food supplements europe

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

May 2021

Acknowledgement: The report was researched and drafted by Dr David P. Richardson in cooperation with the Food Supplements Europe Science Group.

Summary

With the increasing international interest in harmonising methodologies to determining safe levels of intake of vitamins and minerals in food supplements and fortified foods, there is a need to develop and apply scientifically based approaches to nutrient risk assessment and risk management in order to protect consumers and ensure a safe food supply.

Nutritional risk analysis considers the risk of adverse effects from inadequate and/or excessive intakes of nutrients and related substances, and the predicted reduction in risk from proposed risk management strategies. Science-based approaches to nutritional risk assessment and the establishment of upper safe levels of intake for vitamins and minerals are based primarily on principles and guidelines from the Codex Alimentarius Commission (2010) and the report of the joint Food and Agriculture Organisation and the World Health Organisation (FAO/WHO, 2006). The Codex standards act as global reference points for national food control agencies, for consumers, food businesses and for international trade.

For food regulators and policymakers, nutritional risk analysis provides a systematic and structured approach to assess public health and safety risks from food and food supplements and a means to characterise the nature and magnitude of the health risk and how the risk can be managed.

In the European Union, the criteria to be taken into account for setting maximum amounts of vitamins and minerals are set in law for food supplements and fortified foods in:

- Directive 2002/46/EC on food supplements (European Parliament and of the Council, 2012)
- Regulation (EC) No 1925/2006 on the addition of vitamins and minerals to foods (European Parliament and of the Council 2006a)

The main common criteria include:

- 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

In turn, regulatory authorities rely on expert groups of scientific nutritional risk assessors including the European Food Safety Authority (EFSA), the US Institute of Medicine (IOM), the UK Expert Group on Vitamins and Minerals (EVM) and other national sources of information to develop, where possible from the available data, Tolerable Upper Intake Levels (ULs) for each vitamin and mineral. ULs established by EFSA are used where available. In the absence of an EFSA UL, the amounts from the IOM are used. These quantitative values are used by nutritional risk managers and policy makers when assessing potential risk from the cumulative intake of nutrients from all sources, including conventional foods, fortified foods and food supplements. The need for regulation of specific nutrients depends on the severity of the adverse effects and the prevalence of too high population intakes evaluated against the UL.

The risk management approaches described in this updated Food Supplements Europe (FSE) report address the many difficulties and complexities surrounding the setting of maximum levels in food supplements and take the opportunity to use the most recent risk assessments and comprehensive nutrient intake data on vitamins and minerals from the Food Safety Authority of Ireland (FSAI, 2020). This valuable source of information provides nutrient intake data from all sources (including food supplements) and from food sources only (including fortified foods) for Irish adults (both males and females combined, and separately for males and females). The age groups covered were Irish children (5–12 years), teenagers (13–17 years) and adults (18–64 years and older than 65 years). These intake data provide the mean, standard deviation and the 5th, 95th and 97.5th percentile amounts, the latter P95 and P97.5 values representing the highest intakes for most of the essential nutrients. Exposures to nutrients change over time because of changing food choices and patterns of consumption, food fortification practices and the use of food supplements.

The new FSAI data have been used in this updated FSE risk management model to enable comparisons to be made with previous reports published by the European Responsible Nutrition Alliance (ERNA) in 2004, Food Supplements Europe (FSE) in 2014 and Richardson (2015). These data from Ireland are used because they are not only the most comprehensive but because they are consistent with the EC orientation paper (2007) to use the best available data from countries considered to be “mature” markets for both food supplements and fortified foods.

This re-examination of the data has demonstrated that the FSE model has stood the test of time and that the methodology has merit because:

- The case-by-case methodology is consistent with international standards for nutritional risk analysis using quantitative and qualitative risk assessment and risk management data.
- The FSE model relates to current conditions and develops scenarios for modelling of future nutrient intakes according to changing food habits, food choices, food availability, government recommendations and new research data on safety.
- The Population Safety Index (PSI) paradigm used in the FSE risk management model describes a process by which nutrients can be allocated into three categories of risk according to the margin between the UL and the Recommended Daily Amount/Reference Intake (RI).

Population Safety Index (PSI)

For those nutrients with an established UL, this FSE 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:

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

Upper Tolerable Intake Level (UL)

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.

