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Risk management approaches to the setting of maximum levels of vitamins and minerals in food supplements for adults and for children aged 4–10 years

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Abstract:
The European Regulation (EC) 1925/2006 on addition of vitamins and minerals to foods and the Directive 2002/46/EC, which relates to food supplements, set out criteria that must be taken into account for the establishment of maximum amounts of these essential nutrients that are present in products. The current report uses both quantitative and qualitative risk management approaches, including calculations of Population Safety Indices (PSI) for each nutrient, allocation of the nutrients into three groups of risk and proposed maximum levels for each nutrient in food supplements for adults and children aged 4–10 years. The approach takes into account the tolerable upper intake levels (ULs) derived from international risk assessments and the contributions to total intake from conventional foods, fortified foods and food supplements. The proposed maximum levels for food supplements (MLS) for each nutrient balance the risk of deficiency with risk of overconsumption and would not be expected to result in any adverse effects. The report reviews the application of the principles of risk management in order to underpin the regulatory developments. Further dialogue among all the interested parties will be critical to ensure that proportionate risk management measures are used to set maximum levels of nutrients, where appropriate, to protect consumers young and old and to facilitate informed choices.

Key words:
EU regulation: maximum levels; vitamins; minerals; food fortification; food supplements; adults; children.

Summary

There are three major and complementary ways of safely delivering the essential vitamins and minerals for human health and well-being: by promoting the consumption of nutrient-dense foods; by increasing the availability and intake of foods with added nutrients (fortified foods); and by appropriate use of food (dietary) supplements. Regulatory authorities around the world need to ensure that levels of micronutrients in the total diet are safe, and that the cumulative intake from all sources does not lead to excessive intakes and any adverse effects in the population, including sensitive groups such as children, the elderly and women during pregnancy and lactation.

Risk analysis for nutrients differs from other substances in foods because vitamins and minerals are essential for life, and consequently adverse effects can result from suboptimal intakes and deficiencies as well as from excessive intakes. Risk analysis comprises three distinct but closely linked components: risk assessment, risk management and risk communication. The primary objectives are not only to protect the health of consumers but also to take into account other legitimate factors including the facilitation of consumer choice and avoidance of barriers to international trade.

The key regulatory criteria to be taken into account for setting maximum amounts of vitamins and minerals in fortified foods and food supplements are:

- The upper safe levels of each vitamin and mineral 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
- The intake of vitamins and minerals from all dietary sources
- Reference intakes of vitamins and minerals for the population

The current report applies the principles of quantitative and qualitative risk management, taking into account risk assessments from several authoritative groups of scientific assessors including the European Food Safety Authority (EFSA), the US Institute of Medicine (IOM) and the UK Expert Group on Vitamins and Minerals (EVM). For the EFSA and IOM risk assessments, the tolerable upper intake level (UL) is defined as the maximum level of habitual intake from all sources of a nutrient judged to be unlikely to lead to adverse health effects in humans. The EVM risk assessments are based on the UL method, but the scientific committee assigned the term Safe Upper Level (SUL) because the levels refer to long-term supplementary use, not total intakes.

When authoritative risk assessments show no adverse effects and there are no safety concerns about a nutrient, and when a UL cannot be established, these nutrients are placed in Group 1 and no further risk management measures are required. Nonetheless, some policymakers may prefer to establish maximum levels for all the nutrients and an alternative approach could be used that is based on the Highest Observed Intake (HOI). The HOI (defined as the highest level of intake observed, with the available data of acceptable quality, showing an absence of adverse effects up to that intake) could be used when there are no safety concerns concerning an upper safe intake.

For those nutrients with an established UL, this risk management model includes the calculation of a Population Safety Index (PSI) for each nutrient. The PSI paradigm describes a process by which nutrients can be allocated into three categories of risk. The concept of characterising risk using the PSI is set out in the following equation:

$$PSI = \frac{UL - (MHI + IW)}{RDA}$$

For adults, the UL from all sources is established by scientific risk assessment when available. The children's ULs are derived from extrapolated values based on reference bodyweights for 4–6 year olds rather than the UL based on an age range of 7–10 years or an average UL covering children aged 4–6 years and 7–10 years. The use of the lower UL for 4–6 year-old children in this risk management model introduces a substantial precautionary measure. The Mean Highest Intake (MHI) is the 97.5 percentile (P97.5) intake data from food sources (including fortified foods but excluding food supplements) from male adults or 4–10 year-old male children. The IW is the estimated intake of minerals from water and the RDA is the labelling Recommended Daily Allowance. The labelling RDA denominator is used in calculations for adults and children because the value is consistent across all European Member States. The use of the labelling RDA and the UL, where available, also provide fixed points on the intake curve. The model assumes that where the difference between the MHI from food (including fortified foods) and the UL is more than 150% x RDA, the chance of exceeding the UL is extremely low (Group 2). Where the difference between the MHI from food (including fortified foods) and the UL is less than 150% x RDA, there is a potential risk of exceeding the UL (Group 3). In other words, the characterising factor for Group 2, the "low risk of exceeding the UL", is a PSI greater than 1.5 for both adults and children, and for Group 3, the "potential risk of excessive intakes", is a PSI of 1.5 or less.

The fundamental risk management question is not only to determine how large the margin of safety is now, but also is likely to be in the future, allowing for varying dietary contexts. To gain a measure of potential changes in consumer preferences, food supplement use and use of fortified foods, a comparison was made of dietary surveys undertaken in the UK over a period of 15 years. Based on this intake information, the current model assumes a precautionary risk management factor of a 50 per cent increase in dietary intake for all the vitamins from foods, including fortified foods, and a 10 per cent precautionary risk management factor for minerals. These precautionary factors are used, where possible, to estimate proposed maximum levels in food supplements (MLS) using the following equations:

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

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

The characterisation of risk using the PSI to allocate the nutrients into three groups and the proposed maximum levels in food supplements (MLS) for adults and children aged 4–10 years are shown in the summary table overleaf. The reasons for selection of the children's age ranges of four to six years and seven to ten years relate to the reference bodyweights, the availability of nutrient intake data and the age ranges for dietary reference values. Thereafter, safety issues for older children and postpubertal children have to take account of the onset of puberty, the increasing speed of growth and the adolescent growth spurt.

The risk management model for food supplements takes into account the contributions to total nutrient intake from conventional foods, fortified foods and food supplements using the best available data. Theoretical models have also been proposed for setting maximum amounts of vitamins and minerals in fortified foods. Reassuringly, these models have also resulted in three categories of risk similar to those characterised in this report. The methodologies for setting maximum levels of vitamins and minerals in fortified foods are still being developed, including the decision about how to present the values, i.e. per weight or per energy of the food consumed (e.g. per 100 kcal, per 100 g/100 ml, per portion). Typically, the amounts of nutrients added to food products are based on the quantitative criteria for making nutrient content claims.

Factors influencing the stability of vitamins, their retention in food and food supplement products and the impact on tolerances and declared values

of nutrients on food labels are also discussed. The proposed maximum levels for vitamins and minerals include overages and must allow for tolerances so that enforcement authorities can check compliance with levels of nutrients declared in nutrition labelling.

The quantitative and qualitative risk management approaches described in this report attempt to address the many difficulties, limitations and inconsistencies surrounding the establishment of ULs, particularly for children e.g. the limited nutrient intake data from conventional foods, fortified foods and food supplements, the uncertainties and biases in the estimation of habitual nutrient intake distributions and the care needed not only to address the risk of excessive intakes but also the risk of suboptimal intakes and micronutrient deficiencies in vulnerable groups. Food fortification practices and levels of nutrients in food supplements have been shown to be safe and effective for over two decades. The overall purpose of this report is to contribute towards the development of a scientifically-based process for setting maximum levels of essential nutrients in fortified foods and food supplements. Consultation and dialogue between the various interested parties are critical to ensure that proportionate measures are used to protect consumers, young and old, and to facilitate informed choice. In addition, because of the large differences in scientific opinions on the derivation of ULs for certain nutrients (e.g. vitamin B_6, vitamin E, molybdenum, iodine, copper and zinc), there needs to be a thorough scientific reassessment of their safety. These differences in ULs established by EFSA, IOM and EVM scientific risk assessors result from their different assumptions and applications of uncertainty factors. ULs are defined and identified to represent an intake that can be consumed daily over a lifetime without significant risk to health according to available scientific evidence. As such, the conclusions reflect the scientific rigour used in the risk assessments and the fact that the ULs are not only safe, but safe by a comfortable margin.

Nutrient	Proposed Maximum Safe Levels in food supplements (MLS)	
	Adults	Children 4–10 years
GROUP 1[a] No evidence of risk to human health at levels currently consumed	**No further risk management measures required**	**No further risk management measures required**
Vitamin B_1 (mg)		
Thiamin	—	—
Vitamin B_2 (mg)		
Riboflavin	—	—
Biotin (µg)	—	—
Vitamin B_{12} (µg)		
Cobalamin	—	—
Pantothenic acid (mg)	—	—
Vitamin K (µg)	—	—
Chromium III (mg)	—	—
GROUP 2 Low risk of exceeding UL		
Vitamin B_6 (mg) Pyridoxine	18[b]	2.2[b]
Vitamin C (mg)	1700	350
Vitamin D (µg)[c]	83.2	42.4
Vitamin E (mg)	270[b]	98.6[b]
Nicotinamide (mg)	820	162.7
Molybdenum (µg)	350[b]	50[b]
Phosphorus (mg)	1250[b]	550[b]
Selenium (µg)	200	55
Magnesium (mg)	250[b]	250[b]
Folic acid (µg)[d]	600	300
Potassium (mg)	1500	1200
GROUP 3 Potential risk at excessive intakes		
Vitamin A (retinol) (µg)	1200	1000
Beta-carotene (mg)	7	7
Calcium (mg)	1000	500
Copper (mg)	2[b]	1[b]
Iodine (µg)	200[b]	150[b]
Iron (mg)[e]	20[b]	7[b]
Manganese (mg)	4[b]	1.5[b]
Zinc (mg)	15[b]	5[b]

[a] As described in Section 5 and in Table 5 of the report, no maximum levels are set for Group 1 nutrients with no established adverse effects or safety concerns.

[b] Because of the .large differences in scientific opinions on the derivation of the ULs/SULs for these nutrients, there is a need for a systematic reassessment of their safety. For these nutrients, the IOM ULs are significantly higher than those established by EFSA risk assessments, which could result in a higher MLS. For example, vitamin B_6 (93 mg and 35.2 mg MLS for adults and children, respectively), vitamin E (978.3 mg and 285.8 mg for adults and children, respectively).

[c] Higher values were established by the IOM and EFSA risk assessments in 2010 and 2012, respectively.

[d] Folic acid: pteroylmonoglutamic acid.

[e] WHO (2012) recommended a supplemental daily amount of 30–60 mg elemental iron as a safe and effective way to reduce risk of maternal anaemia.

Abbreviations

ADI	Acceptable Daily Intake
AI	Adequate Intake
DRV	Dietary Reference Value
EC	European Commission
EFSA	European Food Safety Authority
ERNA	European Responsible Nutrition Alliance
EU	European Union
EVM	Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organisation
FNB	US Food and Nutrition Board
FSA	UK Food Standards Agency
GI	Gastrointestinal
GL	Guidance Level
HHT	Hereditary haemochromatosis
HOI	Highest Observed Intake
ILSI	International Life Sciences Institute
IOM	US Institute of Medicine of the National Academy of Sciences
IU	International Unit
IUNA	Irish Universities Nutrition Alliance
IW	Intake of minerals from water
LOAEL	Lowest Observed Adverse Effect Level
MHI	Mean Highest Intake
MLS	Maximum level of a vitamin or mineral in a food supplement
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NDNS	UK National Diet and Nutrition Survey
NOAEL	No Observed Adverse Effect level
NRV	Nutrient Reference Value
NTD	Neural Tube Defect
OAC	Oral Anticoagulant
PSI	Population Safety Index
RDA	Recommended Daily Allowance/ Recommended Dietary Allowance
RE	Retinol Equivalents
RfD	Reference Dose
RNI	Reference Nutrient Intake
SACN	UK Scientific Advisory Committee on Nutrition
SCF	EU Scientific Committee on Food
SUL	Safe Upper Level
TSH	Thyroid stimulating hormone
UF	Uncertainty Factor
UK	United Kingdom
UL	UL
UVB	Ultraviolet B radiation
VKM	Norwegian Food Safety Authority
WHO	World Health Organisation
WTO	World Trade Organisation

Table of contents

1. Introduction

There are three major and complementary ways of delivering the essential micronutrients for human health and well-being:

- by promoting the consumption of nutrient-dense foods
- by increasing the availability and intake of foods with added nutrients (fortified foods)
- by the appropriate use of food (dietary) supplements

All these approaches have been demonstrated to provide safe ways of ensuring the nutritional status of populations and individuals at certain times in their lives (World Bank 1994, Food and Agriculture Organisation and International Life Sciences Institute 1997, Micronutrient Initiative 2007). However, it is necessary to ensure that levels of micronutrients in the total diet are safe and that the cumulative intake from all sources does not lead to excessive intakes and any adverse effects. Three authoritative groups of scientific assessors, the European Food Safety Authority (EFSA, 2006), the UK Food Standards Agency (UK FSA) Expert Group on Vitamins and Minerals (EVM, 2003) and the US Institute of Medicine (IOM, 1997, 1998, 2000, 2001), have addressed the setting of tolerable upper intake levels (ULs)[1,2] for each essential nutrient.

Table 1 shows the levels established by these three assessment committees. For example, the European Commission (EC) requested the Scientific Committee on Food (SCF) and later EFSA to provide scientific opinions on ULs for 29 nutrients listed in Annex I of the Food Supplements Directive (European Parliament and of the Council, 2002). This resulted in specific numerical ULs being established for 16 nutrients. Some of the remaining nutrients showed extremely low or non-existent adverse effects, even at very high levels of intake, and for some, lack of sufficient scientific data did not permit the derivation of a numerical UL. Where ULs have not been established, the SCF/EFSA have provided qualitative risk characterisation for the specific nutrients. In contrast, other expert scientific risk assessment committees such as EVM and IOM have set numerical values, and these have been taken into account on a case-by-case basis in the current risk management model.

The derivation of a UL for each vitamin and mineral is based on the principle that the most sensitive members of the general population must be protected from the adverse effects of high nutrient intakes. Some sensitive subpopulations can have responses (in terms of incidence, severity or both) to the nutrient, and these responses may be different from those expected at different life stages or with different physiological status. The risk assessment process recognises that there may be sensitive groups, e.g. infants, children, certain individual adults, the elderly and women during pregnancy and lactation. Even within relatively homogeneous life stage groups, there can be a range of sensitivities to adverse effects, e.g. sensitivity is influenced by bodyweight, lean body mass and extent of adiposity.

[1] UL is defined as the maximum level of habitual intake of a nutrient from all sources judged to be unlikely to lead to adverse health effects in humans. 'Tolerable intake' in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure. ULs may be derived for various life stage groups in the population. The UL is an estimate of the highest level of intake that carries no appreciable risk of adverse health effects. To establish whether an exposed population is at risk requires a risk assessment to determine what is the fraction, if any, of the population whose intake exceeds the UL and the magnitude and duration of the excessive intake.

[2] The EVM used the term Safe Upper Level (SUL) because the levels refer to long-term supplementary use, not total intakes, and the amounts relate to a 60 kg bodyweight adult.

Table 1
A comparison of the upper safe levels for total daily intake from the Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA), the US Institute of Medicine (IOM), and the daily levels for supplementation proposed by the UK Food Standards Agency Expert Group on Vitamins and Minerals (EVM).

Nutrient	Unit	SCF/EFSA total intake (UL)	IOM total intake (UL)	EVM for long-term supplementation (SUL)[a]
Vitamin A	µg	3000	3000	1500 (G, T)
Beta-carotene	mg	Below 15	Not set	7 (not for smokers)
Vitamin D[b]	µg	50→100	50→100	25 (G)
Vitamin E[c]	mg	300	1000	540 (800 IU)
Vitamin K	µg	Not set	Not set	1000 (G)
Thiamin (B_1)	mg	Not set	Not set	100 (G)
Riboflavin (B_2)	mg	Not set	Not set	40 (G) (43T)
Nicotinamide Nicotinic acid	mg mg	900 10	35[d] –	500 (G) (560T) 17
Pantothenic acid	mg	Not set	Not set	200 (G) (210T)
Pyridoxine (B_6)	mg	25	100	200 (short term)[e] 10 (long term)
Folic acid	µg	1000 (+dietary folate)	1000 supp. (+200 diet)	1000 (G) (1500T)
Vitamin B_{12}	µg	Not set	Not set	2000 (G)
Biotin	µg	Not set	Not set	900 (G) S (970T)
Vitamin C	mg	Not set	2000	1000 (G)
Calcium	mg	2500	2500	1500 (G)
Magnesium	mg	250 as supplement	350 as supplement+ diet	400 (G)
Iron	mg	Not set	45	17 (G)
Copper	mg	5	10	1 (10T)
Iodine	µg	600	1100	500 (G) (940T)
Zinc	mg	25	40	25 (42T)
Manganese	mg	Not set	11	4 (G) (9–12T) 0.5 (G) for older people
Potassium	mg	Not set	Not set	3700 (G)
Selenium	µg	300	400	350 (450T)
Chromium (trivalent)[f]	mg	Not set	Not set	10 (G, T)
Molybdenum	µg	600	2000	Not set
Fluoride	mg	Not set	10	Outside terms of reference
Phosphorus	mg	Not set	4000	250 (G) (2400T)

G, guidance level; T, total intake; IU, International Unit.

[a] All EVM amounts relate to 60 kg bodyweight adult and figures in parentheses are total (T) amounts from all dietary sources. Typically, reference bodyweights for adults are higher, and any maximum levels for the proposed risk management model should be increased to reflect a bodyweight of 70 kg. This calculation is consistent with the adult bodyweight used in Section 4 and would apply to all EVM SULs and GLs.

[b] The UL for adults established by SCF in 2003 was 50 µg/day, the same as that from IOM. In 2010, IOM, and in 2012, EFSA, published their reassessments and the ULs were increased to 100 µg/day for adults, including pregnant and lactating women.

[c] D-α-tocopherol equivalents/day.

[d] This UL is applied to the total of all forms of niacin resultant on the IOM's decision to establish a lowest-observed-adverse-effect level (LOAEL) based on skin flushing by nicotinic acid. In the EU niacin supplements and niacin fortification are generally in the form of nicotinamide.

[e] Implied in text of report.

[f] Picolinates are excluded.

2. The setting of ULs for children aged 4–10 years

The extent to which ULs for subpopulations are considered separately from the general population is an area of scientific judgement, and the nutrients are usually assessed on a case-by-case basis. All three groups of scientific risk assessors, EFSA, EVM and IOM addressed the setting of ULs for children, and the accepted method is, where appropriate, to extrapolate the UL derived from adult data.

Major physiological changes in the velocity of growth and in endocrine status occur during childhood and adolescence. The onset of puberty is an extremely anabolic period that is influenced by a marked rise in hormonal activity, which results in a number of physical changes that characterise adolescence. These changes have been well documented and their timing, rates and extent are highly variable (Tanner et al. 1965; Zlotkin, 2006). Over several decades there has been a progressive increase in the heights and weights of children that is associated with trends towards earlier puberty. The enormous variability in the rate and timing of the adolescent growth spurt influences the nutritional requirements of children at different ages and their adaptability to nutrient deficiencies and excess. For the purposes of setting maximum levels in fortified foods and food supplements for children, this review focuses on the younger age groups: 4–6 years and 7–10 years. Thereafter, safety issues for older and post-pubertal children have to take into account their increasing speed of growth and the adolescent growth spurt, where nutritional needs are similar to adults. Moreover, nutritional status and intakes of nutrients tend to deteriorate in older children aged 11–14 years and 15–18 years (Scientific Advisory Committee on Nutrition (SACN) 2008), which means that any risk management measures will have to take into account the risk of suboptimal intakes and deficiencies as well as excess in older children. The reasons for selection of a children's age range of four to ten years relate to the age ranges of reference bodyweights as shown in Table 2, the availability of nutrient intake data (UK Office for National Statistics 2000; Flynn et al. 2009), the age ranges for UK Dietary Reference Values (UK Department of Health 1991), the EFSA opinions on ULs for vitamin D (EFSA 2012) and DRVs for vitamin C and manganese (EFSA 2013), which summarise AIs for age groups four to six years and seven to ten years. Moreover, the IOM (1997) described early childhood as ages four through eight years, and determined that the adolescent age group should begin at nine years.

