chromium. In the past, trade associations have set guidelines for the maximum content of nutrients to be contained in food. These may prove useful to individual companies developing products.

Group B - Low risk of exceeding the UL

For Group B nutrients, risk assessment demonstrates that the chance of exceeding the UL on the basis of current intake from other dietary sources (food, including fortified food) is small. Nevertheless, risk managers may be concerned that, for example, changes in dietary patterns or sales of fortified foods may, over time, lead to significant increases in intakes of vitamins and minerals that may in turn increase the potential of consistently exceeding the UL.

Changes to dietary patterns

An idea of the scale of potential changes to dietary patterns that might develop (due, for example, to changes in consumer preferences or the fortification of products) can be gained from a comparison of surveys undertaken in the UK in 1986/7 and 2000/01.³

Table 5 -
Vitamins

	Mean intake for all men		
	1986/1987 UK Adults Survey	2000/01 NDNS	% change in intake
A (µg)	1679	1017	-39%
Thiamin (mg)	2.01	2.22	+10%
Riboflavin (mg)	2.29	2.33	+2%
Niacin equivalents (mg)	40.9	46.4	+13%
B ₆ (mg)	2.7	3.3	+22%
B ₁₂ (µg)	7.3	6.8	-7%
Folate (µg)	312	359	+15%
Pantothenic acid (mg)	6.6	7.8	+12%
Biotin (µg)	39	44	+13%
C (mg)	74.6	101.4	+36%
D (µg)	3.8	4.2	+11%
E (mg)	11.7	13.4	+15%

Table 6 -
Minerals

	Mean intake for all men		
	1986/1987 UK Adults Survey	2000/01 NDNS	% change in intake
Iron (mg)	14	14	0
Calcium (mg)	940	1016	+8%
Potassium (mg)	3187	3371	+5%
Magnesium (mg)	323	311	-4%
Phosphorus (mg)	1452	1502	+3%
Copper (mg)	1.63	1.48	-9%
Zinc (mg)	11.4	10.7	-6%
Iodine (µg)	243	220	-9%

Although only in the cases of two vitamins, namely C and B6, did intakes increase by more than 20%, to take into account potential changes in dietary patterns, the risk manager may be justified in introducing a precautionary risk management factor of a 50% increase in dietary intake (from foods and fortified foods). In contrast, the experience in the UK suggested little change in mineral intake over the 15-year period -only intake of calcium increased beyond 5%. Given that for technical and taste reasons, mineral fortification is self-limiting, a precautionary risk management factor of 10% could be set.

Taking into account intake from dietary sources (including fortified foods) and water, and a risk management factor that allows for potential changes in intake, maximum supplement levels can be calculated as follows:

For vitamins: $MSL = UL - (MHI \times 150\%)$

For minerals: $MSL = UL - [(MHI \times 110\%) + IW]$

Using data from the United Kingdom, for example, the model would give MSLs for Group B nutrients as follows in Table 7. Data from other countries could lead to some modifications.

Table 7

Group B nutrients	MSL(/day)
B ₆ (mg)	18-93*
C (mg)	1750
D (µg)	35
E (mg)	270-970*
Nicotinamide (mg)	820
Molybdenum (µg)	350
Phosphorus (mg)	1250
Selenium (µg)	200

* In the case of vitamins B₆ and E, the risk assessments undertaken by the EC SCF and US FNB have produced widely divergent ULs. Taking into account these discrepancies, the MSL could ultimately vary between 18 and 93mg/day for B₆ and 270 and 970mg/day for vitamin E.

Magnesium

The UL established by the SCF for **magnesium** is 250mg/day is for supplementation only. For technical reasons, magnesium is unlikely to be used in significant quantities in foods. A further risk management measure beyond the limit established by the SCF is therefore unnecessary. The MSL for magnesium should therefore be 250mg/day.

Folic Acid

The UL established by the SCF for **folic acid** of 1000µg /day is for supplementation only. Folic acid is found foremost in breakfast cereals at levels around 100-150µg per serving. Under current levels of fortification, an individual is unlikely to exceed 400µg/day. A MSL of up to 600µg/day would therefore currently be appropriate. An increase of the RDA from 200 to 400µg/day and the potential effects on population intake will need to be monitored.