Mean Highest Intake (MHI) and Intake from water (IW)

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.

Reference Intake (RI)

The labelling RI denominator is used in calculations for adults and children because the value is consistent across all European Member States and the UK. The use of the labelling RI and the UL, where available, also provide fixed points on the intake curve.

Categorisation of risk into Groups 1, 2 and 3

The model assumes that where the difference between the MHI from food (including fortified foods) and the UL is more than 150% x RI, 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 RI, 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 around 1.5 for both adults and children, and for Group 3, the "potential risk of excessive intakes", is a PSI of around 1.5 or less. Group 1 nutrients are those for which there is no evidence of risk to human health at levels currently consumed.

Table 1 Categorisation of nutrients into three groups of risk using quantitative and qualitative information:

Group 1	No evidence of risk to human health at levels currently consumed	No PSI to be established – no Upper Levels defined
Group 2	Low risk of exceeding UL	PSI > 1.5
Group 3	Potential risk at excessive intakes	PSI < 1.5

Precautionary Risk Management Factor

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 and Ireland over a period of 15–20 years. Although recent data show a downward trend in micronutrient intakes, 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 x 150%)

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

Risk Characterisation

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 2. 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, specific concerns for older children and post-pubertal children have to take account of the onset of puberty, the increasing speed of growth and the adolescent growth spurt.

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.

Maximum Levels for Food Supplements (MLS)

The PSI methodology used in the FSE report of 2014, the use of the FSAI nutrient intake data (2020) and the risk categorisation of the nutrients into three groups demonstrate a scientifically based, transparent and robust methodology for nutritional risk management. Because the intake data are different, the resulting calculations of the PSI and MLS are inevitably different. Despite these differences, the categorisation of nutrients into Groups 1, 2 and 3 remains the same.

Similarly, using quantitative and qualitative risk management approaches for each nutrient, the FSE proposed MLS for 2021 are the same as for 2014, with the exceptions of preformed retinol and beta-carotene for adults and beta-carotene and iron for children aged 4–10 years. The amounts are shown in Table 2.

Table 2 Summary table for proposed FSE Maximum Safe Levels in food supplements (MLS)

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 B1 (Thiamin) (mg)	—	—
Vitamin B2 (Riboflavin) (mg)	—	—
Biotin (µg)	—	—
Vitamin B12 (Cobalamin) (µg)	—	—
Pantothenic acid (mg)	—	—
Vitamin K (µg)	—	—
Chromium III (mg)	—	—
GROUP 2 Low risk of exceeding UL		
Vitamin B6 (Pyridoxine) (mg)	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 RE) (µg)	1500	1000
Beta-carotene (mg)	8	8
Calcium (mg)	1000	500
Copper (mg)	2 [b]	1 [b]
Iodine (µg)	200 [b]	150 [b]
Iron (mg) [e]	20 [b]	14 [b]
Manganese (mg)	4 [b]	1.5 [b]
Zinc (mg)	15 [b]	5 [b]

a As described in Section 3.2 and in Table 8 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.

c Higher UL values from 50 µg to 100 µg per day for adults were established by the IOM and EFSA risk assessments in 2010 and 2012, respectively.

d Folic acid: pteroylmonoglutamic acid.

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

Overall, the objective of the scientifically-based nutritional risk analyses described in this report is to demonstrate a consistency of approach in deriving maximum levels for vitamins and minerals in food supplements. The report attempts to address the many difficulties and complexities involved, and the purpose is to contribute towards the forthcoming discussions in the EU on the principles and methodologies for establishing maximum levels in food supplements and fortified foods.

Consultation, dialogue and sharing of expertise between interested parties are critical to ensuring that proportionate measures are used to protect consumers and to facilitate informed choice.