The scientific data on nutrient requirements, absorption, metabolism and excretion of nutrients in children is extremely limited. Hence, dietary requirements and ULs for children are extrapolated from adult requirements and from adult ULs, respectively. These extrapolations are usually made on the basis of bodyweights by means of either reference bodyweights (SCF 1993) or metabolic bodyweights, BW0.75 (EFSA 2006; FAO/WHO 2006). The large differences in bodyweights between younger and older children shown in Table 2 can markedly influence the magnitude of the UL.

Table 2
Reference bodyweights of population groups in Europe (SCF, 1993).

Age (years)	Mean weight (kg)	
	Male	Female
1–3	13.0	12.5
4–6	20.0	19.0
7–10	28.5	29.0
11–14	44.5	45.0
15–17	61.5	53.5
18–29	74.6	62.1
30–59	74.6	62.1
60–74	73.5	66.1
≥ 75	73.5	66.1

3. Control of risk in fortified foods and food supplements

Risk analysis comprises three distinct but closely linked components: risk assessment, risk management and risk communication (WHO 2002, FAO/WHO 2006, Codex Alimentarius Commission 2010, EFSA 2010, 2012[a]). Each component is integral to the overall risk analysis, and the primary objectives are not only to protect the health of consumers but also to take into account other legitimate factors including the facilitation of consumer choice and avoidance of barriers to international trade.

In Europe, the criteria to be taken into account for the establishment of the maximum amounts of vitamins and minerals in fortified foods and food supplements are set out in Regulation (EC)1925/2006 (European Parliament and of the Council 2006[a]), which makes provisions for the harmonisation of the conditions for the voluntary addition of vitamins and minerals and of certain other substances to foods (often referred to informally as food fortification) and in Directive 2002/46/EC (European Parliament and of the Council 2002) on the approximation of the laws of European Union (EU) member states relating to food supplements that harmonise specific rules on vitamins and minerals in these products. Both legal acts aim to provide a high level of consumer protection and to ensure the effective functioning of the internal market.

The key criteria for setting maximum amounts in fortified foods and food supplements are:

- The 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
- The intake of vitamins and minerals from all dietary sources
- Reference intakes of vitamins and minerals for the population.

The present report applies the principles of quantitative and qualitative risk management taking into account the criteria set out in the European regulations in order to contribute towards the development of an appropriate process for setting maximum levels of vitamins and minerals in food supplements and in foods with added nutrients for adults and children aged 4–10 years. The risk management model includes:

- Calculation of a Population Safety Index (PSI) for each nutrient
- Taking into account the contributions to total nutrient intake from conventional foods, fortified foods and food supplements
- Allocation of nutrients into three categories of risk
- Proposals for maximum safe levels for each nutrient in food supplements (MLS) for adults and children aged 4–10 years and in fortified foods

4. Characterising risk using the Population Safety Index (PSI)

The fundamental risk management question is how to establish an objective process to determine how large the margin of safety is now and is likely to be in the future, allowing for varying dietary contexts, new research findings and their application to food products entering the food supply. The PSI paradigm describes a process by which vitamins and minerals with ULs can be allocated into categories of risk. The concept of characterising risk using the PSI is set out in the following equation, and the PSI calculations for adults and for children aged 4–10 years are shown in Tables 3 and 4, respectively.

$$PSI = \frac{UL - (MHI + IW)}{RDA}$$

where PSI = Population Safety Index

UL = Tolerable Upper Intake from all sources

MHI = Mean Highest Intake from foods (includes fortified foods but excludes food supplements)

IW = Intake of Minerals from water

RDA = Labelling Recommended Daily Allowance as set in Regulation (EC) No 1169/2011 on food information to consumers

Table 3
Calculation of the population safety index (PSI) to characterise risk for adults.

Nutrient and unit of weight	UL (UL)[a]	Mean highest intake from foods only[b] (MHI)	Potential intake from water[c] (IW)	Reference labelling value (RDA) as set in Regulation (EC) 1169/2011	Population safety index (PSI)[d] Average PSI in bold
Group 2 Low risk of exceeding the UL					
Niacin (as nicotinamide) mg	M 900 F 900	47 32	0 0	16 16	53.3 54.3
					53.8
Vitamin E (mg as α-tocopherol equivalent)	M 300 F 300	14.5 12.5	0 0	12 12	23.8 23.9
					23.9
Vitamin C (mg)	M 2000* F 2000*	209 187	0 0	80 80	22.4 22.7
					22.6
Vitamin D (µg)	M 100 F 100	11.2 9.6	0 0	5 5	17.8 18.1
					18.0
Vitamin B_6 (mg)	M 25 F 25	5.9 3.8	0 0	1.4 1.4	13.6 15.1
					14.4
Molybdenum (µg)	M 600 F 600	210* –	20 –	50 –	7.4 –

Folic acid (µg)[f]	M 1000 F 1000	203 153	0 0	200 200	4.0 4.2
					4.2
Selenium (µg)	M 300 F 300	92* –	0 –	55 55	3.8 –
					3.8
Phosphorus (mg)	M 4000* F 4000*	2710 1806	10 10	700 700	1.8 3.1
					2.5
Group 3 Potential risk at excessive intakes					
Iron (mg)	M 45* F 45*	26.4 18.9	0.4 0.4	14 14	1.3 1.8
					1.6
Iodine (µg)	M 600 F 600	407 –	30 –	150 150	1.1 –
					1.1
Copper (mg)	M 5 F 5	3.3 2.8	1 1	1 1	0.7 1.2
					1.0
Zinc (mg)	M 25 F 25	21.3 12.8	1 1	10 10	0.3 2.1
					1.2
Calcium (mg)	M 2500 F 2500	1774 1296	300 300	800 800	0.5 1.1
					0.8
Vitamin A (preformed retinol µg)	M 3000 F3 000	2782 2521	0 0	800 800	0.3 0.6
					0.5
Magnesium (mg)[e]	MF 250	See note	See note	375	0.7

M, male; F, female

[a] UL as established by SCF/EFSA where available, otherwise the IOM*.

[b] Data drawn from Table 6; 97.5percentile, food only.

[c] Data drawn from SCF/EFSA and EVM opinions and used in ERNA (2004).

[d] The lowest PSI for adult men is used in the risk characterisations.

[e] UL for dissociable magnesium salts in supplements only.

[f] The UL established by the SCF for folic acid is 1000 µg/day for supplementation

For adults, the UL from all sources is established by SCF/EFSA when available; otherwise, the IOM UL values are used. The children's ULs are based on extrapolated values for the age range 4–6 years rather than the UL based on an age range of 7–10 years or an average UL covering children aged 4–6 years and 7–10 years. To illustrate, the extrapolation of data from adults to children based on bodyweights uses the following equation:

$$\text{UL children} = \text{UL for adults} \times \frac{\text{weight of child}}{\text{weight of adult}}$$

Based on a reference bodyweight for adults of 70 kg and a child weighing 20 kg, the child's UL for a 4–6 year-old would be estimated to be 29% of the adult value, whereas for a 7–10 year-old child weighing 28.5 kg, the UL would be 41% of the adult UL. The use of the lower UL for 4–6 year-old children in this risk management model introduces a substantial precautionary measure. The children's ULs are taken from EFSA risk assessments where they are set, and these ULs already have built-in precautions for chronic exposure. Otherwise, the children's ULs are derived from IOM adult values as shown in Table 4.

The MHI is the "mean highest intake" from food sources (includes fortified foods but excludes food supplements) based on the 97.5 percentile (P 97.5) mean intake data of male adults or 4–10-year old male children. These intakes in males are all higher than the equivalent intakes by female adults and children, and hence the calculation introduces a small precautionary measure. The IW is the estimated intake of minerals from water drawn from EFSA (2006) and EVM opinions (EVM 2003). For example, for 4 to 10-year-old children, an estimate of water consumption is 0.3 L/day. Estimates of intake of minerals from water (IW) by school age children are determined from data on levels of minerals in drinking water combined with consumption data for water based on EVM estimates. The RDA is the labelling Recommended Daily Allowance—previously called Reference Labelling Value (RLV)—sourced from Annex XIII of Regulation EU No 1169/2011 (European Parliament and of the Council 2011). The labelling RDAs are for the whole population and are generally significantly higher than the reference nutrient intakes (RNIs) for a particular population group, as is the case for children. The higher labelling RDA denominator is used for both calculations for adults and children because the value is consistent across all EU member states, whereas RNI values vary considerably. The use of the labelling RDA not only provides a fixed point on the intake curve but also adds a substantial precautionary measure. The PSI model provides a process by which the vitamins and minerals can be allocated into categories of risk (European Responsible Nutrition Alliance 2004, Richardson 2007, 2010). The model assumes that where the PSI of a nutrient is higher than 1.5, i.e. where there is a margin of safety of 1.5 times the RDA between the P 97.5 intake of food (including fortified foods) plus the estimated intake from water and the UL, the chance of exceeding the UL is low (Group 2). Where the PSI is 1.5 or below, i.e. the P 97.5 of intake from food (including fortified foods) plus the estimate of intake from water is either above the UL or less than 1.5 times the RDA below the UL, there is a potential risk of exceeding the UL (Group 3). In other words, the characterising factor for Group 2, the "low risk of exceeding the UL" is a PSI greater than 1.5 for both adults and children, and for Group 3 the "potential risk at excessive intakes" is a PSI of 1.5 or less. Group 2 includes some nutrients as special risk management cases: potassium, vitamin C, magnesium and folic acid, which are described separately in Appendix 1. Similarly, Group 3 contains manganese as a special case described separately in Appendix 2. Group 1 denotes nutrients without a UL and with no evidence of risk to human health as described in the following section.

Some micronutrients, such as boron, fluoride, silicon, sodium chloride and sulphur, can be used in the manufacture of food supplements in Europe (Commission Regulation (EC) No 1170/2009). These micronutrients have also been considered by risk assessors, and their safety evaluations have been summarised separately in Appendix 3.

Table 4
Data used in calculations of Population Safety Indices (PSIs) for children.

	UL (4–6 year olds) EFSA 2006	MHI P97.5% Males (4–10 years)	MHI x 1.5 for vitamins; x 1.1 for minerals	IW	RDA Regulation (EC) 1169/2011	PSI	MLS/day (calculated using the conditions in Section 3)	UK Dept of Health RNI (7–10 years)
GROUP 2 Low risk of exceeding the UL								
Vitamin B_6 (mg)	7 (40[a])	3.18	4.77	0	1.4	2.72 (26.3[a])	2.23 (35.2[a])[b]	1.0
Vitamin C (mg)	650[a]	197.5	296.3	0	80	5.66	353.7[a],[b]*	30
Vitamin D (µg)[c]	50	5.05	7.57	0	5	8.99	42.4	—
Vitamin E (mg)	120	14.24	21.36	0	12	8.81	98.6	—
Niacin equivalent (mg) as nicotinamide (mg)	— 220	38.2	57.3	0	16	11.36	162.7	12
Molybdenum (µg)	200	—	—	3.0	50	—	[b]	—
Phosphorus (mg)	3000[a]	1494	1643.4	0.66	700	2.15	1356.6[b]	450
Selenium (µg)	90	—	—	—	55	—	[b]	30
Magnesium (mg)	250[d]	293	322.3	15	375	—	[b]	200
Folic acid (µg)	300	348[e]	522	—	200	—	[b]	150
Potassium (mg)	1233[f]	3090	3399	3.6	2000	—	[b]	2000
GROUP 3 Potential risk at excessive intakes								
Vitamin A (retinol) (µg)	1100	698	1047	0	800	0.50	[b]	500
Calcium (mg)	2500[a]	1294	1423	94	800	1.39	983[b]	550
Copper (mg)	2	1.34	1.47	0.3	1	0.66	[b]	0.7
Iodine (µg)	250	312	343	4.5	150	–0.45	[b]	110
Iron (mg)	40[a]	14.9	16.39	0.1	14	1.78	23.5[b]	8.7
Manganese (mg)	3.0[a]	3.74	4.11	—	2	–0.37	[b]	—
Zinc (mg)	10	9.7	10.67	0.45	10	–0.02	[b]	7.0

MHI, mean highest intake; IW, intake of minerals from water; RDA, recommended daily allowance; MLS, maximum level in food supplements; RNI, reference nutrient intake.

[a] Source: IOM.

[b] See qualitative assessment of MLS in text.

[c] In 2012 EFSA raised the UL for children from 25 to 50 µg/day.

[d] Supplemental source only.

[e] Total folate.

[f] Based on EVM supplemental UL.

5. Qualitative risk characterisation of nutrients without a UL and with no evidence of risk to human health: Group 1 nutrients

Qualitative assessments of the risk assessment opinions (EFSA, IOM, EVM) show no adverse effects in healthy individuals associated with high intakes of vitamins B_1, B_2, B_{12}, biotin, pantothenic acid, vitamin K and chromium (trivalent form). All the Group 1 nutrients have extremely low or non-existent toxicity even at high levels of intake. In the absence of adverse effects, there is no scientific risk assessment basis for the establishment of maximum amounts for the Group 1 nutrients. The EC orientation paper (European Commission 2007) also concluded that because of the lack of evidence of adverse effects, a proportionate risk management approach, in line with the principles of better regulation, would be not to establish maximum amounts for these nutrients. A summary of the qualitative risk characterisation of the Group 1 nutrients for which no UL is available and for which there is no evidence of risk is shown in Table 5.

Table 5
GROUP 1 nutrients: qualitative risk characterisation for those vitamins and minerals for which no UL is available from the Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA) together with information on the establishment of GLs by the EVM1 and upper safe levels for supplements from Hathcock (2004)

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. In the absence of established toxicity at any observed intake level, the EVM identified a clinical trial (Maebashi et al. 1993) that involved oral administration of 9 mg per day of supplemental biotin to 20 diabetic patients for up to 4 years without adverse effects. Given the low number of individuals studies, the EVM applied a toxicological UF of 10 to conclude that biotin supplements of 900 µg/day should be considered safe. For guidance purposes, the EVM concluded that 0.9 mg biotin (equivalent to 0.015 mg/kg bodyweight/day in a 60 kg adult) would not be expected to produce adverse effects. In 1995, a study by Velazquez et al. in 22 protein-deficient children administered 10 mg biotin/day for 15 days resulted in no reported adverse effects. Hathcock (2014) observed the absence of adverse effects at 9 mg biotin per day and suggested that biotin supplements at a level of 2500 µg are likely to be safe.
Chromium	No adverse effects have been convincingly associated with excess intake of chromium from food or food supplements. Overall, there is insufficient data from human or animal studies to derive a safe UL for chromium. However, the oral toxicity of the poorly absorbed trivalent chromium appears to be low (EVM 2003). In a number of limited studies, there was no evidence of adverse effects associated with supplementary intake of chromium up to an intake of 10 mg chromium per day. The dietary intake of trivalent chromium in European countries is well below these amounts. In the establishment of a GL, the EVM derived a level of 0.15 mg/kg bodyweight/day or 10 mg/person. This amount was based on an extrapolation from a rat study (Anderson et al. 1997) and allowed for a toxicological UF of 100, 10 for interspecies variation and 10 for interindividual variation. Hathcock (2014) concluded that the available human clinical trial data are sufficient to indicate safety for chromium supplements at levels of up to 1000 µg/day for adults.

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 from clinical studies using high doses of pantothenic acid that intakes considerably in excess of current levels of intake from all sources do not represent a health risk for the general population. The EVM noted that the limited available data have not identified target organ toxicity and the adverse effects that were noted (gastrointestinal disturbances at very high doses) were transient. The General Practitioner Research Group (1980) suggests that amounts of 2000 mg pantothenic acid/day are without adverse effect. The EVM applied a UF of 10 to allow for interhuman variability and calculated a GL for supplemental intake of 200 mg (equivalent to 3.3 mg/kg bodyweight/day for a 60 kg adult). Hathcock (2004) noted the EVM provided evidence that supplemental intakes of 2000 mg did not produce adverse effects (i.e. an HOI), the absence of adverse effects with daily intakes as high as 10 g, and systematic clinical experience with intakes of up to 1000 mg/day. Hathcock (2014) selected an upper safe level for supplements of 1000 mg/day.
Riboflavin	No study has reported significant adverse effects in humans of excess riboflavin consumption from food or food supplements. Although this does not mean that there is no potential for adverse effects from high intakes, and it was not possible, based on the present database, to derive a UL, the limited evidence available from clinical studies indicates that current levels of intake of riboflavin from all sources do not represent a risk to human health. The EVM stated that, in several human studies, riboflavin was well tolerated, with no reports of adverse events. The balance of evidence suggests that ingestion of riboflavin over prolonged periods of time is without harmful effects. In a prophylactic study of migraine, amounts of 400 mg/day for at least 3 months were well tolerated (Schoenen et al. 1998). Only 2 minor, non-specific adverse effects, which could not be unequivocally attributed to the treatment, were reported in 28 patients. The EVM applied a toxicological UF of 10 to allow for interhuman variability because of the small numbers of individuals involved, who may not be representative of the general population, and the incomplete investigation of adverse effects. The resultant EVM GL of 40 mg/day (0.67 mg/kg bodyweight for a 60 kg adult) is regarded as unnecessarily restrictive (Hathcock. 2014). Using a 400 mg/day LOAEL and a UF of 2, Hathcock identified a NOAEL of 200 mg/day.
Thiamin	Systematic data on adverse effects with oral intake of vitamin B_1 in humans are very limited. However, from the available literature it can be concluded that orally ingested vitamin B_1 has a very low risk of adverse effects. The US FNB (1998) concluded that no UL could be achieved if based on inadequate data. The SCF (1993) mentioned no evidence of toxicity at oral intakes up to 500 mg/day for one month. Previous evaluations of micronutrient safety classified vitamin B_1 as a nutrient with no adverse effects. The SCF (2001) concluded that it is not possible to derive a numerical UL for vitamin B_1. However, existing evidence from clinical studies as well as the long history of therapeutic use, at levels up to 200 mg/day for months, indicates that current levels of intake from vitamin B_1 from all sources do not represent a health risk for the general population. The EVM referred to one human supplementation study (Meador et al. 1993), which reported that graduated doses of thiamin hydrochloride, up to 6000–8000 mg/day for 5–6 months, caused no adverse effects in a very small group of patients. Based on a randomised, double-blind placebo-controlled study by Gokhale et al. (1996) with 556 young females aged 12–21 years, who were given 100 mg thiamin for 60 or 90 days, the EVM established a GL of 100 mg/day (equivalent to 1.7 mg/kg bodyweight supplemental thiamin for a 60 kg adult). Hathcock (2014) also concluded that 100 mg supplemental thiamin would not be expected to result in adverse effects.

Vitamin B_{12}	There are no adverse effects known for vitamin B_{12} from foods or from food supplements. There are no clearly defined adverse effects produced by vitamin B_{12} 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 B_{12} absorption who received amounts up to 1000 µg/day orally for prolonged periods. The EVM found no evidence of adverse effects of vitamin B_{12} in humans, but stated that subcutaneous or intraperitoneal injections of 1.5 to 3 mg per kg bodyweight were acutely toxic to mice (Tsao and Myashita, 1993). The EVM set a GL of 2000 µg based on a clinical trial (Juhlin and Olsson, 1997) as well as other data showing no adverse effects. Hathcock and Troendle (1991) noted the lack of adverse effects, the extensive testing and use of oral vitamin B_{12} dosages of up to 1000 µg in pernicious anaemia patients, and considerable clinical experience and evidence of safe oral intakes of 3000 µg/day (an HOI risk assessment, Hathcock (2014)).
Vitamin K	Vitamin K_1 (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. In human studies with limited numbers of subjects, there is no evidence in healthy individuals of adverse effects associated with supplementary intakes of vitamin K up to 10 mg/day for limited periods of time. However, people under medical supervision who were taking coumarin anticoagulant drugs should not increase their phylloquinone intake by dietary change or by using dietary supplements without medical advice because of their antagonistic interaction. Although vitamin K per se is safe and there is no evidence of toxicity in healthy individuals, the exception is patients on oral anticoagulants (OACs) such as coumarin derivatives. OACs have an effect by blocking the utilisation of vitamin K, and this explains the antagonistic effect. OACs are widely used for the treatment and prophylaxis of thromboembolic diseases. High-dose vitamin K is used as an antagonist treatment to stop bleeding. Food supplements up to 100 µg/day have been reported not to interfere with OACs (Schurgers et al, 2004). The EVM (2003) noted that acute doses up to 25,000 mg/kg bodyweight did not cause fatalities in rats, mice or chicks, and that in human supplementation studies, amounts up to 10 mg/day for 1 month are not associated with adverse effects. The EVM applied a toxicological UF of 10 for interindividual variation because of the very limited human database, resulting in a GL for daily supplementary intake of 1 mg/day. Hathcock (2014) commented that the decision of the EVM to use a UF of 10 seems unnecessarily cautious in view of the absence of reports of adverse effects at intakes of 30 mg or more. Hathcock (2014) identified a safe upper level for supplements of 10 mg/day, i.e. HOI, based on the same clinical data as the EVM (Cracium et al. 1998).
Vitamin C	Special case: see Group 2, Appendix 1.
Manganese	Special case: see Group 3, Appendix 2.