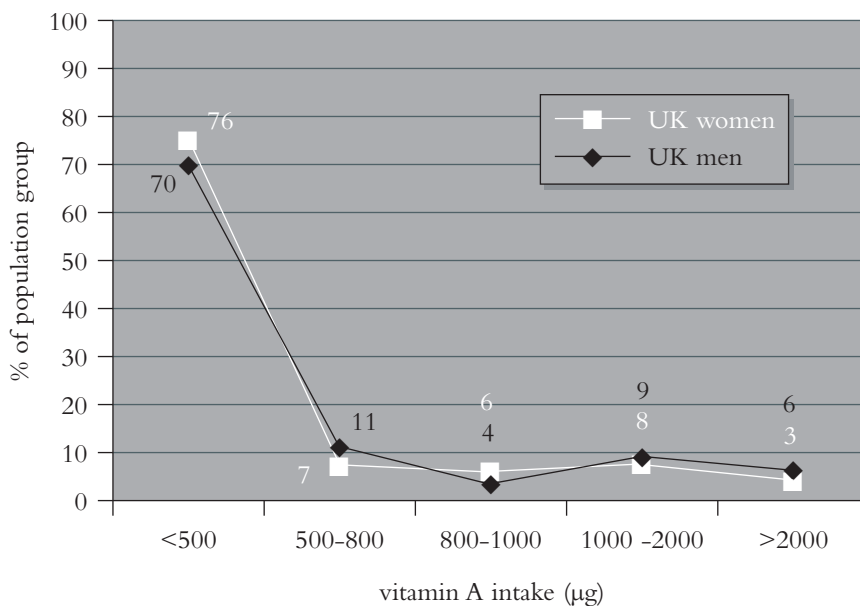
Group C - Potential risk of exceeding the UL

Where there is a narrow range of safe intake and a potential risk that consumers may exceed the UL on a daily basis, it may not be possible for the risk manager to use the UL as a reference point for establishing a MSL. In addition, the risk manager will need to take into account not only the risk of excessive intake, but equally the risk of insufficient intake.

A good example is the preformed retinol form of vitamin A. The EU SCF and the US FNB established a safe upper level of 3000 µg/day, which was based on the risk of possible birth defects. This leaves a narrow margin for safe intake since a significant number of people are at risk for insufficient intake.

A safe level of intake is even more critical when the UK National Diet and Nutrition Surveys (NDNS) demonstrated clearly that the range of intakes for different age and sex groups are very wide indeed, reflecting the limited distribution of preformed retinol in foods. This dependency for retinol from relatively few foods results in the median intakes typically being 20 to 50 per cent less than the average intakes, which highlights the risk of inadequate intakes in sizeable groups of the UK population. Whereas the dietary intake data show the risk of exceeding the UL could theoretically affect a very small proportion of the population (less than 3%), there are substantial groups of the population that fail to achieve the RDA, and thus have a real risk of deficiency. Graph 1 illustrates the intake of preformed vitamin A from all sources 'including food supplements' in the UK and the proportions of the population at risk of deficiency and excess.

Graph 1 -
Intake of preformed
vitamin A from all
sources in the UK



Using this illustration of vitamin A, risk managers have to address the overall balance of the diet, potential nutrient interactions, the contribution of specific foods and food supplements to the nutrient intakes, and clear labelling. In addition, they must take into account, on a case-by-case basis, both the risk of deficiency and excessive intakes.

An overview of Group C nutrients and a possible range of MSLs are provided in Annex III.

Summary

In summary, taking into consideration the risk categorisation of the nutrients and the quantitative estimates of high intake from all other sources, the above discussion leads to the following risk management model for developing strategies in relation to setting maximum levels of vitamins and minerals in food supplements.

	Nutrients	Risk Management measure
Group A. <i>No evidence of risk within ranges currently consumed; does not represent a risk to human health</i>	B ₁ , B ₂ , Biotin, B ₁₂ , Pantothenic acid, K, Chromium	No risk management measure required
Group B. <i>Low risk of exceeding the UL</i>	B ₆ , C, D, E, Nicotinamide	MSL = UL - (MHI x 150%)
	Phosphorus, Molybdenum, Selenium	MSL = UL - [(MHI x 110%) + IW]
	Magnesium	MSL = UL = 250 mg (refers to supplemental magnesium only)
	Folic Acid	MSL = 600µg
Group C. <i>Potential risk at excessive intakes</i>	Vitamin A, Beta-carotene, Calcium, Copper, Fluoride, Iodine, Iron, Manganese, Zinc	A case-by-case assessment taking into account risk of excessive and deficient intake. (see Annex III)