Abbreviations

ADI	Acceptable Daily Intake	AI	Adequate Intake
AROI	Acceptable Range of Oral Intake	BPD	Broncho-Pulmonary Dysplasia
BW	Body Weight	COMA	UK Committee On Medical Aspects
DRV	Dietary Reference Value	EAR	Estimated Average Requirement
EPP	Erythropoietic Protoporphyria	EC	European Commission
EFSA	European Food Safety Authority	EFSA ANS	EFSA Panel on Food Additives and Nutrient Sources Added to Food
EFSA NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies	ERNA	European Responsible Nutrition Alliance
EU	European Union	VM	Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organisation	FNB	US Food and Nutrition Board
FSA	UK Food Standards Agency	FSAI	Food Safety Authority of Ireland
FSE	Food Supplements Europe	GI	Gastrointestinal
GL	Guidance Level	HHT	Hereditary haemochromatosis
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
LRNI	Lower Reference Nutrient Intake	MHI	Mean Highest Intake
MLS	Maximum level of a vitamin or mineral in a food supplement	MSL	FSAI Maximum Safe Level
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
RBC	Red Blood Cell	RDA	Recommended Daily Allowance / Recommended Dietary Allowance
RE	Retinol Equivalents	RfD	Reference Dose
RI	Reference Intake	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
TUL	Tolerable Upper Level	UF	Uncertainty Factor
UK	United Kingdom	UL	Upper Level: The maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans
UVB	Ultraviolet B radiation	VKM	Norwegian Food Safety Authority
WHO	World Health Organisation		

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1. Introduction

The increasing use of fortified foods and food supplements has the potential to improve the intake of nutrients and overall nutritional status of the population. At the same time, the cumulative intake of nutrients from all sources should not lead to adverse effects.

Regulatory authorities rely on expert groups of scientific nutritional risk assessors to develop not only Dietary Reference Values (DRVs), including Reference Intakes (RI), but also Tolerable Upper Intake Levels (UL) of individual vitamins and minerals. These quantitative values are used by risk managers and policymakers when planning and developing nutritional and health policies to assess nutrient adequacy for groups of the population, and when assessing potential risks from the cumulative intake of nutrients from all sources, including food supplements. Three authoritative groups of scientific assessors, the European Food Safety Authority/Scientific Committee on Food (SCF/EFSA, 2006), the US Institute of Medicine (IOM, 1997, 1998, 2000, 2001) and the UK Food Standards Agency (UK FSA) Expert Group on Vitamins and Minerals (EVM, 2003) have addressed the setting of UL. A comparison of the UL for total daily intake from SCF/EFSA and IOM, and the EVM daily safe upper levels (SULs) and guidance levels (GLs) for long-term supplementary use are shown in Appendix 1. Along with the UK EVM risk assessment, the EFSA publication is still considered to be one of the most in-depth risk assessments conducted since that of the IOM. All three UL methods emphasise the concept of quantitative risk assessment where possible and have widespread scientific and policy support around the world. In addition, in Section 5.3, a paper by Pike and Zlotkin (2019) lists a total of nine organisations that have published risk assessment frameworks for adult ULs, and highlights the challenges of the risk assessment methodologies. However, disparities in the selection and interpretation of available scientific literature on safety and the approaches to handling scientific uncertainty have sometimes led to large differences in the ULs for some nutrients (e.g. for vitamins E, B6, niacin, iron, copper, iodine, zinc, molybdenum and phosphorus).

In Europe, SCF/EFSA were requested by the European Commission to provide scientific opinions on ULs for 29 nutrients listed in Annex 1 of the Food Supplements Directive (European Parliament and of the Council, 2002). This request 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, a lack of sufficient scientific data did not permit the derivation of a numerical UL. Where ULs have not been established, SCF/EFSA have provided case-by-case qualitative risk characterisations for the specific nutrients. In contrast, other expert scientific risk assessment committees such as IOM and EVM have set numerical values, and all these UL and SUL and GL values are part of the totality of the available evidence and should be taken into account in the development of risk management models.

It is important to recognise that the ULs represent an intake that can be consumed daily over a lifetime without significant risk to health according to the available scientific evidence. Table 3 illustrates what ULs are and what they are not. 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 at different life stages or with different physiological or health status. The risk assessment process recognises sensitive groups such as infants, children, certain individual adults, the elderly, women during pregnancy and lactation, and those people taking medicines under medical supervision. Even within relatively homogeneous life stage groups there can be a range of sensitivities to adverse effects, and sensitivity can be influenced by bodyweight, lean body mass and extent of adiposity. Appendix 2 illustrates the principles and guidelines for nutritional risk assessment.