[1] All EVM amounts for daily guidance levels (GLs) for supplementation relate to a 60 kg bodyweight adult. Typically, reference bodyweights are higher, and any maximum levels for the proposed risk management model should be increased to reflect a bodyweight of 70 kg. This calculation would be consistent with the adult bodyweight used in Section 4 and would apply to EVM Group 1 nutrient GLs.

The EC orientation paper questions the positioning of two nutrients in group 1, namely chromium and vitamin K. In the case of chromium, the biological effects depend strongly on its specific chemical form, and the nutritive effects are exclusively related to the trivalent form—chromium III. All of the major toxic effects are associated with chromium VI. No credible data or reports have demonstrated any adverse effects of chromium III in humans, and animal data also suggests that orally administered chromium is extremely innocuous. Overall, the risk assessors concluded that there is insufficient data to derive a UL for chromium. However, in their risk characterisation SCF/EFSA concluded that, in the limited number of human studies conducted, there was no evidence of any adverse effects associated with the supplementary intake of chromium at up to 1 mg/day. The dietary intake of trivalent chromium in European countries was also shown to be well below this amount. Similarly, the IOM did not set a UL, and the EVM also concluded that there is insufficient data from human or animal studies to derive a safe upper level for long-term supplementation (SUL) for this nutrient. The EVM further noted that the oral toxicity of poorly absorbed trivalent chromium appears to be low, and it set a guidance level (GL) equivalent to 10 mg/person/day, which indicates that chromium III has a wide safety margin.

In the case of vitamin K, the SCF/EFSA could not establish a UL but the risk characterisation states that in the limited number of human studies carried out to date there is no evidence of adverse effects associated with the supplementary intake of vitamin K in the form of phylloquinone at up to 10 mg/day for limited periods of time. The UK EVM derived a GL of 1 mg for daily supplementary intake and concluded that vitamin K (phylloquinone) would be unlikely to result in adverse effects in normal healthy individuals. However, because of the antagonistic interaction between phylloquinone and coumarin anticoagulant drugs, people taking these drugs should not increase their vitamin K intake significantly by dietary change or by using dietary supplements without medical advice. Similarly, vitamin K activity and vitamin K-dependent clotting functions must be carefully considered before oral antibiotics are prescribed for patients taking coumarin and heparin-based anticoagulants under medical supervision (see table 5).

The major limitation of the UL method as applied by risk managers is that no UL can be set for nutrients without established adverse effects. However, an alternative approach has been developed recently, using what is termed the Highest Observed Intake (HOI) (FAO/WHO 2006). The HOI is derived only when no adverse health effects have been identified. It is the highest level of intake observed or administered as reported within (a)study(ies) of acceptable quality (FAO/WHO 2006). Hence, in the absence of a UL, the HOI is the highest intake with the available data to show, with acceptable confidence, the absence of adverse effects up to that intake. Both the HOI and UL values, even after adjustments for uncertainties related to the strength of the data set, are risk assessment values and both are accepted by the Codex Alimentarius in its Nutritional Risk Analysis Principles and Guidelines for application to the work of the Committee on Nutrition and Foods for Special Dietary Uses (Codex Alimentarius Commission, 19th edition 2010). With this sanction, the HOI acquires global policy and regulatory importance because Codex is recognised as the pre-eminent international authority on food safety by the World Trade Organisation in its Sanitary and Phytosanitary (SPS) Agreement (WTO 2011).

In the risk assessments carried out by EFSA and the IOM, no data were found to identify any hazard related to high intakes of thiamin, riboflavin, vitamin B12, biotin and pantothenic acid. The standard position of these authorities is that a UL cannot be set if a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) cannot be identified owing to the absence of an established adverse effect or hazard. Interestingly, the EVM did not define the HOI or any similar concept, but it did identify

advisory or guidance levels (GLs) , and these are analogous to the definition of HOI. In the development of regulatory values, it is argued that no maximum levels should be set for nutrients with no established adverse effects or safety concerns and where no UL could be established. Nonetheless, it is acknowledged that some policymakers and regulatory authorities prefer to establish maximum levels for all the nutrients, and hence any maximum value could be based on the HOI risk assessment method (Hathcock and Kriengsinyos 2011).Table 5 includes information on the establishment of GLs by the EVM (2003) and upper safe levels for supplements from Hathcock (2014) for the Group 1 nutrients. These levels can be used as guidance when a risk manager needs scientific advice concerning an upper safe intake.

6. Nutrient intake data

Nutrient risk analysis requires an assessment of the current and potential intakes of vitamins and minerals from the various dietary sources. A fundamental problem is the adequacy of the information on nutrient intakes, and much greater attention needs to be paid to the acquisition, development and interpretation of exposure data for essential nutrients for specific population groups (WHO 2002, FAO/WHO 2006). FAO/WHO (2006) recognised that the ability to acquire and maintain useful and up-to-date composition and intake data is a growing challenge because of the changing food supply and the increased use of fortified foods and food supplements. The uncertainties and biases in the estimation of habitual nutrient intake distributions to reflect the reality of the diverse patterns of intake and dietary contexts that exist are also a major challenge. In situations where intake data are limited, mathematical modelling approaches have to be taken to handle uncertainties in the intake estimates and the potential impact of the uncertainties on risk characterisation. Scientific committees draw on a wide array of available consumption data including from household surveys, 24 hour and 48 hour recalls etc. In fact, data from many days are needed to estimate accurately intakes for individuals because day-to-day variation in nutrient intake can be quite large (FAO/WHO, 2006). In the current risk management model, the focus, where possible, is to use four or seven day weighed dietary records as the sources of the best available data. The objective is also to provide clear, transparent and detailed documentation of the approaches used.

In the absence of overall EU data, national diet and nutrition surveys are the best sources of information, despite the fact that most of them have been conducted with different methodologies and may not be up to date. A pragmatic approach used in the current model, which has also been supported in the EC 2007 orientation paper, is to use the best available data. The most complete data, from countries considered to be "mature" markets for both food supplements and fortified foods, are derived from the UK National Diet and Nutrition Surveys (NDNS) (UK Office for National Statistics 1998, 2000, 2003) and the North/South Ireland Food Consumption Survey (Irish Universities Nutrition Alliance, IUNA (2001). In addition, specific nutrients can be assessed on a case-by-case basis by means of validated national data from individual member states for specified population groups.

For the purposes of the current risk management model, it is necessary to determine whether current, actual or potential future intakes from food supplements and fortified foods are safe. Hence, the term "mean highest intake" (MHI) used in the calculation of the PSI has been defined as the P 97.5 intake from foods, including fortified foods. The Irish data for adults shown in Table 6 has been used in the current model for characterising risk.

The UK NDNS (2000) provides data for children aged 4 to 10 years and in particular, the P 97.5 from food sources including fortified foods but excluding food supplements and also intakes from all sources including food supplements. The EVM (2003) made extensive use of the UK NDNS intake data in its risk assessments. Table 7 shows the intake data from all sources including food supplements for male children aged 4–10 years compared with the ULs.

Table 6
Micronutrient intakes in Irish adults aged 19–64 years (North/South Ireland Food Consumption Survey available at www.iuna.net, IUNA 2001; Flynn, personal communication 2007) compared with SCF/EFSA UL for intake from all sources

Nutrient	97.5 percentile (all sources)[a]		97.5 percentile (food only)[b]		UL
	Men	Women	Men	Women	
Retinol, µg	2887	2885	2782	2521	3000
Carotene, µg	6871	6842	6871	6735	Below 15 000
Vitamin D, µg	13.5	15.1	11.2	9.6	100
Vitamin E, mg	28.3	38.3	14.5	12.5	300
Thiamin, mg	4.7	6.4	3.9	2.6	Not set
Riboflavin, mg	4.6	4.7	3.7	2.8	Not set
Vitamin B_6, mg	7.6	30.3[c]	5.9	3.8	25
Vitamin B_{12}, µg	14.8	15.1	13.2	11.6	Not set
Folic acid, µg	294	407	203	153	1000 (supplemental)
Preformed niacin, mg	52	44	47	32	900 (nicotinamide)
Biotin, µg	92	103	75	54	Not set
Pantothenic acid, mg	12.5	14.4	10.5	7.3	Not set
Vitamin C, mg	588	588	209	187	Not set (IOM: 2000)
Calcium, mg	1774	1419	1774	1296	2500
Magnesium, mg	607	431	602	415	250 (as supplement to diet)
Phosphorus, mg	2710	1806	2710	1806	Not set (IOM: 4000)
Iron, mg	28.8	72.2[c]	26.4	18.9	Not set (IOM: 45)
Zinc, mg	23.5	21.8	21.3	12.8	25
Copper, mg	3.5	3.0	3.3	2.8	5

[a] Food (including fortified foods) and food supplements.

[b] Food including conventional foods and fortified foods; excludes food supplements.

[c] The high values reflect the relatively small sample sizes when using P 97.5% values. The equivalent P 97.5% intake is 5.5 mg for vitamin B_6 and 25.5 mg for iron.

Table 7
Intake data from all sources based on the UK FSA National Diet and Nutrition Survey (NDNS) 2000 (male children aged 4–10 years) compared with ULs (ULs for children) (4–6 years and 7–10 years)*

Intake/ day	Vit B_6 (mg)	Vit C (mg)	Vit D (µg)	Vit E (mg)	Niacin equiv (mg)	Phosphorus (mg)	Magnesium (mg)	Folate (µg)	Potassium (mg)	Vit A (µg)
Mean	1.86	75.9	2.61	7.85	24.7	970	184	204	2053	547
Median	1.79	64.3	2.24	6.99	24.3	941	179	195	2010	454
Std. Dev.	0.56	52.5	1.60	4.19	6.8	251	47	62	504	332
P2.5	1.00	19.8	0.73	3.42	14.2	541	101	102	1129	150
P95	2.89	169.6	5.32	13.37	35.5	1417	264	319	2870	1202
P97.5	3.20	216.4	6.74	16.32	40.5	1509	295	355	3090	1423
UL (4–6 years)	7 (40[a])	650[a]	50	120	220[a]	3000[a]	250[b]	—	1233[c]	—
UL (7–10 years)	10 (40[a])	1200[a]	50	160	350[a]	4000[a]	250[b]	—	1757[c]	—

Intake/ day	Retinol (µg)	Beta Carotene (µg)	Calcium (mg)	Iodine (µg)	Iron (mg)	Manganese (mg)	Zinc (mg)	Sodium (mg)	Chloride (mg)	Copper (mg)
Mean	75.9	2.61	7.85	24.7	970	184	204	2053	3384	0.77
Median	64.3	2.24	6.99	24.3	941	179	195	2010	3238	0.74
Std. Dev.	52.5	1.60	4.19	6.8	251	47	62	504	884	0.24
P2.5	19.8	0.73	3.42	14.2	541	101	102	1129	1882	0.37
P95	169.6	5.32	13.37	35.5	1417	264	319	2870	4928	1.22
P97.5	216.4	6.74	16.32	40.5	1509	295	355	3090	5385	1.34
UL (4–6 years)	650[a]	50	120	220[a]	3000[a]	250[b]	—	1233[c]	—	2.0
UL (7–10 years)	1200[a]	50	160	350[a]	4000[a]	250[b]	—	1757[c]	—	3.0

* Male 4–10 years: all sources (including supplements)

[a] IOM UL.

[b] Supplemental magnesium.

[c] Supplemental potassium.

7. Comparison of intakes of high consumers in various European countries with ULs

Dietary data on intakes of vitamins and minerals in different population groups are not available in many EU member states, and where they do exist they are often limited, particularly with respect to intakes from fortified foods and food supplements. In 2009, data from nationally representative surveys on adults and children were collated and analysed (Flynn et al. 2009). Where possible, the separate contributions of conventional foods, food supplements and fortified foods were collected from surveys in Denmark, Germany, Finland, Ireland, Italy, The Netherlands, Poland, Spain and the UK. Intake of high consumers in this study, defined as the 95th percentile (P95) of each nutrient, was compared with the UL. The P95 was chosen versus the higher cut-offs such as P97.5 because the available data was mainly obtained from dietary surveys with a relatively short reference period (e.g. 24-hour recalls), and for some age groups the samples were relatively small. In the current risk management model, the P97.5 intakes from the Irish and the UK NDNS data were used as an additional precautionary measure, and because the intake data were based on the more robust seven-day food and supplements diary and seven-day weighed intake. From Table 6 the micronutrient intakes of Irish adults aged 19–64 years indicate that the P97.5 intakes from males and females from all sources are less than the UL. Patterns of consumption of foods and food supplements and voluntary fortification practices vary widely among countries and the risk of excessive intakes is relatively low for most nutrients, exceptions in some countries being retinol, zinc, iodine, copper and magnesium. Children are the most vulnerable group as they are more likely to exhibit high intakes relative to the UL. In Table 8, the P95 nutrient intakes for children aged 4–10 years are presented from a number of countries for base diet (including mandatory fortified foods), base diet plus supplements and base diet plus supplements plus discretionary (voluntary) fortified foods. The data shown include P5 and P95 nutrient intakes, the mean intake based on the number of countries and the ranges of intakes for seven vitamins and eight minerals. The calculation of the mean P95 intakes is a simple and direct way of providing a common estimate of high intake (Anderson and Tetens 2009).

Because children generally have a higher intake of food and nutrients expressed per kg bodyweight compared with adults and are potentially the most vulnerable group to exceed the UL, each of the 15 nutrients is considered separately on the basis of observations by Flynn et al. (2009) and shown in Appendix 4.

From Table 7, the P97.5 intakes from the UK NDNS data for male children aged 4–10 years for iodine, manganese and zinc from all sources exceed the children's UL for 4–6 year-old children. As previously indicated, the children's ULs that are used in the PSI calculations are for the lowest age group of children, and the fact that the P97.5 intakes exceed, or are close to (in the case of retinol) the UL is therefore not surprising. If the higher UL for the two groups aged 4–6 and 7–10 years are used, only the P97.5 for iodine exceeds the higher UL. If P95 intakes are used, no intake level exceeds the higher children's UL. The UL value for folic acid is based on studies in the elderly and is not relevant to the setting of a UL for children. Furthermore, the total folate intake includes contributions from natural folate and folic acid. The children's UL of 250 mg for magnesium refers to supplemental sources of readily dissociable magnesium salts and does not include the magnesium normally present in foods and beverages (EFSA 2006). The UL for potassium also refers to supplemental sources.

For most nutrients, adults and children generally consume considerably less than the UL, even when the total intakes from non-fortified foods, fortified foods and food supplements are

Table 8
ILSI Europe data (Flynn et al. 2009) Nutrient intakes of children aged 4–10 years

Nutrient	P95 base diet including mandatory fortified foods	P95 base diet plus supplements	P95 base diet plus supplements and fortified foods	Children's ULs (EFSA 2006)		Mean total intake	P5 base diet plus supplements and fortified foods
				4–6 yr	7–10 yr		
Calcium (mg)	1259 (8) (1107–1721)	1344 (5) (1134–1775)	1266 (3) (1151–1400) 1107 (UK)	2500[a]	2500[a]	852 (3) (811–898) 694 (UK)	518 (3 (442–658)
Copper (mg)	2.7 (4) (1.6–4.2)	1.6 (1)	1.18 (UK)	2	3	0.73 (UK)	0.7 (1)
Iodine (µg)	220 (5) (140–280)	249 (3) (140–335)	271 (2) (266–277)	250	300	146 (2) (145–147)	58 (2) (47–68)
Iron (mg)	12.9 (8) (8.3–16.6)	14.2 (5) (9.9–18.2)	14.0 (4) (12.0–15.4)	12.9	18.3	9.3 (4) (7.6–11.8)	5.8 (4) (4.6–8.3)
Magnesium (mg)	304 (7) (249–430)	331 (4) (254–430)	293 (3) (282–309) 257 (UK)	250	250	214 (3) (188–248) 176 (UK)	149 (3) (119–191)
Phosphorus (mg)	1538 (8) (1381–1926)	1548 (5) (1334–1926)	1495 (3) (1379–1623) 1320 (UK)	3000[a]	3000[a]	1094 (3) (996–1290) 929 (UK)	764 (3) (640–1006)
Selenium (µg)	49 (5) (7.5–14.7)	57 (3) (39.3–65.3)	53 (2) (39.8–65.3)	90	130	35 (2) (26.5–43.1)	20.1 (2) (16.5–23.6)
Zinc (mg)	11 (7) (7.5–14.7)	12 (5) (8.2–17.2)	9 (3) (8.4–10.2)	10	13	6 (3) (5.7–6.4)	3.7 (3) (3.4–3.8)
Folic acid (µg)	No data	25 (2) (40–72)	172 (2) 135–209)	300	400	62 (2) (52–71)	2 (2) (0–2)
Folate (µg)	292 (8) (149–418)	358 (4) (260–464)	310 (4) (192–399)	—	—	178 (4) (136–218)	96 (4) (69–114)
Nicotinamide (mg)	18.7 (2) (16.3–21.1)	22.5 (2) (20.3–24.6)	29.5 (1)	220	350	16.5 (1)	8.6 (1)
Retinol (µg)	878 (5) (452–1312)	999 (1)	965 (2) (865–1065)	1100	1500	342 (2) (317–367)	92 (2) (81–103)
Vitamin B_6 (mg)	2.2 (8) (1.3–3.3)	2.6 (5) (1.9–3.3)	2.7 (4) (2.2–3.4)	7 (40[a])	10 (40[a])	1.7 (4) (1.5–1.9)	0.9 (4) (0.7–1.0)
Vitamin D (µg)	4.0 (8) (2.3–5.9)	7.5 (4) (5.0–13.6)	5.1 (4) (3.0–6.8)	50	50	2.3 (4) (1.8–2.7)	0.8 (4) (0.4–1.0)
Vitamin E (mg)	13.4 (7) (9.1–19.5)	17.4 (4) (13.4–21.0)	12.8 (3) (9.1–16.2)	120	160	7.5 (3) (5.8–9.2)	3.8 (3) (3.4–4.3)

P95 nutrient intakes for 4- to 10-year-old children from base diet (including mandatory fortified foods), base diet plus supplements plus discretionary fortified foods for children aged 4–10 years compared with ULs and mean P5 intakes (number of countries and ranges in parentheses)

[a] IOM UL.

combined. Even in high consumers, P95 total intakes are significantly lower than the UL for most nutrients. For zinc, copper and retinol the UL is low relative to the observed intakes, particularly in children. Although for adults and children intakes of copper, iodine, zinc and retinol in some countries may approach or exceed the UL by a small amount, there are no reported adverse health effects. It should be borne in mind that ULs are established using uncertainty factors to ensure that at this level of intake the risk of adverse effects is negligible even for the most sensitive individuals in the population, including the children. Consequently, while an intake of a nutrient exceeding the UL is not without some risk, the probability of adverse effects occurring in the small proportion of individuals exceeding the UL by a modest amount is low (Flynn et al.2009).

8. Future intakes of vitamins and minerals

To gain a measure of potential changes in consumer food preferences, food supplement use and the increased fortification of food products that might develop, a comparison of surveys undertaken in the UK in 1986–1987 and 2000–2001 was made UK NDNS 2003).