Annex I: Calculation of PSI

Nutrient	Tolerable Upper Intake Level UL ⁴	Mean Highest Intake from Foods (MHI ⁵)	Intake from water (IW) ⁶	SCF RLV 2003	PSI UL-(MHI+IW) / RLV
Nicotinamide (mg)	900	56	0	16	52.8
E (mg a-TE)	300	21	0	12	23.2
C (mg)	2000*	237	0	80	22.0
B ₆ (mg)	25	4.4	0	1.4	21.9
D (µg)	50	10	0	5	8.1
Molybdenum (µg)	600	210	20	50	7.4
Selenium (µg)	300	92	-	55	3.6
Phosphorus (mg)	4000*	2497	10	700	2.1
Iron (mg)	45*	23	0.4	14	1.5
Iodine (µg)	600	407	30	150	1.1
Copper (mg)	5	3.21	1	1	0.8
Calcium (mg)	2500	1825	300	1000	0.6
Zinc (mg)	25	20	1	10	0.4
A - Preformed retinol (µg)	3000	3971	0	800	-1.2
Magnesium (mg)	250sup ⁷	520	-	375	-
Folic acid (µg)	1000 ⁷	536(folate)	0	400	-

* US FNB values.

⁴ UL is that established by the EC SCF where available and the US FNB where not.

⁵ The data reflect the mean of intake at 97.5 percentile in Netherlands, Ireland, Italy and UK for the highest risk group (male adults) See UK Office for National Statistics, *The National Diet & Nutrition Survey (NDNS): adults aged 19 to 64 years* (2003), Irish Universities Nutrition Alliance (IUNA), *The North-South Ireland Food Consumption Survey (2001)*, *Gezondheidsraad, Enkele belangrijke ontwikkelingen in de voedselconsumptie* (2002), Turrini A, Saba A, Perrone D, Cialfa E, & D'Amicis A (2001): Food Consumption Patterns in Italy: the INN-CA Study 1994-96, *European Journal of Clinical Nutrition*, Vol. 55, 7, pp. 571-588.

⁶ Data drawn from SCF opinions on Tolerable Upper Levels of Intake and Darret, G. et al. "Estimation of minerals and trace elements provided by beverages for the adult in France." *Ann Nutr Metab*, 1986;30(5):335-44.

⁷ UL for supplementation only.

Annex II: Intake from Food Supplements

Nutrient	Highest average intake from supplements in UK*	SCF RLV 2003	UK Supplement Intake as percentage of RLV	Highest average intake from supplements in Germany*	German Supplement Intake as percentage of RLV
Nicotinamide (mg)	7.7	16	48%	8.5	53%
E (mg a-TE)	7.6	12	63%	6.7	56%
C (mg)	113	80	141%	115	144%
B ₆ (mg)	1.2	1.4	86%	1.1	79%
D (µg)	2.6	5	52%	***	***
Molybdenum (µg)	***	50	-	***	***
Selenium (µg)	***	55	-	***	***
Phosphorus (mg)	25	700	4%	***	***
Iron (mg)	4.1	14	29%	***	***
Iodine (µg)	23	150	15%	***	***
Copper (mg)	0.3	1	30%	***	***
Calcium (mg)	324**	1000	18%	***	***
Zinc (mg)	2.5	10	25%	***	***
A - Preformed retinol (µg)	263	800	33%	***	***
Magnesium (mg)	17	375	5%	***	***
Folic acid (µg)	68	400	17%	152	38%

* Average male intake at the 97.5 percentile. Data taken from UK Office for National Statistics, *The National Diet & Nutrition Survey (NDNS): adults aged 19 to 64 years (2003)* and Robert Koch Institut, *Was essen wir heute?: Beiträge zur Gesundheitsberichterstattung des Bundes.* (2002).