Table 3 Characteristics of Upper Levels (ULs)

Definitions
The maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans [a]
Highest average daily intake of a nutrient that is likely to pose no risk of adverse effects for nearly all persons in the general population [b]
Are:
• Based on scientific risk assessment's assumptions and uncertainties. • Not only safe, but safe by a comfortable margin, thus providing a level of security for healthy populations. • Defined and identified to reflect safety of chronic intakes. • Values that take account of identified sensitive populations.
Are not:
• Thresholds for adverse effects. • "Safety limits". • Applicable to temporarily elevated intakes. • For individuals receiving the nutrient under medical supervision or for individuals with extreme and distinct vulnerabilities due to genetic predisposition or other considerations [c]

a European Food Safety Authority. 2006
b Dwyer *et al.* 2014
c European Food Safety Authority, 2021

2. Nutritional risk management and developments in the European Union

The starting point for risk managers is to utilise the scientifically based approaches to the establishment of upper safe levels of intake by risk assessment, and to adopt a uniform approach that is recognised internationally. The risk assessors can establish the risk and provide the information to equip the risk manager to determine if the risk warrants immediate action, close monitoring, or no action at the current time. Nutritional risk management can be effected through quantitative measures or qualitative guidance, and risk managers can make decisions about which options are appropriate, e.g. suitability of foods for addition of nutrients, labelling advice intended to mitigate nutritional risks to public health, e.g. advisory statements, educational campaigns, increased dialogue with industry, for specifying standards for product formulation, quality control etc. More information for use by nutrient risk managers relative to the need to take a particular action is contained in the FAO/WHO report (2006).

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 law by Regulation (EC)1925/2006 (European Parliament and of the Council 2006a), 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.

The key criteria for setting maximum amounts in fortified foods and food supplements are set out in Table 4:

Table 4 Legal criteria for setting maximum amounts in fortified foods and food supplements

European regulatory approaches to the setting of maximum amounts of vitamins and minerals in food and food supplements
Directive 2002/46/EC on food supplements (European Parliament and of the Council, 2012) • Maximum amounts of vitamins and minerals present in food supplements per daily portion of consumption as recommended by the manufacturer shall be set, taking the following into account: (a) upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups; (b) intake of vitamins and minerals from other dietary sources. • When the maximum levels are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

European regulatory approaches to the setting of maximum amounts of vitamins and minerals in food and food supplements

Regulation (EC) No 1925/2006 on the addition of vitamins and minerals to foods (European Parliament and of the Council 2006a)

- The maximum amounts referred to in paragraph 1 and the conditions referred to in paragraph 2 shall be set taking into account:
  (a) upper safe levels of vitamins and minerals established by scientific risk assessment based on generally acceptable scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different groups of consumers; and
  (b) intakes of vitamins and minerals from other dietary sources.
- When the maximum amounts are set, due account shall also be taken of reference intakes of vitamins and minerals for the population.
- When the maximum amounts are set for vitamins and minerals whose reference intakes for the population are close to the upper safe levels, the following shall also be taken into account, as necessary:
  (a) the contribution of individual products to the overall diet of the population in general or of sub-groups of the population;
  (b) the nutrient profile of the product established as provided for by Regulation (EC) No 1924/2006.

This FSE 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. It updates the Food Supplements Europe (FSE) 2014 risk management model and the European Responsible Nutrition Alliance (ERNA) reports from 2004. It utilises the most recent and comprehensive nutrient intake data from the Food Safety Authority of Ireland (FSAI) report, The Safety of Vitamins and Minerals in Food Supplements—Establishing Tolerable Upper Intake Levels and a Risk Assessment Approach for Products Marketed in Ireland, Revision 2 (2020). In addition, this updated FSE report highlights the differing approaches to risk management by some European Union (EU) Member States and provides examples of national adherence to, and divergence from, the basic principles of nutritional risk analysis (see Appendix 2).

3. Approaches to the setting of maximum levels of vitamins and minerals in food supplements for adults and children aged 4–10 years

The proposed risk management model for setting maximum levels of nutrients in food supplements for adults applies the principles of quantitative and qualitative risk assessment and takes into account the legal criteria in the European Regulations as set out in Table 4.