Table 9 shows the mean adult intakes for men—the population group with the highest nutrient intakes generally—reflecting their higher energy intake compared with women. Although an increase in intake of more than 20 per cent was recorded for only two of the vitamins (C and B6), to take into account potential future changes in dietary patterns, the current model assumes a precautionary risk management factor of a 50 per cent increase in dietary intake for all the vitamins from foods, including fortified foods, i.e. the mean highest intake (MHI) is increased by 50 per cent.

In contrast to the data for vitamin consumption, the results for the UK over the 15-year period show a reduction in mean intake for men for many essential minerals, with only calcium intake increasing by more than five per cent. Given that, for technical and taste reasons, mineral fortification is self-limiting, the current model assumes a precautionary risk management factor of 10 per cent as the potential future increase for all mineral intakes. These precautionary risk management factors that allow for future changes in intake from food, including fortified food, are used to estimate proposed maximum levels in food supplements (MLS). There is also the potential for the intake of certain minerals via ingestion of water alone, water-based drinks and water used in the preparation of foods, and this amount has to be taken into account when assessing potential dietary intakes.

Table 9
Changes in nutrient intakes based on a comparison of National Diet and Nutrition Surveys (NDNS) undertaken in the UK in 1986/1987 and 2000/2001 (from: UK Office for National Statistics 2003)

Vitamins	Mean intake for all men		
	1986/1987 UK adults survey	2000/2001 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)	40.0	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%

Minerals	Mean intake for all men		
	1986/1987 UK Adults Survey	2000/2001 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%

[a] Food (including fortified foods) and food supplements

[b] Food including conventional foods and fortified foods; excludes food supplements.

[c] The high values reflect the relatively small sample sizes when using P 97.5% values. The equivalent P 97.5% intake is 5.5 mg for vitamin B_6 and 25.5 mg for iron.

9. Characterisation of risk using the PSI, allocation of the nutrients into three groups, and proposed maximum levels in food supplements (MLS) for adults and children aged 4–10 years

As previously stated, the PSI values for nutrients in Groups 2 and 3 are shown in Tables 3 and 4 for adults and children, respectively, together with the data used in the calculations. Taking into account the risk categorisation of nutrients using the PSI and the quantitative estimates of future potential higher intakes from all other food sources including fortified foods, the current risk management model has been applied to determine maximum levels of vitamins and minerals in food supplements where possible using the following equations:

For vitamins: MLS = UL – (MHI x 150%)

For minerals: MLS = UL – [(MHI x 110%) + IW]

The three groups of nutrients and the proposed maximum levels for each nutrient in food supplements (MLS) for adults and children aged 4–10 years that would not be expected to result in any adverse effects are shown in Table 10. These proposed MLS for each nutrient in Groups 2 and 3 can be usefully compared with the EVM (2003) values for long-term supplementation (SUL) and the ULs for total daily intake from the IOM and SCF/EFSA as shown in Table 1.

Group 1 (No UL/no PSI)

No evidence of risk within the ranges currently consumed—does not represent a risk to the health of adults or children. For the Group 1 nutrients vitamins B_1, B_2,biotin, vitamin B_{12},pantothenic acid, vitamin K and chromium, no ULs have been set, and hence there are no PSIs.

As described in Section 5, no maximum levels are set for Group 1 nutrients with no established adverse effects or safety concerns.

Group 2 (PSI ≥ 1.5)

In this group, there is a low risk of exceeding the UL. For adults and children, the PSI values for nicotinamide, vitamin E, vitamin C, vitamin B_6, vitamin D and phosphorus are greater than 1.5. For molybdenum and selenium, there are no data from the UK NDNS and for adults, data were used from the IOM risk assessments. For folic acid, it is not possible to distinguish between natural folate and folic acid from the intake data. The UL for adults is for folic acid and, as previously explained, the children's UL is not appropriate.

Group 3 (PSI ≤ 1.5)

In this group there is a potential risk of exceeding the UL. The nutrients in Group 3 have low or negative PSIs, which in part results from the combination of precautionary measures used, e.g. for children, the lower UL for 4–6 year-old children, the higher intake data for 4–10 year-old children and the adult labelling RDA. However, the method of categorisation indicates that for iron, iodine, copper, calcium, zinc and preformed retinol there is a potential risk of exceeding the UL. Interestingly, the categorisation of nutrients by means of the PSI approach is consistent with earlier classifications and with the theoretical model for safe additions of nutrients to foods (Flynn et al. 2003 and Renwick et al.2004).

Quantitative and qualitative case-by-case risk management approaches have been used for Groups 2 and 3 in order to balance the risk of excessive intake and the risk of suboptimal intakes and deficiency. The detailed risk management analyses are shown in Appendices 1 and 2, respectively.

Table 10
Proposed maximum safe levels in food supplements (MLS) for adults and children aged 4–10 years

Nutrient	Proposed Maximum Safe Levels in food supplements (MLS)	
	Adults	Children 4–10 years
GROUP 1[a] No evidence of risk to human health at levels currently consumed	No further risk management measures required	No further risk management measures required
Vitamin B_1 (mg) Thiamin	—	—
Vitamin B_2 (mg) Riboflavin	—	—
Biotin (µg)	—	—
Vitamin B_{12} (µg) Cobalamin	—	—
Pantothenic acid (mg)	—	—
Vitamin K (µg)	—	—
Chromium III (mg)	—	—
GROUP 2 Low risk of exceeding UL		
Vitamin B_6 (mg) Pyridoxine	18[b]	2.2[b]
Vitamin C (mg)	1700	350
Vitamin D (µg)[c]	83.2	42.4
Vitamin E (mg)	270[b]	98.6[b]
Nicotinamide (mg)	820	162.7
Molybdenum (µg)	350[b]	50[b]
Phosphorus (mg)	1250[b]	550[b]
Selenium (µg)	200	55
Magnesium (mg)	250[b]	250[b]
Folic acid (µg)[d]	600	300
Potassium (mg)	1500	1200

GROUP 3 **Potential risk at excessive intakes**		
Vitamin A (retinol) (µg)	1200	1000
Beta-carotene (mg)	7	7
Calcium (mg)	1000	500
Copper (mg)	2[b]	1[b]
Iodine (µg)	200[b]	150[b]
Iron (mg)[e]	20[b]	7[b]
Manganese (mg)	4[b]	1.5[b]
Zinc (mg)	15[b]	5[b]

[a] As described in Section 5 of the report, no maximum levels are set for Group 1 nutrients with no established adverse effects or safety concerns. Provisional MLS for these nutrients are stated in Table 5 and are based on an approach analogous to the FAO/WHO HOI risk assessment methodology.

[b] Because of the .large differences in scientific opinions on the derivation of the ULs/SULs for these nutrients, there is a need for a systematic reassessment of their safety. For these nutrients, the IOM ULs are significantly higher than those established by EFSA risk assessments, which could result in a higher MLS. For example, vitamin B_6 (93 mg and 35.2 mg MLS for adults and children, respectively), vitamin E (978.3 mg and 285.8 mg for adults and children, respectively).

[c] Higher values were established by the IOM and EFSA risk assessments in 2010 and 2012, respectively.

[d] Folic acid: pteroylmonoglutamic acid.

[e] WHO (2012) recommended a supplemental daily amount of 30–60 mg elemental iron as a safe and effective way to reduce risk of maternal anaemia.

10. Setting maximum amounts of vitamins and minerals in fortified foods

The most comprehensive theoretical model has been prepared by the ILSI Europe Addition of Nutrients to Foods Task Force (Flynn et al. 2003). The methodology identifies a number of critical factors that determine the risk of unacceptably high intake for each micronutrient at high levels of food/energy intakes. These factors include:

- ULs
- high micronutrient intakes in Europe at the 95th percentile intake for each nutrient
- the proportion of foods to which micronutrients could practically be added
- a range of estimates for the fractions of foods that might actually be fortified for each nutrient.

A maximum level was set up for each micronutrient per typical serving or 100-kcal portion. Reassuringly, the ILSI model also resulted in three categories of risk characterisation for the micronutrients that could be added safely to appropriate foods at specified levels similar to the categories described in this report. In addition, preformed retinol was highlighted as a special case. The ILSI model has been modified to consider the intakes from food supplements and to take into account the impact of the new regulation on nutrition and health claims (European Parliament and of the Council 2006b). Rasmussen et al. (2006) and Kloosterman et al. (2007) have also proposed risk assessment approaches that are based on the ILSI model, all of which express the maximum levels of certain nutrients in fortified foods in weight units (mg or µg) per 100 kcal. Whilst for food supplements the maximum amount will be set per daily amount of consumption of the supplement (e.g. per one/two/three tablets or capsules, or other measure indicated by the manufacturer), for fortified foods the maximum level is likely to be set per weight or per energy of the food consumed (e.g. per 100 kcal, per 100 g/ml, per quantified portion). The EC's orientation paper (2007) states that, in order to ensure that health-driven practices are preserved and a minimum significant amount of the nutrient is present in foods without a risk of excess intakes, there may be a need for limitations and restrictions to the addition of certain vitamins and minerals in normal foods (e.g. addition of iodine restricted only to salt and addition of vitamins A and D reserved for specific products). Several foods are mandatorily fortified, or additions of nutrients are officially encouraged (such as vitamin D in fat spreads and iodine in salt). An understanding of fortification practices in specific countries is important, and this information has been tabulated by Flynn et al. (2009). When maximum amounts are set in normal foods for vitamins and minerals, whose reference intakes for the population are close to the upper safe levels, according to Regulation EC 1925/2006 the following criteria should also be taken into account: (i) the contribution of individual products to the overall diet of the population in general, or of subgroups of the population; and (ii) the established nutrient profile of the product, as provided for by Regulation (EC) 1924/2006 (European Parliament and of the Council 2006b).

Typically, the amounts of nutrients added to food products are based on making a nutrient content claim. The Regulation on Nutrition and Health Claims (2006b) sets out the criteria for 'source' and 'high' in vitamins and minerals. A claim that a food is a source of vitamins and/or minerals, and any claim likely to have the same meaning for the consumer, may only be made when the product contains the vitamins and/or minerals in at least a significant amount, as defined in Annex XIII Part A of Regulation EU No 1169/2011 on food information to consumers, i.e. 15% nutrient reference value (NRV) per 100 g or 100 ml of products other than beverages, or per portion of a food if the package contains only a single portion and 7.5% of the NRV per 100 ml in the case of beverages. A claim that a food is 'high' in vitamins

and/or minerals may only be made if the product contains at least twice the value of 'source'. In the case of foods that are a natural source or are high in vitamins and minerals, the term 'naturally' may be used as a prefix to the claim.

As a result of the legislation, most nutrients are added to foods and beverages to make nutrient content claims, unless there is a specific nutritional rationale to have higher proportions of the RDA. For the most common fortificants, which are in group 1 and group 2 of the risk characterisation (e.g. vitamin B_1 (thiamin), vitamin B_2 (riboflavin), nicotinamide, folic acid, vitamin B_6, vitamin B_{12}, biotin, pantothenic acid, vitamin D and vitamin E), the margins for additional fortification above current levels that are already accounted for in the current risk management model are sufficiently large to pose a very small risk to human health from excessive intakes. Some nutrients used in food supplements tend not to be added to food products either for technical reasons or because consumers have not been made aware of their particular nutritional benefits; e.g. chromium, vitamin K and several trace elements such as magnesium, phosphorus, manganese, zinc and copper. Beta-carotene is used as a food additive or as provitamin A. Iodine, as previously noted, is commonly added to table salt. Attempting to add nutrients such as iron, calcium and magnesium at high levels often presents technological problems with colour, texture and taste, as well as having implications for the shelf-life of products (Richardson 1997). Folic acid fortification of cereal grain products is aimed at reducing the risk of neural tube defects. However, concerns have been expressed over the possibility that an increased folic acid intake might delay the diagnosis of vitamin B_{12} deficiency and even exacerbate its neurological and neuropsychiatric effects in the elderly. The policy decisions and scientific issues related to folic acid fortification have been reviewed by Smith (2007).

Bearing in mind the scientific discussions and technical limitations, as well as the fact that the consumption of nutrient-dense and fortified foods is constrained by the energy density and satiating aspect of the food or meal, the risk of excessive intakes of vitamins and minerals from foods is small. Preformed retinol merits further detailed consideration, as noted previously. Nevertheless, present levels of retinol addition to foods, e.g. restoration, substitution and fortification, as well as current levels used in food supplements appear to pose no problems in the diets of Europeans. The impact of fortified foods on total dietary consumption was analysed by Godfrey et al. (2004). The percentage of each food category that was fortified was estimated. The data indicated that, overall, about 75% of foods and drinks consumed in European diets are rarely or never fortified. Fortified foods were found rarely to contribute more than 3% of the total diet on a per capita basis, an exception being in countries where it is mandatory to fortify a staple food (e.g. as in the case of flour in the UK). The authors estimated that high-level consumers of fortified foods are unlikely to obtain more than 10% of their diet in fortified form. Hennessy et al. (2013) concluded that, in general, total micronutrient intakes (including fortified foods and food supplements) of high consumers (defined by the 95th percentile of intake) in adults and children across Europe do not exceed the UL set by EFSA. Although the population of children consuming fortified foods is greater than adults, and for some micronutrients small proportions of the population, particularly children, exceeded the UL, Hennessy et al. concluded that there is little risk of adverse effects occurring in the small proportions of individuals exceeding the UL by a modest amount, given the use of adequate safety factors (uncertainty factors, UF) in establishing ULs.

The methodology for setting maximum levels of vitamins and minerals in fortified foods is currently being developed to decide the best way to set the maximum amounts of the nutrients, i.e. per weight or per energy of the food consumed (e.g. per 100 kcal, per 100 g/ml, per portion). The methodology, however, uses the same groups, 1, 2 and 3, to characterise risk as described in this report.

11. Factors influencing the stability of vitamins, their retention in food and food supplement products and the impact on tolerances and declared values of nutrients on food labels

The use of vitamins such as preformed retinol in fortified foods and food supplements poses a number of technological challenges.
The stability of the vitamins is influenced by several factors: temperature, moisture, oxygen, light, pH, oxidising and reducing agents, presence of metallic ions (e.g. iron and copper), presence of other vitamins, other components of food such as sulphur dioxide and various combinations of the above. Vitamin deterioration takes place naturally during storage of foods and food ingredients, losses occur during processing and preparation, and the factors that affect the degradation of vitamins are the same whether the vitamins are naturally occurring or are added to the food or food supplement from synthetic sources (Berry Ottaway, 1993). As the rates of degradation of each of the vitamins can differ significantly, the technologist needs to know, as far as possible, the stability of the various vitamins added to a particular formulation in order to ensure that any legal requirements of maintaining the label claim are complied with throughout the shelf-life of the product. Data from manufacturing processes, effects of the food matrix (solid, liquid etc) and the packaging,and the probable storage conditions can be obtained from well-designed stability trials. This information is used to determine a realistic shelf-life and expiry date, which will be based on the retention rate of the most unstable component. For the most sensitive and labile vitamins, such as vitamin A (retinol), the amounts in the product are adjusted above the declared value in order to ensure that all label declarations are met at the end of the stated shelf-life of the product. These increases over the declared values are termed “overages”. Because of the varied nature of each vitamin, the possibility of each combination of nutrients interacting in different ways with the food matrix or food supplement, as well as the infinite number of ways of manufacturing, preparation and storage, it is virtually impossible to generalise on the effects of individual factors on stability and nutrient retention. Nevertheless, a huge amount of information has been collected on the behaviour of individual vitamins, and in the majority of cases it is possible to make good predictions as to losses to be expected for foods and food supplements.

In December 2012, the European Commission published a guidance document (European Commission, 2012) for competent authorities for the control of compliance with EU legislation regarding nutrition labelling of foodstuffs and the setting of tolerances for nutrient values declared on a label. The nutrient content of foods should not deviate substantially from labelled values to the extent that such deviations could lead to consumers being misled. Levels of vitamins and minerals are measured by Member States’ control authorities in order to ensure compliance with levels of nutrients declared in nutrition labelling on foods and food supplements. The factor of food safety, both risk of excessive intake and of deficiency, has to be taken into account when setting tolerances for vitamins and minerals added to foods, including food supplements. Should the amount at the upper end of the tolerance range for a declared value exceed the limit of the maximum level, the guidelines state clearly that the maximum level has priority over the tolerance range. In other words, the proposed maximum levels for vitamins and minerals include overages and must also allow for tolerances.

The tolerances for vitamins and minerals in food supplements (which are deviations around the mean), including measurement uncertainty, are shown in Table 11. The footnote states that for vitamin C in liquids, higher upper tolerance values could be accepted. In the case of preformed retinol, the upper tolerance is likely to be at the highest tolerance level + 50%.
For a food supplement with a declaration to meet

the labelling RDA of 800 µg of vitamin A over the entire shelf-life, and an overage of 50%, the estimated maximum amount would be calculated to be around 1200 µg.

Table 11
Tolerances for vitamins and minerals including measurement uncertainty (European Commission, 2012)

For foods other than food supplements		
	Tolerances	
Vitamins	+50%**	–35%
Minerals	+45%	–35%
For food supplements		
	Tolerances	
Vitamins	+50%**	–20%
Minerals	+45%	–20%

12. Conclusions

Risk assessment and risk management for nutrients differ from other substances in foods because vitamins and minerals are essential for human life, and consequently adverse effects can result from suboptimal intakes and deficiencies as well as from excessive intakes. In order to establish the risk to the population of exceeding the UL, risk managers have to draw together information on the range of safe intake—sometimes referred to as the "acceptable range of oral intake" (AROI) (WHO 2002). For the purposes of the current risk management model, the convenient set points to determine the safe range of each nutrient are for the upper end, UL, and for the lower end, the labelling RDA. It should be noted that the RDAs and ULs are determined by two completely different conceptual approaches and the two values have been used only as indicators to establish the extent of the range of safe intake and to help categorise nutrients on the basis of the risk associated with exceeding their ULs. In other words, where the UL and RDA are closer together, the safe range of intake is relatively small; where they are further apart, the safe range of intake is relatively large. The use of the labelling RDA as denominator in the PSI calculation in the proposed model complies with the legal criterion (European Parliament and of the Council 2002, 2006) that due account must be taken of reference intakes of vitamins and minerals for the population, and helps to establish the breadth of the range of safe intakes, as well as a process for risk characterisation. Some European member states have proposed that the maximum amounts in fortified foods and food supplements should be based on, or limited to, fractions or multiples of the RDA. However, the legislation requires the establishment of maximum levels based on scientific risk assessment, and the RDA-based approach has been recognised as unscientific and arbitrary (see Appendix 5 for why RDA-based upper safe levels are not scientific or appropriate). As a result, it has been rejected by the EC and condemned by the European Court of Justice. Furthermore, it is essential to go beyond the standard micronutrient RDA methodology and paradigm, which focus on vitamins and minerals and prevention of deficiencies, to one that reflects recent scientific research on longer-term health benefits (Hanekamp and Bast 2007).

The scientific risk assessments for determining ULs depend on the availability of good data on the nature, frequency and severity of adverse effects detected at different levels of intake. The database supporting the safety-in-use of vitamins and minerals is limited and there is rarely adequate consideration given to potentially vulnerable population subgroups such as children or the elderly. It is important for risk managers to recognise that the UL is defined as the maximum level of chronic daily intake of a nutrient (from all sources) that is judged to have no appreciable risk of an adverse effect occurring at some specified level of exposure. Similarly, the EVM (2003) defined safe upper levels (SULs) as an intake for long-term supplementation that can be consumed daily over a lifetime without any significant risk to health, on the basis of available evidence. Guidance Levels (GLs) are also defined by the EVM as levels that represent an approximate indication of levels that would not be expected to cause adverse effects but have been derived from limited data and are less secure than SULs. The determination of SULs or GLs relate to the amounts of vitamins and minerals that potentially susceptible individuals could take daily on a lifelong basis without medical supervision and in reasonable safety (EVM 2003). The setting of upper safe levels by risk assessors and the setting of maximum levels in fortified foods and food supplements by risk managers builds in levels of precaution and provides a framework within which the consumer can make an informed decision about intake, having confidence that harm should not ensue. The upper safe levels set

in risk assessments tend to be conservative, and it is possible that for some vitamins and minerals, e.g. vitamin B_6 and vitamin C, larger amounts could be considered for shorter-term consumption because the available data are limited and relate to differing time periods. As a consequence of the limited data, risk assessors build in uncertainty factors and apply the precautionary principle of allowing for the variable quality of information and for risk managers to weigh up the different safety margins between necessity and adverse effects. As the markets, and hence the exposures, vary over time, risk managers will need to monitor changing patterns of addition of nutrients to different foods and the use of food supplements in order to review the risk management options (Verkaik-Kloosterman et al. 2012). There will also be a need for regular review of the scientific basis for the establishment of lower and upper safe intakes of micronutrients, particularly for those nutrients with narrow safe ranges of intake. The recent risk assessments for vitamin D and for beta-carotene illustrate this point (IOM 2010, EFSA 2012b, 2012c). Any changes in either RDAs or ULs will also impact on the risk management options.