** Average female intake at the 97.5 percentile, male intake being negligible

*** Intake data not available

Annex III: Case-by-Case Assessment of Group C Nutrients and Proposed MSL

Nutrient	Qualitative risk characterisation	Proposed MSL
Vitamin A	<p>The teratogenic effect of preformed retinol on the newborn child is well documented because of the severe and irreversible nature of this form of toxicity. The EU SCF UL is 3000µg retinol equivalents (RE) per day, which applies to intakes from both foods and food supplements. Recent epidemiological data have suggested that risk of hip fracture in older people may be associated with intakes as low as 1500 µg RE/day. As the RDA for vitamin A is 800 µg RE/day and the distribution of intakes is great, risk management of preformed retinol is particularly challenging to avoid risk of deficiency as well as excess.</p>	800-1000µg
Beta-carotene	<p>Until recently, beta-carotene was considered to show no adverse effects in humans. The promise of beta-carotene for cancer prevention led to two large-scale primary prevention studies in very high-risk populations of chronic heavy smokers. Surprisingly, beta-carotene supplementation at levels of 20 mg/day showed increased incidence of lung cancer in the high-risk groups. As beta-carotene may produce adverse effects in smokers in the general population, its use as a supplement is now regarded with caution.</p>	4.8-7mg
Calcium	<p>Excessive chronic intakes of calcium are associated with kidney stone formation, hypercalcaemia and renal insufficiency. Calcium is also known to interact with the absorption of other essential minerals. However, most acute adverse effects relate to abdominal pain and diarrhoea. Subpopulations known to be susceptible to high levels of calcium include individuals with renal failure, those using thiazide diuretics and those with low intakes of minerals that interact with calcium, e.g. iron, magnesium and zinc.</p>	1000-1500mg

Annex III cont.

Nutrient	Qualitative risk characterisation	Proposed MSL
Copper	<p>Mild and reversible gastrointestinal effects have been reported when water containing 3 g/litre has been consumed. The occurrence of either acute or chronic copper toxicity in humans is rare. Liver damage is used as a reliable indicator of long-term ingestion of copper, and the NOAEL of 10 mg/day is based on the absence of adverse effects on liver function. The SCF applied an Uncertainty Factor of 2 and derived a UL of 5 mg/day.</p>	1-2mg
Fluoride	<p>The primary adverse effects associated with chronic excess fluoride intake are teeth enamel and skeletal fluorosis. Most investigators consider the former as a cosmetic effect rather than a functional adverse effect, while the latter is extremely rare. In establishing a maximum level, intake must be considered from food, water and also dental products.</p>	3.5mg
Iodine	<p>Acute adverse effects include reports of burning of the mouth, throat and stomach together with abdominal pain, diarrhoea, seizure and coma. These are quite rare and are associated with levels of many grams. There are biological mechanisms to protect against exposure to high levels of iodine. A change in thyroid function with elevated thyroid stimulating hormone (TSH) is used as the indicator for increased risk of developing clinical hypothyroidism and the critical adverse effect on which to base a UL. For most people, iodine intake from foods and supplements is unlikely to exceed the UL.</p>	150-200µg

Annex III cont.

Nutrient	Qualitative risk characterisation	Proposed MSL
Iron	<p>High levels of iron are frequently associated with gastrointestinal effects, especially constipation, but also with nausea, diarrhoea and vomiting. Chronic iron overload at levels in excess of 50 mg in adults may result in tissue damage, including cirrhosis of the liver. Excessive intakes of iron are very rare in adults except for people with a genetic disturbance known as hereditary haemochromatosis (HHT). Accidental ingestion of adult iron food products sold as prescription medicines by children accounts for most cases of acute iron toxicity. Fortunately, most cases are not fatal and without serious morbidity.</p>	14-20mg
Manganese	<p>Miners and smelters chronically exposed to manganese dusts and fumes suffer from “manganism”—a neurotoxic condition similar to Parkinson’s disease. Contaminated drinking water is associated with neurological and behavioural effects. Subgroups of the populations of potential concern are elderly people, individuals with iron-deficiency anaemia and people with liver disease. The risk of an adverse effect from excess from food and food supplements appears to be low. However, the safety margin in both humans and animals appears to be low.</p>	2mg
Zinc	<p>Adverse effects of acute excessive exposure give rise to abdominal pain, nausea and vomiting. Prolonged consumption at high levels can result in changes in copper balance. The SCF noted an absence of any adverse effects on a wide range of indicators of copper status at an intake of 50 mg/day (NOAEL) and recommended a UL of 25 mg/day.</p>	10-15mg

Annex IV: Glossary of Terms

EFSA	European Food Safety Authority
EVM	UK Expert Group on Vitamins and Minerals
FNB	US Food and Nutrition Board, Institute of Medicine
IW	Intake from water
LOAEL	Lowest Observed Adverse Effect Level
MHI	Mean Highest Intake from Food
MSL	Maximum Supplement Level (maximum level for daily supplement consumption)
NDNS	National Diet & Nutrition Survey
NOAEL	No Observed Adverse Effect Level
RDA	Recommended Daily Allowance
PSI	Population Safety Index
RLV	Reference Labelling Values
SCF	EU Scientific Committee for Food
UL	Tolerable Upper Intake Level