The model includes:

- Calculation of a Population Safety Index (PSI) for each nutrient
- Taking into account the contribution to total nutrient intake from all sources including conventional foods, fortified food, food supplements and, where appropriate, water
- Evaluation of the risk management options for current and future intakes of nutrients from all sources
- Categorisation of nutrients into three groups of risk using quantitative and qualitative information:
  - Group 1: No evidence of risk to human health at levels currently consumed
  - Group 2: Low risk of exceeding UL
  - Group 3: Potential risk at excessive intakes
- Proposals for maximum safe levels for each nutrient in food supplements (MLS) for adults and children aged 4–10 years

The risk management model uses the risk assessments from three authoritative groups of scientific assessors including SCF/EFSA, IOM and EVM. For the EFSA and IOM risk assessments, the 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 assessment is based on the UL method, but the scientific committee used the terms SUL or GL because these levels refer to long-term supplementary use, not total intakes (see Appendix I).

3.1 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 and a safe range of intake for each nutrient is now and is likely to be in the future, allowing for different dietary contexts, new research findings and their application to food and food supplement 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 PSI calculations for adults are shown in Table 5 and the 2014 and 2021 values (using different sets of intake data) demonstrate that the nutrients remain in the same categorisation of risk.

Table 5 Calculations of the population safety index (PSI) to characterise risk for adults, comparisons of MLS between 2014 and 2021 together with the calculated FSAI MSL

Nutrient and unit of weight	UL [a]	Mean highest intake from foods only [b] (MHI)	MHI x 1.5 for vitamins x 1.1 for minerals [c]	Potential intake from water [d] (IW)	Reference labelling value (RI) as set in Regulation (EC) 1169/2011	Population safety index (PSI) [e] Average PSI in bold		FSE MLS [f]		FSAI MSL [g] calculated
						2014	2021	2014	2021	
								(calculated) proposed		
Group 2: Low risk of exceeding the UL										
Niacin (as nicotinamide) mg	M 900 F 900	55.6 38.1	83.4	0 0	16 16	53.3 54.3 **53.8**	52.8 53.9 **53.4**	(829) 820	(817) 820	855
Vitamin E (mg as α-tocopherol equivalent)	M 300 F 300	20.9 17.5	31.3	0 0	12 12	23.8 23.9 **23.9**	23.3 23.5 **23.4**	(278) 270	(269) 270	283
Vitamin C (mg)	M 2000* F 2000*	224 214	336	0 0	80 80	22.4 22.7 **22.6**	22.2 22.3 **22.3**	(1686) 1700	(1966) 1700	1809 (1800 actual)
Vitamin D (µg)	M 100 F 100	10.2 8.5	15.3	0 0	5 5	17.8 18.1 **18.0**	17.9 18.3 **18.1**	(83.2) 83.2	(84.7) 83.2	92.1 (75 actual)
Vitamin B6 (mg)	M 25 F 25	6.6 4.3	9.9	0 0	1.4 1.4	13.6 15.1 **14.4**	13.1 14.8 **13.9**	(16.2) 18	(15.1) 18	20.1 (20 actual)
Molybdenum (µg)	M 600 F 600	210*	231	20	50	7.4 **7.4**	7.4 **7.4**	(369) 350	(369) 350	390
Folic acid (µg)	M 1000 F 1000	310 252	465	0 0	200 200	4.0 4.2 **4.2**	3.5 3.7 **3.6**	(695) 600	(535) 600	771 (500 actual)
Selenium (µg)	M 300 F 300	92	101.1	0	55 55	3.8 **3.8**	3.8 **3.8**	(199) 200	(199) 200	208
Phosphorus (mg)	M 4000* F 4000*	2677 1936	2944.7	10 10	700 700	1.8 3.1 **2.5**	1.9 2.9 **2.4**	(1009) 1250	(1055) 1250	1762
Magnesium (mg) [j]	M 250 F 250	567 412	See note [j]	See note [j]	375	See note [j]	See note [j]	250	250	250 (actual)