Although different risk management models have already been developed to set maximum amounts of nutrients in fortified foods and food supplements for adults (Flynn et al. 2009, Kloosterman et al. 2007, Rasmussen et al. 2005), none has specifically addressed the implications for young children. In Europe, market practices for food supplements differentiate between products intended for adults and children, whereas for food fortification, the issues are complicated by the fact that many foods with added nutrients are consumed by adults and children. Hence, it is necessary to know the contribution of individual products to the overall diet of adults and children. Furthermore, if maximum levels in fortified foods are set on a per 100 kcal basis, it will be necessary to calculate the actual amounts present and likely to be consumed per 100 g or 100 ml and per quantified serving. To date, the majority of food products and current voluntary food fortification practices aim to achieve a claim for ”source” or “high” levels of a nutrient. These fortification approaches have been used safely and effectively for many years. The authorisation of health claims for the well-established functions of vitamins and minerals in Regulation (EC) No 432/2012 (Commission Regulation 2012) may also stimulate additional food fortification, and risk managers will need to monitor the impact of the new legislation on both fortified food and food supplement consumption patterns (Richardson 2012). .

Risk assessors are often faced with inadequate or limited data, insufficient dose-response or exposure data and variability and sensitivity of individuals or certain population groups (World Health Organisation 2002, 2006; Dufour et al. 2010). Risk assessments such as those by EFSA (2006), IOM (1997, 1998, 2000, 2001) and EVM (2003) set a safe upper level (SUL) or UL, where possible, that was based on the identification of a NOAEL or the LOAEL and a critical endpoint followed by an uncertainty assessment. For children, the imprecision of the data available, lack of data and adequacy of the data on variability are major limitations for risk assessors and risk managers. Considerable scientific judgement is used to develop ULs for children, especially when the critical endpoints and uncertainty factors relate to adults. Nevertheless, ULs for children have been established on the basis of known differences in body size, physiology, metabolism, absorption and excretion of a nutrient. When data are lacking for children and adolescents, extrapolations are made from adult ULs based on reference bodyweights. Zlotkin (2006) identified specific examples of the difficulties in deriving a UL for children using inadequate data and uncertain uncertainty factors (sic) from adult risk assessment data, and its subsequent use as a safety benchmark. The overall conclusion was that, when intakes exceed the extrapolated UL by relatively small amounts, the significant uncertainties surrounding the derivation of the children’s UL makes it likely that intakes are not the problem, and that the application of a UL with inadequate data is the problem. For some

nutrients, the narrow range between the RDA and UL is unjustified, especially when there is a lack of demonstrated adverse effects at current intakes above the UL. Zlotkin (2006) also identified plausible arguments indicating that the setting of adult ULs for zinc, retinol and folic acid may be too low.

There are significant challenges to the development of scientifically plausible models for nutrient risk assessment and management to set maximum levels in fortified foods and food supplements for adults and population subgroups (Verkerk and Hickey 2009). Rodricks and Levy (2013) summarised the key messages from a National Research Council (NRC) advisory report on human health risk assessment, entitled Science and Decisions: Advancing Risk Assessment (2009). The authors comment that risk assessment provides an interpretative and analytical framework to be used for systematically dealing with the available scientific information and its associated uncertainties, and for identifying research needed to reduce those uncertainties. One key area is the long-standing problem of biological variability, affecting cross-species extrapolation and interindividual differences in response among members of the human population (human heterogenicity). The use of "uncertainty factors" to determine a reference intake such as a UL has a number of operational limitations, including often the absence of scientific knowledge. However, given the complexities, appropriate risk assessment and risk management models can be proposed that are pragmatic and scientifically justified as well as proportionate and consistent with regulatory developments and health policies.

The present report notes these difficulties and recognises that regulatory agencies are frequently confronted with the need for decision making in the face of insufficient data. However, risk management is about evaluating the magnitude of a possible risk, and caution is needed not only in allowing particular levels of vitamins and minerals in fortified foods and in food supplements for adults and children but also in not being overly restrictive in their use. It is important to take into account the typical or prescribed patterns of consumption of foods or food supplements and to provide clear labelling for daily use.

The information about, and process for derivation of, proposed maximum levels for adults and children have been made as transparent and explicit as possible to stimulate further consultation and dialogue between regulators, risk assessors, the academic community and industry. The rationale and data presented in this report identify the sources of the ULs, the intake data relevant to the calculation of the PSIs, the proposed maximum levels of vitamins and minerals in food supplements (MLS) and the development of suitable approaches to setting maximum levels in fortified foods. Despite the inconsistencies in the various datasets, the risk management model does permit the characterisation of the nutrients into three groups of risk. Quantitative and qualitative approaches have been used to propose maximum levels that would not be expected to result in adverse effects. Although several mathematical models and qualitative approaches have been proposed to set maximum levels, none has included a comprehensive series of scientific judgements relating specifically to children. Because of the increased interest in, and availability of, fortified foods and food supplements, it is critical to undertake appropriate risk management measures to ensure consumer protection.

The risk management approaches in this report attempt to address the many difficulties and inconsistencies surrounding the establishment of ULs, particularly for children, the limited nutrient intake data from conventional foods, fortified foods and food supplements and the care needed not only to minimise risk of excessive intakes but also the risk of suboptimal intakes and micronutrient deficiencies in vulnerable groups. Food fortification practices and current levels of nutrients used in food supplements for over two decades have been shown to be safe and effective. The applicability of the risk management model described in this report

depends on the availability of the input data, particularly data on nutrient intakes from food consumption surveys that cover all member states of the EU. Currently, such data are sparse. However, the PSI calculation can be applied to several different sets of nutrient intake data, and in the current report the method has been applied using the most comprehensive data from the UK and Ireland. The overall purpose of the report is to contribute towards the development of a scientifically-based process for the setting of maximum levels of essential nutrients in fortified foods and food supplements. Consultation and dialogue between the various interested parties are critical to ensure that proportionate measures are used to protect consumers, young and old, and to facilitate informed choice.

13. Appendices

Appendix 1. Risk management analysis of Group 2 nutrients

Vitamin B_6

- In adults, both deficiency and excess of pyridoxine may produce neurological disturbances. Pyridoxine is neurotoxic at high levels of intake (2–6 g/day), but for some individuals neuropathy may occur after doses of 300–500 mg/day. Neurotoxicity has not been reported at doses of 100 mg/day when consumed for a period of up to a few months. However, the development of symptoms at high doses is slow. As a result, EFSA (2006) decided to apply uncertainty factors: two for deficiencies in the database and two to allow for long-term versus short-term intakes. The resultant adult UL is 25 mg/day. Mild adverse effects at levels up to 200 mg/day are reversible.
- The complete absence of adverse effects at 100 and 150 mg provides confidence in the adult UL of 25 mg/day (EFSA 2006). The IOM (1998) derived an adult UL of 100 mg/day and established ULs of 40 mg and 60 mg/day for children aged 4–8 and 9–13 years, respectively. These levels contrast sharply with the ULs derived by EFSA (2006). The EFSA ULs for children are 7 mg/day and 10 mg/day for children aged 4–6 years and 7–10 years, respectively.
- No adverse effects have been associated with high intakes of vitamin B_6 from food sources. The ULs relate to large oral supplemental doses used to treat conditions such as carpal tunnel syndrome and premenstrual syndrome. The risk of adverse effects arising from excess intake of vitamin B_6 from food and supplements appears to be very low even at the highest intakes observed (IOM 1998).
- UK NDNS (2000) showed a deficiency of pyridoxine in 10% of the 4–18 year age group.
- P97.5 and P95 intakes from all sources is well below the UL in the UK NDNS and ILSI Europe intake data.
- The calculated MLS using the risk management model (Richardson 2007) is 18 mg/day for adults and 2.23 mg/day for children based on EFSA ULs. If the IOM values are considered, the calculation gives a maximum level of 93 mg/day for adults and 35.2 mg/day for children. These MLS values are shown in Table 10 with the IOM values referred to in footnote b.
- Because of the large differences in scientific opinions on the derivation of the ULs for vitamin B_6, key questions arise for a thorough reassessment of its safety and for the determination of the validity and use of different levels of this nutrient in different circumstances.

Vitamin C

- A UL was not established by EFSA because of limited data. In contrast, the IOM found that the data were sufficiently conclusive to establish a UL of 2000 mg/day. The EVM (2003) set a Guidance Level of 1000 mg/day for long-term supplementation.
- Vitamin C has a low order of toxicity and in humans, acute adverse effects are characterised by transient gastrointestinal disturbances, with doses of 3–4 g/day, which are reversible within a week. There are no dose-response data on the acute gastrointestinal intolerance for either adults or children. EFSA (2006), IOM (2000) and EVM (2003) found no credible reports of adverse effects other than gastrointestinal distress, bloating and diarrhoea at higher doses. These effects are usually mild, transient and self-limiting through discontinuation or lowering of the amount consumed.

- Vitamin C is water-soluble and is one of the most labile nutrients in the diet, easily destroyed by oxygen, metal ions, increased pH, heat or light.
- Vitamin C enhances non-haem iron absorption. Iron is in short supply in the diets of many children, particularly girls.
- The IOM ULs for children are extrapolated from the adult UL of 2000 mg on the basis of bodyweight. The UL values from all sources, rounded to the nearest 50 mg, are 650 mg/day for children aged 4–8 years and 1200 mg/day for children aged 9–13 years.
- Using the equation in the section on setting maximum levels for children, the calculated maximum level in a food supplement for children aged 4–10 years is 353.7 mg. This level is rounded down to 350 mg/day. Similarly, the calculated MLS for adults is 1700 mg/day rounded from the mean of 1686.5 mg/day for males and 1719.5 for females.

Vitamin D

- IOM (2010) and more recently, EFSA (2012b) have published their reassessments of the UL for vitamin D. In both cases a NOAEL of 250 µg/day was established and the UL for adults including pregnant and lactating women and for children and adolescents aged 11–17 years was adapted by EFSA to 100 µg/day. The new UL for older children takes into account the rapid bone formation during this period of rapid growth and development, and it is unlikely that this age group has a lower tolerance for vitamin D compared with adults. These new ULs are double the previous EFSA and IOM ULs and are based on new scientific evidence (EFSA 2012b, IOM 2010).
- For children aged 1–10 years, the new UL of 50 µg/day was proposed by EFSA taking into account the smaller body size of this age group. This new EFSA UL is double the previous amount set by EFSA and IOM.
- Excess vitamin D may lead to hypercalcaemia, which is the critical adverse effect. However, amounts up to 275 µg/day do not lead to persisting hypercalcaemia or hypercalciuria in adults (EFSA 2012b).
- EFSA reported that data from surveys in 14 European countries indicates that vitamin D intakes in high consumers are below the revised ULs for vitamin D in all population groups.
- The main determinants of vitamin D status are intake, skin pigmentation and sun exposure. In the absence of UVB sunlight exposure, dietary vitamin D becomes an essential nutrient. Vitamin D is found in only a few natural foods, e.g. fatty fish, liver, fish liver oils and egg yolks that contain vitamin D_3 (cholecalciferol). Some higher fungi such as mushrooms are a natural source of vitamin D_2 (ergocalciferol). Cholecalciferol is produced in the skin in response to ultraviolet B (UVB) radiation from sunlight.
- Serum 25 (OH) D is a good marker of vitamin D status since it reflects both dietary vitamin D intake and endogenous dermal vitamin D production. How to define precisely the thresholds for vitamin D deficiency, insufficiency and optimal status is still a matter of debate.
- The past decade has seen a renewed interest in the functions of vitamin D related not only to bone health but to potential non-skeletal benefits for cardiovascular function, diabetes mellitus, cancer, multiple sclerosis, allergy and infection by strengthening the immune system etc. An assessment of the level of evidence for the various potential benefits has been undertaken by Thacher and Clarke (2011).
- Vitamin D deficiency is widespread around the world. The risk of vitamin D deficiency with age and low vitamin D status is associated with increased bone loss and osteoporotic fracture risk in the elderly. Vitamin D deficiency and insufficiency are globally very common, especially in risk groups such as young children,pregnant and lactating women, elderly

and non-western immigrants to northern countries (van Schoor and Lips 2011 Vitamin D deficiency is a re-emerging health problem and has become an epidemic in children. Rickets has become a global health issue.

- In 2013, the Norwegian Scientific Committee for Food Safety (VKM) noted that less than 50% of the adult population meets the recommended intake of vitamin D. The recommended intake of vitamin D is 10 µg/day for children above 2 years, adolescents and adults, and 20 µg/day for the elderly over 75 years. The VKM concluded that, to ensure an intake of 20 µg of vitamin D per day in the elderly, a daily amount of 20 µg from food supplements would be justified. The VKM suggested that the maximum limit for vitamin D be increased to 20 µg/day for all age groups.
- Most food supplements contain 10 µg or less and there are no reports of adverse effects at this level. The scientific conservatism of previous risk assessments has been corrected recently, with the resulting conclusion that much larger amounts of vitamin D are considered safe. The data of Vieth and co-workers (2006, 2007) reduce the uncertainty about the safety of maximum supplementary use of vitamin D at levels of 60 µg/day for adults.
- Using the risk management model, the calculated MLS for use in food supplements for adults and children aged 4–10 years are 83.2 µg/day and 42.4 µg/day, respectively.
- Bearing in mind that the vitamin D content of unsupplemented diets is, for the most part, low, and that data from European populations indicate that vitamin D intakes from all sources in high consumers are below the UL (EFSA 2012b) for all population subgroups (i.e. about 25%, 75%, 30% and 8% of the ULs for adults, infants, children and adolescents, respectively), the proposed MLS are 83.2 µg/day and 42.4 µg/day, respectively.

Vitamin E

- SCF EFSA decided that the critical effect of vitamin E is on blood clotting and established a NOAEL of 540 mg/day. An uncertainty factor(UF) of 2 covers interindividual differences, and the UL was established as 270 mg/day rounded to 300 mg/day for adults including women during pregnancy and lactation. The UL for children and adolescents is derived by scaling the adult UL on the basis of body surface area (bodyweight0.75). The ULs for 4–6 and 7–10 year-olds are 120 mg/day and 160 mg/day, respectively. IOM calculated a UL of 1000 mg/day for adults based on animal data. The UL values apply to all forms of vitamin E. EVM (2003) established a safe upper level for long-term supplementation of 540 mg D-α-tocopherol equivalents/day, equivalent to 9.0 mg/kg bodyweight/day in a 60 kg adult. For a 70 kg adult and for a 20 kg child, these safe upper levels would be 630 mg/day and 180 mg/day, respectively.
- In Europe, current estimated intakes from base diet, fortified foods and food supplements, including the P95 and the P97.5, in the population are generally in the range 10–38.2 mg/day and well below the UL (Flynn et al. 2009).
- Vitamin E has a low risk of adverse effects from excess intake.
- Based on EFSA ULs, the calculated MLS for adults and children are shown in Table 10 270 mg/day and 98.6 mg/day, respectively. The calculated MLS values based on the IOM ULs are 978.3 mg/day for adults and 285.8 mg/day for children.
- Because of the large differences in scientific opinions on the derivation of the ULs and SUL for vitamin E, there is clearly a need for a thorough reassessment of its safety.

Nicotinamide

- The term "niacin" may refer to nicotinic acid and nicotinamide. Niacin supplements and use in fortified foods are generally in the form of nicotinamide. Large amounts of nicotinamide do not cause vasodilation or flushing and do not lower serum lipid concentrations. Although the IOM set a UL of 35 mg/day for both forms based on flushing, most risk assessors establish a safe level for nicotinamide distinct from that for nicotinic acid.
- Nicotinamide intakes of more than 3000 mg/day for 3–36 months have resulted in adverse gastrointestinal and liver effects.
- SCF/EFSA (2006) concluded that clinical studies strongly support a NOAEL of 25 mg/kg bodyweight/day for nicotinamide. A UF of 2 was used to allow for the fact that adults may eliminate nicotinamide more slowly than subjects aged younger than 18 years, who were used in many of the trials. The upper level for nicotinamide is established at 12.5 mg/kg bodyweight/day or approximately 900 mg/day for adults. This upper level for nicotinamide is not applicable during pregnancy or lactation because of inadequate data. The ULs for children of 220 mg/day and 350 mg/day for 4–6 and 7–10 year-olds are based on their bodyweights.
- EVM (2003) concluded that there are insufficient data to establish a safe upper level for nicotinamide and set a GL of 560 mg/day for total intake, equivalent to 9.3 mg/kg bodyweight/day in a 60 kg adult. The level for long-term supplementary use was set at 500 mg/day, assuming a maximum intake of 57 mg/day from food.
- Nicotinamide products generally contain levels ranging from 150 mg/day to 450 mg/day.
- The calculated MLS for nicotinamide in food supplements are 820 mg/day and 163 mg/day for adults and children, respectively. These values are shown in Table 10.

Molybdenum

- SCF/EFSA (2006) and IOM (2001) concluded that there were no well-designed studies from which to establish a UL value, so animal data were used. The adverse effects of high molybdenum intake on reproduction of rats and mice served as the basis for the identification of a NOAEL of 0.9 mg per kg bodyweight per day. Using this NOAEL, IOM selected a composite UF of 30 (10 for interspecies differences and 3 for intraspecies variations) and corrected to a human adult bodyweight of 68.5 kg to derive a UL of 2000 µg/day for molybdenum from all sources. SCF/EFSA (2006) selected a composite UF of 100 (10 for interspecies differences and 10 for intraspecies variations) to derive a UL of 10 µg per kg bodyweight per day and applied a 60 kg bodyweight to calculate a daily UL of 600 µg for adults, which also covers pregnant and lactating women. This UL has been reaffirmed by EFSA in its scientific opinion on dietary reference values for molybdenum (EFSA, 2013a). SCF/EFSA extrapolated the UL of 200 µg/day for children aged 4–6 years and 250 µg for 7–10 year-olds from the adult UL on a bodyweight basis using reference bodyweights for Europe.
- EVM (2003) concluded that there were insufficient data on the safety of intakes of molybdenum in excess of those actually occurring in the diet (230 µg/day). The representative range of mean estimates of intake in different countries is 80–250 µg/day (EFSA 2006). However, the upper range of intakes can be as high as 500 µg/day.
- The US Environment Protection Agency utilised human epidemiological data that suggested a LOAEL of 140 µg per kg bodyweight per day. The Reference Dose (RfD) was calculated by applying a composite UF of 30 (10 for LOAEL to NOAEL and 3 for variability within the human population. The resultant RfD is 5 µg per kg bodyweight per day or 350 µg per day for a 70 kg person.

- Considering both the large degree of uncertainty and the relatively small intake of molybdenum from food, the proposed MLS are 350 µg/day and 55 µg/day for adults and children, respectively.
- Because of the large differences in scientific opinion on the derivation of the ULs for molybdenum, there needs to be a thorough reassessment of its safety. Using the IOM UL would result in a higher MLS.