Nutrient and unit of weight	UL[a]	Mean highest intake from foods only[b] (MHI)	MHI x 1.5 for vitamins x 1.1 for minerals[c]	Potential intake from water[d] (IW)	Reference labelling value (RI) as set in Regulation (EC) 1169/2011	Population safety index (PSI)[e] Average PSI in bold		FSE MLS[f] (calculated) proposed		FSAI MSL[g] calculated
						2014	2021	2014	2021	
Group 3: Potential risk at excessive intakes										
Iron (mg)	M 45* F 45*	27 21.2	29.7 21.2	0.4 0.4	14 14	1.3 1.8 **1.6**	1.3 1.5 **1.5**	20	20	23.2[h]
Iodine (µg)	M 600 F 600	417 280	458.7	30	150 150	1.1 **1.1**	1.02 1.45 **1.2**	200	200	284
Copper (mg)	M 5 F 5	3.0 2.4	3.3	1 1	1 1	0.7 1.2 **1.0**	1 1.6 **1.3**	2	2	2.7
Zinc (mg)	M 25 F 25	18.7 13.4	20.6	1 1	10 10	0.3 2.1 **1.2**	0.5 1.1 **0.8**	15	15	9.1
Calcium (mg)	M 2500 F 2500	2017 1442	2218.7	300 300	800 800	0.5 1.1 **0.8**	0.2 0.9 **0.6**	1000	1000	880
Vitamin A (preformed retinol µg)[i]	M 3000 F 3000	995 835	1492.5	0 0	800 800	0.3 0.6 **0.5**	2.5 2.7 **2.6**	1200	1500	2232 (1700 actual)

M, male; F, female

a UL as established by SCF/EFSA where available, otherwise IOM marked with asterisk *

b MHI based on P97.5 nutrient intake data for males from food sources only.

c MHI estimates including precautionary risk management factors for future intakes.

d IW estimates are drawn from SCF/EFSA, EVM opinions and European/UK standards.

e PSI is an estimate of the safety margin between UL and RI using equation [UL-(P97.5+IW)]/RI and is used to categorise nutrients into Groups 2 and 3.

f Amounts for MLS 2014 and 2021 for each nutrient in Groups 2 and 3 for adults are based on quantitative and qualitative risk analyses, as described in Appendices 4 and 5. For Group 2 nutrients, the calculated amounts using both FSE 2014 and FSAI 2020 intake data are similar. For consistency, the proposed MLS remain the same. For Group 3 nutrients, all the MLS for adults are based on qualitative risk analysis and remain the same, with the exception of the MLS for preformed retinol.

g FSAI MSL maximum safe level for food supplements is calculated using equation TUL–P95 for adults (male and female combined) = MSL. Actual values are in parentheses.

h Iron P95 adult data in FSAI report (2020), table 12a is questionable. Intake P95 is 5.9 mg, whereas P97.5 is 21.8 mg. The latter figure is used in the calculation of maximum levels.

i Preformed retinol is a special case. MLS and MSL are based on differences in intake data and risk management decisions apply. FSAI (2020) used a P95 value of 1275 µg/day for > 65 years instead of 768 µg/day for 18-64 year-olds.

j UL is for dissociable magnesium salts in supplements only. Intake data refer to total dietary magnesium.

The concept of characterising risk using the PSI is set out in the following equation:

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

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
- RI = Labelling Recommended Daily Allowance and Reference Intake (RI) as set in Regulation (EC) No 1169/2011 on food information to consumers

For adults, the UL from all sources is established by SCF/EFSA when available; otherwise, the IOM UL values are used. The MHI is the "mean highest intake" from food sources (includes fortified foods but excludes food supplements) based on the 97.5 percentile (P97.5) mean intake data of male adults. The intakes of nutrients in male adults tend to be higher than the equivalent intakes in female adults, and hence the calculation introduces a small precautionary measure. The IW is the estimated intake of minerals from water drawn from EFSA (2006), EVM (2003), from European Standards (Directive 98/83/EC) and the Drinking Water Inspectorate 2019-Report for England.

The Reference Intake (RI - previously referred to as the RDA value) is the labelling Reference Intake (or the Nutrient Reference Value (NRV)) for labelling purposes from Annex XIII of Regulation (EU) No 1169/2011 (European Parliament and of the Council 2011). The labelling RI are for the whole population and are generally significantly higher than the reference nutrient intakes (RNIs) for a particular population group. The higher labelling RI denominator is used in the calculations for both adults and children because the value is consistent across all EU Member States, whereas Reference Nutrient Intake (RNI) values vary considerably. The use of the labelling RI not only provides a fixed point on the intake curve (see Figure 1, Appendix 2) 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. The model assumes that where the PSI of a nutrient is higher than around 1.5, i.e. where there is a margin of safety of 1.5 times the RI between the P97.5 intake of food (including fortified foods) plus the estimated intake from water (where appropriate) and the UL, the chance of exceeding the UL is low (Group 2). Where the PSI is 1.5 or below, i.e. the P97.5 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 RI 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 around 1.5", and for Group 3, the "potential risk at excessive intakes" is a PSI of around 1.5 or less. Group 2 includes some nutrients as special risk management cases, e.g. potassium, vitamin C, magnesium and folic acid, either because no UL was established by SCF/EFSA or, as in the case of magnesium, the UL of 250 mg/day refers to supplemental sources of readily dissociable magnesium salts and the UL of 1000 µg/day is for supplemental folic acid. Similarly, Group 3 contains manganese as a special case because SCF/EFSA could not establish a UL (ERNA 2004, Food Supplements Europe 2014). See Appendices 3, 4 and 5 for specific risk management cases for Groups 1, 2 and 3, where each nutrient is considered systematically and any judgements or assumptions made, and scientific uncertainties involved, are described in the text.