Phosphorus

- With normal kidney function, phosphorus is readily excreted, and no imbalance in calcium metabolism occurs except at extreme intakes.
- The IOM UL for adults is 4000 mg/day and the IOM UL of 3000 mg/day for children aged 1–8 years from all sources is calculated by dividing the NOAEL for adults (10.2 g/day) by a UF of approximately 3.3 to account for potentially increased susceptibility due to smaller body size. In contrast, the EVM (2003) identified a NOAEL of 750 mg supplemental phosphorus per day and by applying a UF of 3 to this NOAEL, a Guidance Level of 250 mg supplemental phosphorus was identified. EFSA (2006) concluded that the available data are not sufficient to establish a UL for phosphorus, and commented that the panel did not consider the mild gastrointestinal effect as a suitable critical endpoint for setting an upper level. The high NOAEL identified by the IOM is offset by the low, and very conservative, NOAEL identified by the EVM. In 1991, the UK Department of Health set a maximum tolerable daily intake of 70 mg/kg bodyweight, which is about 4.5 g/day for a 65 kg mass.
- An appropriate ratio of calcium: phosphorus intake is 1: 1 or 1: 1.2. An adult MLS of 1250 mg/day is proposed based on this ratio and the mean calculated MLS values for males (1009 mg/day) and females (1500 mg/day) using the IOM UL of 4000 mg/day.
- EFSA (2006) indicated that adults can tolerate phosphorus intakes up to at least 3000 mg/day without adverse effects. There is no evidence of adverse effects associated with current intakes of phosphorus from all sources.
- Net absorption of phosphorus from a mixed diet is estimated to be 65–90% in children. In most studies, phosphorus supplementation results in increased phosphate excretion and decreased calcium excretion.
- Consumption of soft drinks with added phosphate has been associated with hypocalcaemia in children. This, however, is probably related to low calcium intakes rather than soft drinks per se (IOM 1997).
- The intake of phosphorus from fortified foods and supplements is very low or not observed for the children's age groups (Flynn et al. 2009).
- The risk of adverse effects from high dietary intake of phosphorus from foods, including fortified foods and food supplements, is considered to be low (Flynn et al 2009).
- EFSA published a statement (EFSA 2013d) based on its scientific assessment of concerns raised in a narrative review that suggested an association between high intake of phosphates as food additives and increased cardiovascular risk in the general population. EFSA concluded that it was not possible to make causal inferences from the available studies, and that the published results show inconsistent and contrasting findings (EFSA 2013d).
- The calculated MLS of 1353.6 mg/day shown in Table 4 is based on the IOM UL for children aged 1 to 8 years. Bearing in mind the differences in the scientific risk assessments, the observations that only a small percentage of the children is likely to exceed the UL, the P2.5, P5 and mean intakes, the fact that phosphorus supplements are not widely consumed, and a recommended calcium: phosphorus ratio of 1: 1.1, a maximum level of 550 mg/day is proposed for children aged 4–10 years.

Selenium

- Chronic selenium toxicity results in symptoms of selenosis (changes to the hair, nails and skin, and neurological effects) at levels of about 1200 µg/day.
- SCF/EFSA identified a NOAEL of 850 µg/day, applied a UF of 3 and rounded the UL to 300 µg/day. IOM identified a NOAEL of 800 µg/day and applied a UF of 2 to derive a UL of 400 µg/day. EVM (2003) used a LOAEL of 910 µg/day, applied a UF of 2 and derived a total UL of 450 µg/day, of which a supplemental level was set at 350 µg/day.
- The IOM ULs for children aged 4–8 years and 9–13 years are 90 µg/day and 280 µg/day, respectively. These levels are based on the fact that the infant (0–12 months) UL and adult UL are similar on the basis of bodyweight (7 µg/kg bodyweight).
- Bearing in mind the risks of deficiencies and excess for adults and children, the MLS of 200 µg/day and 55 µg/day, respectively, would not be expected to result in any adverse effects.

Magnesium

- All three risk assessments found no evidence that magnesium in foods causes osmotic diarrhoea, the adverse effect of concern. Other sources such as food supplements, laxatives and antacids have the potential to produce these mild, reversible adverse effects at levels above 400 mg/day. The IOM established a UL for adolescents (older than 8 years) and adults of 350 mg supplementary magnesium.
- SCF/EFSA (2006) also determined that osmotic diarrhoea is the critical effect for identification of a UL for magnesium. A LOAEL of 360 mg/day and a NOAEL of 250 mg/day were identified for readily dissociable magnesium salts, e.g. sulphate, chloride, phosphate, citrate and carbonate. Selecting a UF of 1.0 for application to the 250 mg NOAEL, SCF derived a UL of 250 mg/day for supplemental sources of magnesium for adults including pregnant and lactating women, and children from four years on. The UL applies to daily intake of magnesium consumed on two or more occasions. This UL does not include magnesium normally present in foods and beverages.
- EVM (2003) established a guidance level of 400 mg/day of non-food magnesium for long-term supplementation because it would not be expected to result in any significant adverse effects. As the EVM GL includes usage in fortified foods and in food supplements, the proposed MLS for both adults and children is 250 mg/day.

Folic acid/folate

- Folate is used as a generic term for a family of chemically and functionally related compounds based on the folic acid structure (Pietrzik et al. 2010). According to the Food Supplements Directive 2002/46/EC (European Parliament and of the Council 2002) and Regulation (EC) 1925/2006 (European Parliament and of the Council 2006a), two substances are authorised as folate sources for use in food supplements and foods: folic acid (pteroylmonoglutamic acid) and calcium-L-methylfolate (calcium L-5-methyl-tetrahydrofolate or calcium L-5-MTHF). Folic acid is an oxidised synthetic form of the vitamin, which does not exist in nature but may be added to fortified foods, food supplements and pharmaceuticals. Folic acid itself is not active. After absorption it must be metabolised to the reduced folate forms for biological activity (Obeid et al. 2013, Pietrzik et al. 2010). In contrast, the reduced folate form L-methylfolate is the predominant form of folate found naturally in foods, the principal form of circulating folate and the preferred substrate for transport into peripheral tissues. The cellular uptake of circulating L-methylfolate is subject to tight cellular control, whereas folic acid, which is not subject to this cellular control, is retained even in folate-replete individuals (Pietrzik et al. 2010). Calcium L-methylfolate is the calcium derivative of L-methylfolate, and in aqueous

media calcium L-methylfolate dissociates readily and completely into calcium and L-methylfolate ions (EFSA 2004).

- SCF/EFSA established a UL of 1000 µg/day for supplemental folic acid, basing their findings on a LOAEL of 5000 µg and a UF of 5, and also a NOAEL of 1000 µg and a UF of 1. Similarly, IOM and EVM (2003) established a UL of 1000 µg for folic acid.
- The risk of progression of neurological symptoms in vitamin B_{12}-deficient patients is considered to be the most serious potential adverse effect. EFSA concluded that amounts up to 1000 µg/day are unlikely to cause masking of vitamin B_{12} deficiency. The data on the effects of intakes between 1000 and 5000 µg/day are limited, but in nearly all of the studies the neurological side effects of folic acid supplementation were associated with levels exceeding 5000 µg/day. In an integrated risk-benefit analysis of folic acid, Hoekstra et al. (2008) commented that the risk of masking vitamin B_{12} deficiency appears negligible compared with the health gain resulting from the reduction of risk of neural tube defects (NTDs). The adult UL, based on masking of haematological signs in pernicious anaemia is not relevant for setting ULs for children and adolescents. However, the IOM extrapolated ULs for children aged 4–8 years and 9–13 years are 400 µg/day and 600 µg/day, respectively. Similarly, EFSA set extrapolated ULs of 300 µg/day and 400 µg/day for 4–6 year olds and 7–10 year olds, respectively.
- There is no record of adverse effects caused by food polyglutamylfolates, perhaps because of the lower bioavailability and/or limited range of intakes observed. Similarly, there is no evidence for risk associated with high intakes of natural, reduced folates and thus no data to set a UL for natural folate (EFSA 2006).
- The symptoms of vitamin B_{12} deficiency include both haematological and neurological effects. While the haematological effects are reversible, the associated neurological effects may be irreversible. Unlike folic acid, methyl folate cannot correct the haematological signs of vitamin B_{12} deficiency and does not interfere with the timely diagnosis of vitamin B_{12} deficiency. Details of the metabolism of L-methylfolate and folic acid in vitamin B_{12} deficiency can be found in papers by Lamers et al. (2004), Smulders et al. (2006), Hasselwander et al. (2006), Pietrzik et al. (2010) and Scott (2011).
- EVM (2003) established a guidance level for supplemental folic acid use of 1000 µg/day (equivalent to 17 µg/kg bodyweight/day) for a 60 kg adult. Hence, for children weighing 20 kg and 28.5 kg, the supplemental upper levels would be 340 µg/day and 484.5 µg/day, respectively. The average value for the age group 4–10 years is 412 µg/day.
- Reduced maternal red blood cell folate is a risk factor for neural tube defects (NTDs) in the developing foetus. Evidence suggests that younger women and women from more disadvantaged backgrounds are at a greater risk of an NTD-affected pregnancy. It is estimated that 70% of NTDs can be avoided by adequate folate levels in women of childbearing age during the periconceptional period (about one month before and one month after conception).
- The EFSA NDA Panel concluded that a cause and effect relationship has been established between increasing maternal folate status by supplemental folate intake and reduction of risk of NTDs. In order to obtain the claimed beneficial effect, 400 µg supplemental folate should be consumed daily for at least one month before and up to three months after conception. The target population is women of childbearing age (EFSA 2013b).
- Voluntary fortification with folic acid and a healthy diet are insufficient to raise women's folate levels. The proposals mandatorily to fortify bread and flour with folic acid would require monitoring of potential effects on population intakes.

- Most national guidelines state that 400 µg/day is the recommended amount for supplementation for the normal population of women of childbearing age. Four to five milligrams of folic acid is recommended by many national governments and health agencies for women who have had a previous pregnancy affected by an NTD.
- Supplementation of 800 µg folic acid has been shown to shorten effectively the period for the red blood cell (RBC) folate concentration to reach the threshold of 906 nmol/L (Brämswig et al. 2009). This is important as the risk of having an NTD-affected pregnancy is lowest amongst women with a RBC folate concentration greater than 906 nmol/L (Daly et al. 1995).
- According to Brämswig et al. (2009), to reduce the risk of NTD, supplementation of folic acid in amounts higher than 400 µg/day should be considered. Czeizel et al. (2011) concluded that pre-pregnant and pregnant women should supplement with an amount of 700–800 µg folic acid per day.
- The most recent Cochrane Collaboration (2010) shows that the protective effect of daily folic acid supplementation for reduction of risk of NTD under medical supervision comes from amounts ranging from 360 µg to 4000 µg/day.
- Typical adult mean intakes for total folate in Europe range from 251 to 398 µg/day. Mean intakes hide low intakes of folate/folic acid in some groups of the population such as children, as illustrated in Appendix 4.
- Most food supplements available in Europe contain 400 to 500 µg folic acid (pteroylmonoglutamic acid). MLS of 600 µg folic acid/day for adults and 300 µg folic acid/day for children aged 4–10 years would not be expected to result in any adverse effects, based on the UL for folic acid of 1000 µg/day.

Potassium

- The adverse effects of prolonged high intakes of potassium are determined by (a) local effects on the gastrointestinal tract, and (b) metabolic effects determined by the maximum capacity for excretion by the kidney, and to a lesser extent, by colonic excretion. Daily intakes of potassium from the habitual diet generally do not exceed 5–6 g/day, and this level has not been associated with any negative effects in healthy individuals.
- Supplementation trials in adults have found no adverse effects of potassium chloride at daily potassium intakes of 1900 mg (Siani et al. 1991) or 2340 mg (Fotherby and Potter, 1992). Amounts of 1250 mg administered three times a day (giving a total of 3750 mg) produced only minor gastrointestinal (GI) symptoms. Supplementation studies have generally not reported side effects. However, chronic ingestion at higher levels can cause GI adverse effects characterised by abdominal pain, nausea, vomiting and diarrhoea. Large quantities of potassium ingested as potassium chloride can produce adverse GI effects, which may be more likely if the total is ingested all at once, particularly on an empty stomach.
- EFSA (2006) did not establish a UL owing to insufficient data. In 2004 IOM concluded that large amounts of potassium can cause acute or chronic toxicity, but that there were not enough appropriate data to support a UL. Similarly, the EVM (2003) decided that the evidence was not sufficient to set an SUL, but it could support a GL of supplemental amounts up to 3700 mg potassium per day. The EVM (2003) stated that this level of supplemental intake 'appears to be without overt adverse effects, but may be associated with GI lesions diagnosed by endoscopy.
- A meta-analysis of clinical trials on potassium (mostly potassium chloride, KCl) for possible lowering of blood pressure in adults indicated that this mineral 'appeared to be well tolerated in all studies' (Whelton et al. 1997).

The amounts of supplementary potassium in these studies ranged from 1876 to 7820 mg/day. Together, all of the clinical trials show no adverse effects for supplemental potassium of 1500 mg/day.

- Epidemiological evidence and clinical trials data on larger amounts of dietary potassium from fruits and vegetables and using KCl supplements both indicate that this nutrient has a wide margin of safety.
- Adverse effects of potassium are more likely to result from renal insufficiency arising from decreased kidney function or decreased water intake than from excess consumption (McLaren 1999; Heimburger et al. 2006). Hyperkalaemic states, similarly, depend heavily on kidney function and adequacy of hydration.
- Dietary trends with decreased consumption of vegetables and fruit and increased consumption of foods with higher salt/sodium content favour reduced potassium and increased sodium intakes.
- Potassium is needed for lean tissue synthesis during growth and development. Deficiencies can alter the electrophysiological characterisation of cell membranes causing weakness of skeletal muscles, adverse effects on cardiac muscle and changes in gut motility.
- According to recent food consumption surveys (EFSA 2006), food supplements contribute up to only 5% of total potassium intake.
- Overall, the clinical trial data on potassium chloride, together with the epidemiological evidence supporting the safety of larger amounts of potassium from fruits and vegetables, indicate that this nutrient has a wide margin of safety. For adults, clinical trials show no pattern of adverse effects at 1500 mg/day—a level that, if taken three times a day with meals with no greater than 500 mg consumed on each occasion, poses no risk.
- The EVM(2003) Guidance Level for supplementary potassium is 3700 mg/day for an adult of 60kg body weight. Although the EVM commented that extrapolation on the basis of bodyweight may be inappropriate, using the rationale described in Section 4 and children's bodyweights of 20 kg and 28.5 kg and an adult bodyweight of 70 kg, the estimated Guidance Level for children aged 4–6 years would be 1233 mg/day, and for children aged 7–10 years, 1757 mg/day
- The proposed MLS for adults of 1500 mg/day and for children of 1200 mg/day would not be expected to result in any adverse effects, with the provision that the amounts be consumed on three separate occasions with meals.

Appendix 2. Risk management analysis of Group 3 nutrients

Preformed retinol

- 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 UL of 3000 µg RE/day (SCF 2002) applies to both dietary and supplemental intakes of vitamin A. This value is about 2.5-fold lower than the lowest daily intake associated with hepatotoxicity during chronic intake. The 97.5 percentile intake for adults in most of Europe is greater than 3000 µg RE/day, whereas the 95 percentile intake is below the UL for adults and children. As the RDA for vitamin A is 800 µg RE/day and the distribution of intakes is great, especially in relation to consumption of liver and liver products, risk management for preformed retinol is particularly challenging to avoid deficiency as well as excess.

- Recent epidemiological data have indicated that the risk of hip fracture in older people may be associated with intakes as low as 1500 µg RE/day, but there remains some doubt among academic experts as to whether this is a real effect at normal intake levels.

- SCF/EFSA (2006) states that, because current intakes may exceed the UL, careful consideration should be given to the appropriateness of the enrichment of human foods with vitamin A, and to the potential effects on human exposure of the addition of vitamin A to animal feed. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP, 2008, 2013) published scientific opinions on the consequences for the consumer of the use of vitamin A in animal nutrition. The FEEDAP Panel was of the opinion that all consumer exposure calculations show that liver is the only food of animal origin the consumption of which poses a risk to adult consumers. EFSA (2008a) is of the opinion that this risk can be considerably reduced, but not eliminated, by following proposals for a reduction of the maximum vitamin A content in feedingstuffs and by closely following the nutritional recommendation to reduce the quantity of liver eaten during pregnancy. The EFSA proposals on reduced levels in feedingstuffs are almost certain to be implemented in the expected implementing regulation reauthorising the use of vitamin A in feed (currently under discussion in the Standing Committee on the Food Chain and Animal Health).

- The difference between the mean and median values of intake indicates a skewed distribution of intakes that arises from the uneven distribution of preformed retinol in the food supply, and very high intakes by consumers of foods such as liver and liver products. The dependency on retinol from relatively few foods (mainly liver) results in the median intakes being typically 20–50% lower than the mean intakes. Day-to-day variations in intake are large (Willett 1998). Mean intakes are significantly below the nutrient reference values, and as illustrated in Table 9, there has been a substantial decline in mean vitamin A intakes over the period between the two UK NDNS dietary surveys.Indeed, the accuracy of the data relating to vitamin A intake from liver is questionable from several perspectives including:

  – A small population group that regularly consumes liver

  – Infrequent consumption not well recorded in short-term food consumption diaries

  – Variation in liver content of vitamin A between and within animal species.

  – Old data on vitamin A content in composition tables not reflecting the current usual vitamin A concentrations in the liver

Hence, it has proved difficult to reconcile liver intakes according to intake surveys and the quantities of liver known to enter the human food chain.

- Vitamin A is one of the more labile vitamins, and factors such as its sensitivity to oxygen, UV light, pH etc. can result in significant decreases in bioactivity.
- There are significant numbers of children who fail to achieve the RDA and even the Lower Reference Nutrient Intake (LRNI).
- The EFSA (2006) UL for children is extrapolated from adult data, where the adverse effect is related to teratogenic risk to the newborn. The UL for children is corrected for differences in basal metabolic rate compared to adults by means of scaling according to body surface area (bodyweight 0.75) and is associated with hepatotoxicity during chronic intake at extremely high levels.
- Chronic adverse effects in adults are associated with regular supplemental amounts greater than 7500 µg up to 15 000 µg RE/day over weeks, months and years. Most symptoms are reversible. For guidance (as described in the section on setting ULs for children), on a simple bodyweight basis, 7500 x 20 kg/70 kg bodyweight results in an extrapolated level greater than 2143 µg/day for 4–6 year-old children. The UK Department of Health guidance (1991) on high intakes recommended that regular daily intakes from all sources should not exceed 3000 µg for 4–6 year olds, 4500 µg for 6–12 year olds and 6000 µg for adolescents.
- The highest intakes of preformed retinol from all sources in the UK NDNS and ILSI Europe data are below the ULs. There are no reported adverse health effects associated with children exceeding the UL (Flynn et al. 2009).
- Young women and those considering pregnancy have been repeatedly advised to avoid consumption of liver because of the claimed risk for very high levels of preformed vitamin A in liver. The UK SACN advised pregnant women and women trying to conceive to avoid supplements containing vitamin A (retinol) as too much can have harmful effects on the unborn baby. Current advice is that pregnant women should not consume liver or liver products including fish liver oil because of their high vitamin A content. Vitamin A is not included in the UK's Healthy Start women's vitamin tablets (http://www.healthystart.nhs.uk/for-health-professionals/vitamins/).

  The UK Chief Medical Officer (Department of Health 2013) advice on vitamin D supplements for pregnant and breastfeeding women states that vitamin D supplements containing 5–10 µg of vitamin D must not contain retinol. However, the risk of too high vitamin A intake in the form of preformed retinol exists, if at all, only during the first four weeks of pregnancy, but not later. Furthermore, assuming an absorption rate of 40%, it is hardly possible to consume critical amounts of vitamin A from 100 g of liver (Strobel et al. 2007).
- Strobel et al. (2007) point out that the actual teratogenic substance is not retinol but its metabolite retinoic acid, which does not occur in foods and can only be synthesised from retinol in the body. Since the synthesis of retinoic acid from retinol in normal metabolism is strictly controlled, even excessive retinol intakes will not result in supra-physiological levels of retinoic acid.
- The warnings against liver consumption and potential concerns over intakes of preformed retinol need to be reassessed urgently as they may have caused the low consumption of liver to decrease even further, especially among young women and mothers. Not only may the health of the mother be at risk if vitamin A intakes are insufficient, but also the development of the child. The overall development of the baby and especially lung development and maturation of the embryo is dependent on a sufficient supply of vitamin A. If vitamin A supply is low, vitamin A stores in the lung, especially in pre-term babies,

are low. It is critical to develop sufficient vitamin A stores in the lung, which happens in the third trimester of pregnancy. If not, these children will be at increased risk for broncho-pulmonary dysplasia (BPD), one of the most frequent and life-threatening respiratory diseases in preterm infants.

- In January 2013, the Norwegian Scientific Committee for Food Safety (VKM) assessed the existing maximum limit for vitamin A in food supplements for children above three years of age, adolescents and adults, which is 1500 µg RE/day. Based on the available data of intake (mean, median, 95th percentile and 5th percentile) of retinol from regular food, fortified food and food supplements and knowledge of the main sources of retinol in the Norwegian diet (e.g. butter, margarine and oils and meat, blood and offal such as liver), it was found that among men and women not using food supplements, more than 50% do not reach the recommended intake of vitamin A, while intake among children seemed to be more adequate. Supplementation lowers the percentage not reaching the recommended intake. The VKM decided that the maximum limit for preformed retinol in food supplements should not be increased for any age group and remain at the existing level of 1500 µg RE/day. The UK Chief Medical Officer, in advice on vitamin D supplements has limited the amount of vitamin A to 233 µg/day for infants and young children, stated that products for pregnant and breastfeeding women must contain no retinol and products for people aged 65 years or over and those not exposed to much sun must not contain more than 800 µg of retinol.
- To determine a proposed maximum level for preformed retinol clearly poses challenging scientific, technical and policy issues. Taking into consideration the reference nutrient intakes, the most recent assessments of food safety from Norway, mean intakes and risks of deficiencies and excess, the proposed MLS for adults and children based on the qualitative safety assessment above are set at 1200 µg/day and 1000 µg/day, respectively.

Beta-carotene

- The safety of beta-carotene has been evaluated recently (EFSA 2012c), and the Panel on Food Additives and Nutrient Sources added to Food (ANS) concluded that exposure to beta-carotene from its use as a food additive and as a food supplement at a level below 15 mg/day does not give rise to concerns about adverse health effects in the general population, including heavy smokers. This opinion was based on an extensive review of the scientific literature, which concluded that the increased incidence of lung cancer in smokers supplemented with beta-carotene was specific to individuals who chronically smoke more than 20 cigarettes per day. Epidemiological studies reported no increased lung cancer incidence in heavy smokers at supplemental levels of beta-carotene varying between 6–15 mg/day for about five up to seven years.
- The risk of inadequate intakes of vitamin A is greater than the risk of excess. Provitamin A carotenoid beta-carotene is an essential dietary source of vitamin A. Basic sources of provitamin A are orange and dark green vegetables, the consumption of which is often low in some European countries (Strobel et al. 2007).
- The role of beta-carotene as a precursor of vitamin A should not be underestimated (Grune et al. 2010). Restrictions on beta-carotene that are largely relevant to smokers should be considered carefully in relation to the optimisation of vitamin A intakes for children and young women, especially those considering pregnancy.
- People who regularly consume liver or other organ meats and who have high intakes of retinol should not consume supplements that contain preformed vitamin A, but they may safely consume vitamin A in the form of its precursor, beta-carotene. When vitamin A status in good, beta-carotene is not cleaved into vitamin A. Hence, there is no risk of excess of vitamin A due to intake of beta-carotene. Reversible yellowing of the skin

(hypercarotenaemia) has been reported at very high doses of beta-carotene (60–180 mg/day) when used as a therapeutic drug in patients with erythropoieticprotoporphyria (EPP), which is used to reduce the severity of photosensitivity reactions (i.e. as an ultraviolet screen).

- The EFSA ANS Panel concluded that the use of beta-carotene as a food additive and as a food supplement should remain below 15 mg/day. The Panel also concluded that, based on the presently available dataset, no ADIs for mixed carotenes and beta-carotene can be established, and that the use of synthetic beta-carotene and mixed beta-carotenes obtained from palm fruit oil, carrots and algae as a food colour is not of safety concern, provided the intake from this use as a food additive and as a food supplement is not more than the amount likely to be ingested from the regular consumption of the foods in which they occur naturally (5–10 mg/day).
- The SCF estimated that the intake of beta-carotene and related carotenoids from additives to be about 1–2 mg/person/day, in addition to an average of 2–5 mg/person/day or up to a maximum of 10 mg/person/day consumed from natural food sources. The total intake from these sources was consequently considered to be 3–7 mg/person/day or up to a maximum of 10 mg/person/day depending on seasonal and regional variations.
- There is uncertainty regarding intakes of beta-carotene, and the EFSA ANS Panel calculated that typical levels of use of beta-carotene as a food additive could result in the mean exposure of beta-carotene of 0.06 mg/kg BW/day and an exposure at the P97.5 of 0.11 mg/kg BW/day, which for a 70 kg adult equates to 4.2 mg/day and 7.7 mg/day, respectively. The same scenario for children resulted in an average exposure in the range of 0.03–0.22 mg/kg BW/day and at the P97.5 in the range of 0.09–0.43 mg/kg BW/day, which equates to 4.4 mg/day and 8.6 mg/day, respectively, for the higher end of the range of exposures.
- In summary, the proposed MLS of 7 mg/day for adults and children reflects the available datasets. It should be noted that the current UK EVM (2003) supplemental recommended daily amount is 7 mg (excluding smokers), and that the new EFSA opinion extends the range of safe use to include heavy smokers as well as the general population.

Calcium

- Reported adverse effects relate to hypercalcaemia. The evidence supporting an increased risk of kidney stones with a high calcium intake is far from clear and it has been contradicted by more recent credible evidence (IOM 1997). High dietary calcium levels can influence the bioavailability and absorption of many trace elements in individuals with low intakes; e.g. magnesium, iron, manganese and zinc. No dose-response data exist regarding these interactions in children or the development of adaptation to chronic high intakes (IOM 1997).
- Acute adverse effects relate to constipation, abdominal pain and diarrhoea.
- Subpopulations known to be susceptible to high levels of calcium include individuals with renal insufficiency, alkalosis and dehydration due to vomiting and anorexia, and those using thiazide diuretics.
- The recent EFSA re-evaluation of the safety in use of calcium (EFSA 2012d) and IOM both derived a UL of 2500 mg/day for total intake from all sources and the EVM (2003) set a GL for supplemental calcium at 1500 mg/day, stating that such a supplemental level would not be expected to result in any adverse effect.
- Although EFSA (2012d) concluded that there are no data to set a numerical UL for children and adolescents, no appreciable risk was identified even with current extreme (high) levels of calcium intake in this age group. The IOM (1997) recommends a UL of 2500 mg/day from diet and supplements for children aged one

through 18 years. The IOM comments that after nine years of age, rates of calcium absorption and bone formation begin to increase in preparation for pubertal development. The EVM (2003) suggests that for guidance purposes, amounts up to 1500 mg/day of supplemental calcium for adults, but no GL for children is proposed.

- Calcium must be in a soluble form or bound to soluble organic molecules to be absorbable. Depending on solubility, chemical form and on other factors of the food, between 10 to 40% of dietary calcium is absorbed.
- Intakes from supplements and fortified foods are low, and inclusion of these sources with base diet has a minimal effect on P95 intake (Flynn et al. 2009). Dairy products and fortified foods are major sources of calcium, and high intakes are associated with consumption of milk and dairy products (Flynn et al. 2009).
- The highest intakes of calcium from all sources in the UK NDNS and ILSI Europe data are below the UL set by the IOM (1997).
- Potential benefits of increased consumption for those children with low and inadequate intakes of calcium far outweigh risk of adverse effects.
- The EVM (2003) GL of 1500 mg/day for supplemental calcium is based on an adult bodyweight of 60 kg. In Table 2 the reference weight for 4–6 year-old children is 20 kg. Hence, the extrapolated UL for children is calculated to be 500 mg/day for food supplements.
- MLS of 1000 mg/day for adults and 500 mg/day for children are proposed and are shown in Table 10, based on the qualitative safety assessment above.

Copper

- The occurrence of either acute or chronic copper toxicity in humans is rare and tends to be confined to certain populations with high copper concentrations in drinking water and to those individuals who have a hereditary predisposition to copper toxicity (Wilson's disease).
- Liver damage is used as a reliable indicator of the long-term ingestion of copper and is selected as the critical endpoint on which to base a UL for adults (EFSA, 2006; IOM, 2001). The NOAEL of 10 mg/day is based on the absence of any adverse effects on liver function using supplemental copper gluconate. From essentially the same studies, IOM and SCF/EFSA derived ULs of 10 mg and 5 mg/day, respectively, and the EVM (2003) derived an SUL from animal studies of 10 mg/day for total intake.
- EFSA (2006) derived for adults a UL of 5 mg/day using the absence of any adverse effects on liver function from a supplementation study with 10 mg/day copper for 12 weeks. The children's ULs were extrapolated on the basis of relative bodyweight. Whereas EFSA decided on a UF of two to allow for potential variability within the normal population, the IOM (2002) considered the NOAEL of 10 mg/day to be protective of the general population. The EVM (2003) set the SUL for total daily consumption by an adult over a lifetime at 0.16 mg/kg bodyweight/day (equivalent to 10 mg/day in a 60 kg adult).
- From the available data, copper can cause adverse effects in humans. However, as there appears to be an absence of adverse effects at intakes in the range of 10–12 mg/day, and typical and 97.5 percentile intakes are less than 2 mg/day and 3 mg/day, respectively, an MLS of 2 mg is proposed.
- Acute copper toxicity in drinking water appears to have a threshold of approximately 6 mg/L. The SCF/EFSA notes that copper intakes from drinking water may be appreciable, and may thus need to be taken into account.
- The available studies show, and EFSA concluded, that the mean copper intakes of children are below the UL. For some countries, the higher intakes are close to the ULs (Flynn

et al. 2009), which, in the view of EFSA (2006), are not a matter for concern. Based on current practices for both food supplements and fortified foods, the risk of adverse effects is low.

- The major dietary sources of copper are shellfish, offal, nuts and wholegrain cereals, which are often in short supply in the diets of children.
- The P2.5 and P5 and mean intakes demonstrate suboptimal intakes and potential risk of deficiency.
- MLS of 2 mg/day for adults and 1 mg/day for children are proposed, based on the qualitative safety assessment above.
- Because of the large differences in scientific opinions on the derivation of the ULs for copper, there needs to be a thorough reassessment of its safety. Using the IOM and EVM risk assessments would result in a higher MLS.

Iodine

- Excessive intake of iodine can occur as a result of the ingestion of large amounts of seaweed, kelp, marine fish, ground beef containing thyroid, iodised water, bread or salt and iodide-containing food supplements. Toxic effects are not observed in humans until daily intakes have exceeded 11000µg, but intakes of 2000 µg are regarded as excessive and potentially harmful. Toxicity is related to intakes over 5000 µg/day, and normal individuals receiving 1000–2000 µg/day showed an increased iodine concentration in the thyroid gland but no other changes.
- Except for rare cases of hypersensitivity, humans can tolerate high intakes of iodine because of biological mechanisms that protect against such exposure. When they are overcome, clinical symptoms of acute toxicity include gastrointestinal upset and metabolic acidosis. A change in thyroid function with elevated levels of thyroid stimulating hormone (TSH) is used as an indicator of an increased risk of developing clinical hypothyroidism and is the critical adverse effect on which to base the UL. Excess iodine, as well as deficiency, can lead to thyroid dysfunction and elevated thyroid stimulating hormone (TSH). TSH levels are not associated with any clinical adverse effects at iodine intakes of 1700–1800 µg/day.
- The SCF/EFSA set a UL of 600 µg/day, and data from European populations indicate that intakes of iodine from all sources in adults are unlikely to exceed the UL. For example, for the UK, where iodine intake is considered to be high relative to other European countries, the 97.5 percentile intake in men is 434 µg.
- Adverse effects are sometimes associated with excess iodine intake in national fortification programmes to address iodine deficiency in the population, and it is recognised that these populations are more sensitive to iodine exposure (EFSA, 2006). ILSI Europe data show that the main source of iodine in the base diet in Poland is from fortified salt (Flynn et al. 2009).
- There is no evidence of increased susceptibility in children. The ULs for children were derived by adjustment of the adult UL on the basis of body surface area (bodyweight 0.75).
- UK NDNS survey data showed that iodine intakes of young children may vary from 87–309 µg/day, with almost all the iodine deriving from milk. The UK Committee on Toxicity (2000) and EFSA (2006) noted that the higher intakes were unlikely to be a risk to health, and that the UL may be exceeded for short periods without appreciable risk to health.
- The ILSI Europe data for children showed the P95 iodine intake from the base diet ranged from 140 µg/day in Germany to 280 µg/day in Denmark in the age group 4–10 years. Inclusion of supplements increased the P95 intake of iodine in Denmark to more than 300 µg/day for the age group 7–10 years (Flynn et al. 2009).
- It is necessary to consider the P2.5, P5, mean and median intakes and the potential risk of deficiencies.

- The IOM ULs are 1100 µg/day for adults and 300 µg/day for children aged 4–8 years and 600 µg/day for 9–13 year olds. The EVM established GLs of 500 µg/day and 900 µg/day for supplementary and total intakes, respectively.
- MLS of 200 µg/day for adults and 150 µg/day for children are proposed and are shown in Table 10. These MLS values are based on the qualitative safety assessment above.
- Because of the large differences in scientific opinion on the derivation of the ULs for iodine, there needs to be a thorough reassessment of its safety. Using the IOM and EVM risk assessments would result in a higher MLS.

Iron

- Adverse gastrointestinal effects in adults (i.e. nausea, epigastric discomfort, constipation) have been reported after short-term oral amounts of 50–60 mg daily of supplemental non-haem iron sources, particularly if taken without food (EFSA, 2006). However, the EFSA panel concluded that the data were not a suitable basis for establishing a UL for iron from all sources. The EVM (2003) also concluded that the evidence was insufficient to set a UL, but it set a GL for adults for long-term supplementation of 17 mg/day rounded to 20 mg/day. The IOM identified a supplemental LOAEL of 60 mg/day, to which it added 10 to 11 mg/day from dietary sources, and subsequently derived a UL from all sources of 45 mg/day for adults
- Elevated serum ferritin levels and transferrin saturation are indicators of iron overload.
- Epidemiological associations between high iron intake and/or stores and an increased risk of chronic diseases such as cardiovascular disease, type 2 diabetes and cancer are conflicting and do not provide convincing evidence of a causal relationship.
- Chronic iron overload may result from increased absorption from the diet, but it is very unusual except in people with a genetic disturbance of iron metabolism (hereditary haemochromatosis, HHT). Up to 0.5% of the population is sensitive to iron overload (HHT) and should avoid iron supplements and highly iron-fortified foods.
- Iron poisoning is rare except for accidental acute ingestion of adult iron food supplements by children, which accounts for most cases of acute iron toxicity. Most cases are non-fatal and without serious morbidity. The adverse effects that may result from accidental acute ingestion of large amounts of iron have no bearing on the safety of appropriately used iron supplements.
- Mild gastrointestinal effects are not pathological and are reversible.
- Bioavailability varies according to the source of iron, its chemical form (ferric versus ferrous) and the food and diet consumed. Technically, the addition of iron sources to foods is difficult because forms of iron that are easily added to foods without causing adverse effects on colour, taste or stability are generally poorly absorbed, whereas the highly bioavailable form of iron, such as ferrous salts, may affect the storage and organoleptic properties of the final product for the consumer (Richardson 1993, 1997).
- Growing children need iron for increases in haemoglobin mass and increases in muscle tissue. The coefficient of variation for weight gain velocity in rapidly growing children is estimated to be 40% for boys and girls (IOM 2001).
- Anaemia and tissue iron deficiency contributes to impaired work performance and functions of skeletal muscle, as well as impairments of cognitive performance.
- EFSA (2006) stated that some groups at special risk of poor iron status such as children and menstruating females could benefit from additional iron intake and/or improved availability of dietary iron.
- WHO estimates that 41.8% of pregnant women worldwide are anaemic, and at least half of

this anaemia burden is assumed to be due to iron deficiency. As a result, WHO published two guidelines in 2012, stating that intermittent iron (and folic acid) supplementation in non-anaemic pregnant women were strongly recommended as a public health measure to improve gestational outcomes. Daily oral iron supplementation of 30–60 mg iron was suggested for pregnant women as part of the recommendations for antenatal care to reduce the risk of low birthweight, maternal anaemia and iron deficiency. Women receiving 60 mg or more of iron per day were at increased risk of high haemoglobin concentrations, i.e. greater than 130 mg/L, and they reported side effects. A supplemental daily amount of 30–60 mg of elemental iron is considered safe and effective to reduce risk of maternal anaemia. However, in settings where anaemia in pregnant women is a severe public health problem (40% of higher), a daily dose of 60 mg of elemental iron is preferred over a lower dose (WHO, 2012).

- The risk of adverse effects from high iron intake from food sources including fortified foods is considered to be low (EFSA 2006; Flynn et al. 2009). The inclusion of supplemental intake resulted in an increase in P95 intake that was additive with P95 from base diet (Flynn et al. 2009).
- The IOM (2001) considered the NOAEL for supplemental non-haem iron for young children to be 40 mg/day and applied a UF of 1, because there is little uncertainty regarding the range of intakes that are likely to induce gastrointestinal effects.
- Because of the difficulties of reconciling the various risk assessment approaches to the setting of ULs for adults and children, it is proposed that the UL values for children are extrapolated directly from the IOM adult UL on a bodyweight basis, as described in the section on setting ULs for children. The resultant ULs are 12.9 mg/day and 18.3 mg/day from all sources for children aged 4–6 years and 7–10 years, respectively.
- Taking into account the P2.5, P5 and mean intakes of iron from intake data, MLS of 20 mg/day for adults and 7 mg/day of iron for children aged 4–10 years are proposed and are shown in Table 10. These levels are based on calculated MLS and the qualitative assessment of safety above.

Manganese

- Miners and smelters who are chronically exposed to manganese dust suffer from 'manganism'—a neurotoxic condition similar to Parkinson's disease. Oral intake of manganese via drinking water is associated with neurological and behavioural effects in the elderly. Owing to limitations in the human data, the SCF/EFSA could not establish a UL. The IOM found no evidence of toxicity at intakes of less than 11 mg/day and set a UL of 11 mg/day. The EVM (2003) established a GL of 4 mg/day based on data that indicated no adverse effects from 4 mg of manganese in addition to the amounts present in foods (mean intake: 4.9 mg; 97.5 percentile: 8.2 mg/day) and a GL of 0.5 mg/day for 'older' people. The risk of an adverse effect from excess manganese from food and food supplements appears to be low. At the same time, the safety margin in both humans and animals also appears to be low.
- Major sources are tea, nuts, whole grain cereals and vegetables, all of which are not likely to be major contributors to the intake of children.
- Manganese is regarded by the UK Department of Health (1991) as one of the least toxic of all elements because when excess is consumed, there is a homeostatic control mechanism that lowers the amount absorbed. The amount of manganese absorbed across the GI tract in human adults is reported to be variable, typically averaging about 3–8% (EFSA, 2009). That which is absorbed is efficiently excreted via the bile and kidneys.
- The IOM (2001) based its UL on the work of Greger (1999) and established a NOAEL of 11

mg/day of manganese from food. The IOM also mentions work by Schroeder et al. in 1996 in vegetarians consuming 13–20 mg manganese per day. No adverse effects were noted. In their study (1992), Davis and Greger used 15 mg of supplementary manganese per day for between 25 and 90 days. The results were used to set a LOAEL. The IOM (2001), however, divided the NOAEL of 11 mg/day by an uncertainty factor (UF) of 1.0 to obtain a UL of 11 mg/day of total manganese intake from food, water and supplements for an adult. The ULs for children were extrapolated from the adult value and are 3 mg/day for children aged 4–8 years and 6 mg/day for children aged 9–13 years.

- As shown in Table 7, the P95 and P97.5 intakes from all sources are close to, or above, the IOM ULs for 4–8 year olds. The uncertainty surrounding the derivation of the adult ULs and the subsequent extrapolations makes it likely that intake is not a problem.
- EFSA (2006) commented that, given the neurotoxicity findings and the potential higher susceptibility of some subgroups (i.e. older people) in the general population, oral exposure to manganese beyond the levels normally present in food and beverages could represent a risk of adverse health effects without evidence of any health benefit. It is, however, necessary for risk managers to take into account the P2.5, P5 and mean intakes and potential risks of inadequate intakes in adults and children.
- EFSA (2009) stated that in European adults, the daily average manganese intake is on average between 1.4 and 4.9 mg/person/day, and the 97.5 percentile of manganese intake varies from 4.8 to 8.2 mg/person/day. The EFSA Panel on Food Additives and Nutrient Sources (EFSA, 2009) concurred with earlier SCF/EFSA considerations (2006), namely that exposure to manganese should remain low and should not exceed that found in the diet. EFSA further considered that supplemental intakes set by the EVM in 2003 of 4 mg of manganese/day for the general population and 0.5 mg of manganese/day for older people (over 50 years), respectively, are unlikely to produce adverse effects. This level of supplementation would result in total intakes of 12.2 mg of manganese/day in the general population and 8.7 mg of manganese/day for older people, respectively, taking into account a level of dietary manganese intake of 8.2 mg/day.
- The risk of an adverse effect resulting from an excess intake of manganese from food and food supplements therefore appears to be low at the highest intakes observed.
- MLS of 4.0 mg/day for adults and 1.5 mg/day for children are proposed, consistent with the EFSA scientific opinion on nutrient sources of manganese (2009) and the EFSA scientific opinion on Dietary Reference Values for manganese (EFSA 2013c) and based on the qualitative assessment of safety above.

Zinc

- Excessive intake can cause adverse effects in humans and animals. In humans, the effects of acute zinc toxicity are gastrointestinal disturbances giving rise to abdominal pain, nausea and vomiting. Chronic zinc toxicity is associated with changes in copper balance leading to symptoms of copper deficiency. Chemical similarities cause zinc and copper to interact metabolically. Large quantities of zinc can interfere with copper uptake. In adults, prolonged consumption of high doses (75–300 mg/day) of zinc can result in copper deficiency. In short-term studies, 50 mg interfered with iron and copper metabolism.
- The SCF/EFSA 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. The IOM UL for zinc is 40 mg/day from all sources, and the EVM (2003) derived an SUL of 25 mg for supplemental zinc. The available studies show that mean zinc intakes of adults and children in EU countries are below the UL.

The 97.5 percentiles of total zinc intakes for all age groups are close to the ULs, which, in the view of the SCF/EFSA, are not a matter of concern.

- ILSI Europe data (Flynn et al. 2009) show P95 zinc intake from base diet ranged from 8 to 15 mg/day in the age group 4–10 years, and it exceeded the UL for 4–10 year old children in some countries by a small amount. The limited data on intakes from food supplements showed a consumption of 5 mg/day in Denmark for age group 4–10 years. The P95 intakes from base diet and supplements was additive. Intake from fortified food was very low, and zinc is added to foods only infrequently. In Table 7 the UK NDNS data show that mean intakes of zinc fell below the children's RNI. The same is true for all age groups, both adult and child.
- In the risk categorisation, EFSA (2006) states that the available studies show that the mean zinc intakes of children in EU countries are below the UL. The P97.5 values for total zinc intakes for all age groups including children are below the UL. The P97.5 of total intake is close to the UL or exceeds the UL for 4–10 year olds in some countries by a small amount.
- There are no reported adverse health effects associated with the small proportion of children (and adults) exceeding the UL for zinc. EFSA (2006) indicated that this was not a matter for concern.
- With inappropriately high zinc intakes, homeostasis of the element is achieved by sequestration in the mucosal cells by metallothionein, a cysteine-rich protein (UK Department of Health 1991).
- Studies of zinc intake show a wide range, which probably reflects daily variations in intake and the short periods over which intakes were assessed. The P2.5, P5, mean and median intakes indicate that the risk of deficiency and suboptimal intake of zinc is high.
- MLS of 15 mg/day for adults and 5 mg/day for children are proposed and are shown in Table 10. These MLS are based on the qualitative assessment of safety above.
- Because of the large differences in scientific opinion on the derivation of the ULs for zinc, there needs to be a thorough reassessment of its safety. Using the IOM and EVM risk assessments would result in a higher MLS.

Appendix 3. Notes on other micronutrients included in Annex I of Commission Regulation (EC) No 1170/2009 that may be used in the manufacture of food supplements in Europe

1. Boron (as borates and boric acid)

Although boron has not been established as an essential nutrient for humans, there is some evidence that boron influences the metabolism and utilisation of other nutrients, particularly calcium. Boron may have beneficial effects on bone calcification and maintenance. Recommended intakes for boron have not been established. EFSA (2006) considered that the data on adverse effects of boron in humans were not adequate for the establishment of a UL. However, a NOAEL of 9.6 mg/kg BW/day for decreased foetal bodyweight in rats resulting from boron intake during pregnancy was extrapolated to humans by dividing by a UF of 60 (to allow for variability between rats and humans and between-person variability in humans) to derive a UL of 0.16 mg/kg BW/day, which is equivalent to a UL of 10 mg/person/day in adults. This UL also applies to pregnant and lactating women, and UL values for children were derived by extrapolating from the UL for adults on a body surface area basis. , giving values of 4, 5, 7 and 9 mg/day, respectively, for children aged 4–6, 7–10, 11–14 and 15–17 years. The IOM (2001) used the same NOAEL as EFSA but used a UF of 30 (10 for extrapolating from animals to humans and 3 for intraspecies variability), resulting in a UL for adults (≥ 19 years) of 20 mg/day boron. There are no reports of boron toxicity in children and adolescents, and the ULs were extrapolated on the basis of relative bodyweights. For example, the ULs for children are 6 mg/day and 11 mg/day for 4–8 and 9–13 year olds. The EVM established an SUL for daily consumption over a lifetime of 9.6 mg boron/day for a 60 kg adult.

Based on the totality of the data, and the fact that intake from food rarely exceeds 3 mg/day, an MLS of 6 mg/day is unlikely to have any adverse effects for adults and children aged 4–10 years.

2. Fluoride

Fluoride is not essential for growth and development but is beneficial in the prevention of dental caries. Fluoride toxicity is well known, and the critical adverse effects are dental fluorosis in children and skeletal fluorosis in adults. There is a narrow margin between recommended intakes for the prevention of dental caries and the ULs. For children, EFSA (2006) proposed an intake of 0.1 mg/kg BW/day, resulting in ULs of 1.5 mg/day and 2.5 mg/day for children aged 1–3 years and 4–8 years, respectively. For older children (9–14 years) and adults (≥ 15 years) EFSA proposed an intake of 0.12 mg/kg BW/day, which converts on a bodyweight basis to 5 mg/day and 7 mg/day, respectively. This adult value is based on a bodyweight of 60 kg. The IOM (1997) set UL values of 2.2 mg for 4– 8 year olds and an adult UL of 10 mg/day from all sources, based on an adult NOAEL of 10 mg and a UF of 1.0. Fluoride intake from food is generally low except when food is prepared from fluoridated water. An exception is tea, which can contain considerable amounts of fluoride (0.34–5.2 mg/l). Intakes from food and unfluoridated water is approximately 1 mg/day and the intake from fluoridated toothpaste is about 1 mg/day (0.3 mg per brushing). For children older than 8 years and adults, the probability of exceeding the UL of 5–7 mg fluoride/day on a normal diet is estimated by EFSA (2006) to be generally low. However, consumption of water with a high fluoride content, e.g. more than 2–3 mg/L predisposes to the exceeding of the UL. Based on a calculated EFSA UL of 8.4 mg/day for a 70 kg adult, the IOM adult UL of 10 mg/day and an estimated intake level from all sources of around 3 mg/day, the proposed supplemental level of 3.5 mg/day would not be expected to result in any adverse effects. Assuming an intake of 4 mg/day from fluoridated drinking water, the sum could be 6 mg/day (EFSA, 2006). The EVM (2003) concluded that the determination of maximum

levels for food fortification and food supplements is inappropriate because fluoride supplements are usually recommended for caries prevention as a public health measure and are regulated as drugs on prescription.

As fluoridation of water is often carried out as a public health measure, and taking into account the possible intake from fluoridated toothpaste, the determination of maximum levels for food supplements and for food fortification has to take place within the context of local exposure and involves consideration of risks and benefits

3. Silicon

Silicon has not been shown to be essential for humans. EFSA and IOM risk assessors found no suitable data for the establishment of a UL. In addition to naturally occurring silicon in the diet, food also contains silicon in the form of additives. Silicate additives are used as anticaking and antifoaming agents, and their bioavailability is considered to be low. Although silicon is thought to be essential, recommendations on adequate intake levels have not been established. The EVM estimated total intake from food, supplements and water (50 + 500 + 10 mg, respectively) to be 560 mg/day. No high intake or vulnerable groups were identified. The EVM also concluded that few data are available on the oral toxicity of silicon in humans, and that they are inadequate for risk assessment. However, the EVM established an SUL of 700 mg/day for supplemental intake of elemental silicon derived from a chronic dietary study in rats where no relevant adverse effects were observed at doses of up to 50, 000 ppm silica in the diet, corresponding to 2500 mg/kg BW/day. Uncertainty factors of 10 for interspecies variation and 10 for interindividual variation were applied to give a supplemental silica SUL of 25 mg/kg BW/day, which is equivalent to 1500 mg/day for a 60 kg adult. In terms of elemental silicon, this is equivalent to an EVM SUL of 12 mg/kg BW/day or 700 mg/day for a 60 kg adult for supplemental silicon. The proposed MLS for adults and children aged 4–10 years are, therefore, 700 mg/day and 240 mg/day, respectively.

4. Sodium chloride

Sodium is an essential nutrient involved in fluid and electrolyte balance, and it is required for normal cellular function. Sodium is present in foods as a normal constituent at a low level. It is also added to foods, mainly as sodium chloride, the main reasons being for flavour, texture and preservation. EFSA concluded that the available data are not sufficient to establish a UL for sodium from dietary sources.

The EVM concluded that sodium chloride is not ordinarily suitable for use in food supplements and decided to consider it as a salt, rather than separate elements. There were no relevant data available relating to the toxicity of the chloride ion. The EVM did not establish an SUL for sodium chloride because there appears to be a graded response across doses that include the current estimated intake in the UK (mean intake from food, 7.2 g/day; 97.5 percentile, 13 g/day). Opinion is divided concerning the long-term influence of dietary sodium chloride intakes greater than 6 g/day on the development of essential hypertension. Sodium chloride causes an increase in blood pressure at customary dietary intakes in susceptible individuals, leading to dietary recommendations for a reduction in intake.

With regard to the chloride ion, the mean daily intakes of populations in Europe range from about 5 to 7 g (equivalent to about 8–11 g salt). Available evidence indicates that both the chloride and sodium ions in excess contribute to an elevated blood pressure. In the case of potassium chloride, the adverse effects with very high intakes appear to be attributable to the potassium rather than the chloride ion. EFSA (2006) concluded that the available data are not sufficient to establish an upper level for chloride from dietary sources.

5. Sulphur/sulphate

Few data are available on dietary sulphur intake. It has been estimated that the human diet contains approximately 1% sulphur (EVM 2003), largely consisting of the sulphur-containing amino acids

and other food components including sulphites, and to a lesser extent, sulphates. Assuming that adults consume 1 kg food per day, this would represent a sulphur intake of 10 g or 143 mg/kg BW for a 70 kg adult.

Risk assessments of essential vitamins and minerals have not included sulphur or the sulphur-containing compounds. However, EFSA (2008b) published a scientific opinion on calcium sulphate for use as a source of calcium in food supplements. With respect to the sulphate ion, EFSA considered a "worst case" scenario that assumed the consumption of calcium sulphate up to the UL of 2500 mg calcium per day. This amount corresponds to an intake of 8.5 g calcium sulphate (anhydrous) per day, which equates to a daily intake of 6 g sulphate ion per person. For sodium sulphate, there are few studies in experimental animals, but none raised concerns about the toxicity of the sulphate ion. Sodium sulphate is used clinically as a laxative. In clinical studies in which 2–4 oral doses of up to 4.5 g sodium sulphate decahydrate were used per person (9–18 g per person), only occasional loose stools were reported. These amounts correspond to 2.7–5.4 g sulphate ion (EFSA 2004). Because of the low solubility of calcium sulphate compared with sodium sulphate, the EFSA Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) concluded that studies with dose levels up to 5.4 g sulphate ion from sodium sulphate per person provided sufficient reassurance over the safety of the sulphate ion from calcium sulphate up to 6 g/day (EFSA 2008b).

Appendix 4. Commentary on intakes of selected nutrients from foods, from fortification and from supplements by children aged 4–10 years from the report commissioned by the International Life Sciences Institute (ILSI) Europe Addition of Nutrients to Food Task Force (Flynn et al. 2009)

Calcium

The P95 intake from the base diet ranged from 1107 to 1721 mg/day in the age group 4–10 years. Higher intakes were associated with higher consumption of milk and dairy products. The limited data on intakes of calcium from supplements and fortified foods indicate that intakes from these sources are very low, and that inclusion of these sources with base diet has only a minimal effect on P95 intake. All the intakes are well within the children's ULs. The P5 data indicate levels well below the RDA.

Copper

The P95 intake exceeded the ULs from base diet in Germany, associated mainly with consumption of meat and offal products. From the few data available, it appears that there is little contribution from supplements or fortified foods in children. EFSA (2006) concluded that mean copper intakes are below the UL, and that P97.5 intakes close to the UL were not a matter for concern.

Iodine

The P95 of iodine intake from base diet ranged from 140 (Germany) to 280 µg/day (Denmark). The P95 intake from base diet exceeded 250 µg/day UL by a small amount for the age group 4–6 years, but it was less than the 300 µg/day UL for children aged 7–10 years in Denmark, Ireland and the UK. Inclusion of supplements increased the P95 intake of iodine in Denmark to over 300 µg/day, but it had little effect on P95 intakes in Ireland. Inclusion of voluntarily fortified foods for Ireland and the UK had little effect on the P95 intake. The data were extremely limited and the P5 intakes were well below the RDA. While an intake exceeding the UL is not without some risk, the probability of adverse effects occurring in the small proportion of individuals exceeding the UL by a modest amount is low.

Iron

The P95 iron intake from base diet ranged from 8 to 16 mg/day. The limited data on intakes of iron from supplements indicated that P95 of iron intake from supplements ranged up to 12 mg/day. Similarly, P95 intakes from voluntarily fortified foods were about 5 mg/day. The IOM UL (2001) for children is 40 mg/day. When the extrapolated children's ULs based on bodyweights are used (see Section 6.5), the P95 intakes exceed the lower UL for 4–6 year olds but none exceeds the UL for 7–10 year olds. Based on these estimates of iron intakes in European countries, the risk of adverse effects from high iron intakes is considered to be low, whilst anaemia and other developmental effects associated with low intake are all too real.

Magnesium

The P95 of magnesium intake from the base diet ranged from 250 mg/day (Ireland) to 430 mg/day (Germany). The P95 of intake from supplements ranged up to 60 mg/day. The limited data available on intakes of magnesium from fortified foods indicate that they are low and have only a minimal effect on P95 intake of the total diet. The UL of 250 mg refers to magnesium sources used for fortification and in food supplements and does not include magnesium normally present in conventional foods and beverages.

Phosphorus

The P95 of phosphorus intake from the base diet ranged from 1331 mg/day (UK) to 1926 mg/day (Denmark). The limited data on intakes from supplements and fortified foods for children indicate that intake from these sources is very

low or not observed, and that inclusion of these sources with base diet has little effect on P95 intake. The intakes are well below the children's UL and the risk of adverse effects is considered to be low.

Selenium

The P95 intake of selenium in children and adolescents was less than the UL for base diet and when supplements and voluntary fortification were included. Few data are available on the use of selenium in voluntarily fortified foods, and this trace element is added to foods only infrequently.

Zinc

The P95 of zinc intake from base diet ranged from 7.5 to 14.7 mg/day and it exceeded the UL in some countries by a small amount. The main sources of zinc in Germany and Poland are meat, meat products, bread and milk products. Limited data from Denmark showed that intake of zinc from food supplements was additive and increased the P95 intake to levels that exceeded the UL. The limited data on fortified foods showed that intake from this source is low. The observed zinc intakes close to the children's ULs are not a matter for concern (EFSA, 2006).

Folic acid

The P5 intakes were very low. The P95 intake of folic acid from supplements alone ranged up to about 40 µg/day, increasing to about 210 µg/day when voluntary fortification was included. Data on folic acid intake from fortified foods alone were available for one country (Ireland) and ranged up to about 170 µg/day. As indicated earlier, it is not appropriate to apply the UL for folic acid derived from the adult UL by the SCF to children or adolescents since the adverse effect on which this UL is based is not relevant to this age group. Nevertheless, the intake of folic acid from all sources is well within the ULs for children set out by EFSA (2006).

Folate

There is no evidence for risk associated with high intakes of natural, reduced folates, and thus no data to set a UL for natural folate (EFSA 2006).

Nicotinamide

The P95 intakes are all well below the ULs. There are no concerns regarding intakes of nicotinamide (preformed niacin) within the range currently consumed in foods from all sources including fortified foods and food supplementation in European countries. Intakes at the P95 level from all sources are around 10% of the UL.

Retinol

The P95 of retinol intake from base diet ranged from 452 to 1312 µg/day. The P95 intake for 4–10 year olds exceeds the UL in Poland and Denmark and may be associated with higher consumption of sausages and liver. The P95 intake for older children remains below the UL. The limited data on intake from fortified foods indicate no significant contribution to total retinol intake. The limited data on supplemental intake of retinol for children indicate that they can contribute to an increase in the P95 intake from total diet. The UL is low relative to the observed habitual intakes, and the amounts in the total diet may exceed the UL by a small amount in some cases.

Vitamin B_6

The P95 intakes are well below the ULs. In children aged 4–6 years, the highest intakes from all sources range from 31 to 49% of the UL.

Vitamin D

The P95 intake from base diet ranged from 2.3 to 5.9 µg/day. From the limited data available, intakes from supplements and fortified foods are low (except for supplements in Denmark) and inclusion of these sources with base diet has only a minimal effect on P95 intake. Even in countries where there is wide use of supplements (Denmark

and Finland) and where there is semi-mandatory fortification of milk with vitamin D, the P95 intakes are well below the UL.

Vitamin E

The P95 intakes are all well below the ULs, and even for the highest intakes, the levels did not exceed 18% of the UL for 4–6 year olds.

Appendix 5 Why Recommended Daily Amount (RDA)-based upper safe levels are not scientific or appropriate to establish maximum levels of vitamins and minerals in food supplements

1. Classically, the requirement of an individual for a nutrient has been the amount of that nutrient required to prevent clinical signs of deficiency. While this must always be an important part of defining a requirement, scientific committees recognise that in addition to satisfying the basic need to avoid deficiency, some allowance should be made, where appropriate, to ensure nutritional adequacy. For example, a degree of storage of a nutrient to allow for periods of low intake or high demand without detriment to health.

2. The estimates of requirements can be characterised as follows:
   - The intakes of a nutrient by individuals and by groups that are associated with the absence of any signs of deficiency disease
   - The intakes of a nutrient associated with an appropriate biological marker of nutritional adequacy
   - The intakes of a nutrient needed to maintain a given circulating level or degree of enzyme saturation or tissue concentration
   - The intakes of a nutrient needed to maintain homeostatic balance, taking into account that the period over which such balance needs to be measured differs for different nutrients and between individuals

3. The RDA is defined as the average daily intake level that is sufficient to meet the nutrient requirement for nearly all (97–98%) of healthy individuals in a particular life stage and gender group.

4. The RDA is not defined or identified to describe safety or to represent a safety limit for total or supplemental intake of a nutrient. Arbitrary multiples of RDA to set maximum levels of vitamins and minerals in food supplements have no scientific validity.

5. Scientific risk assessments and risk management approaches are the only valid methods to identify maximum levels of vitamins and minerals (and other substances with nutritional or physiological effects) in food supplements, as well as in foods with added nutrients.

6. Nutrient-related hazard identification and characterisation should recognise the methodological differences in assessment of nutritional risk of inadequate and excessive intakes, and the scientific advances in these methodologies.

7. Nutrient reference standards that are used to characterise nutrient-related hazard(s) related to adequacy of intake include measures of average requirement, whereas nutrient reference standards that characterise nutrient-related hazard(s) linked to excessive intakes include the tolerable upper intake level and highest observed intake determined by scientific risk assessment.

8. The use of RDA-based safe upper limits in food supplements could be misleading to consumers and promote hypothetical safety concerns about a particular vitamin or mineral. An interesting example is the fact that the natural amounts of vitamin B12 in conventional foods, such as liver and some shellfish, can be many multiples of the RDA.

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