The PSI calculations depend on quantitative values for ULs and estimates of high intakes of the nutrient.

Usually, the P95 and P97.5 percentile intakes are used to represent consumers with high intakes. The use of P95 intakes rather than higher percentiles is considered appropriate considering the conservatism implicit in the setting of a UL such that 5% of the population exceeding the UL by a modest amount would be unlikely to give rise to a risk of adverse health effects in the population (Flynn *et al.* 2016; FSAI 2020). However, in the FSE model the P97.5 intake level is used to provide a substantial level of precaution. The EVM also utilised the P97.5 levels of intake for all nutrients in the setting of SULs.

3.2 Nutrients for which no UL can be established and that do not represent a risk to human health (Group 1)

When authoritative risk assessments show no adverse effects in healthy individuals, when there are no safety concerns about a nutrient, and when a UL cannot be established, these nutrients (vitamins B1, B2, B12, biotin, pantothenic acid, vitamin K and chromium (trivalent form) are placed in Group 1, and no further risk management measures are required. Since there is no scientific basis for establishing a maximum level for these Group 1 nutrients, the European Commission orientation paper (2007) 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.

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. A summary of the qualitative risk characterisation of the Group 1 nutrients for which no UL is available is shown in Appendix 3.

Table 6 shows a summary of the quantitative risk characterisation of the vitamins and minerals based on the PSI.

Table 6 Risk categorisation of vitamins and minerals

1. No evidence of risk within ranges currently consumed; does not represent a risk to human health	2. Low risk of exceeding the UL	3. Potential risk at excessive intakes
Vitamin B1	Vitamin B6	Vitamin A (preformed retinol)
Vitamin B2	Vitamin C	Beta-carotene (smokers)
Biotin	Vitamin D	Calcium
Vitamin B12	Vitamin E	Copper
Vitamin K	Nicotinamide	Iodine
Chromium [a]	Molybdenum	Iron
Pantothenic acid	Phosphorus	Manganese
	Selenium	Zinc
	Magnesium	
	Folic acid	
	Potassium	

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

4. Nutrient intake data

4.1 Adequacy of data

A fundamental problem for all risk assessments and risk management approaches to setting maximum levels for food supplements (and fortified foods) is the adequacy of the information on nutrient intakes. 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 the case of ULs, chronic intakes above these values increase the risk of adverse effects (Garcia-Casal *et al*. 2019).

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 from countries considered to be “mature” markets for both food supplements and fortified foods. In the FSE 2014 report, intake data were 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 this update of the FSE model, all the nutrient intake data used are from the Food Safety Authority of Ireland (FSAI) in the following recently published reports:

- The Safety of Vitamins and Minerals in Food Supplements: Establishing Tolerable Upper Intake Levels and a Risk Assessment Approach for Products Marketed in Ireland (Revision 2, 2020)
- Guidance for Food Businesses: The Safety of Vitamins and Minerals in Food Supplements—Establishing Maximum Safe Levels and Risk Assessment Approach for Products Marketed in Ireland (August 2020).

These two FSAI reports provide not only updated risk assessments for each nutrient based primarily on the EFSA and IOM ULs but also the most recent intake data. This comprehensive source of intake data provides information on vitamins and minerals from all sources (including food supplements) and from food sources only (including fortified foods) for Irish adults (both males and females combined, and separately for males and females). The age groups covered were Irish children (5–12 years), teenagers (13–17 years) and adults (18–64 years and older than 65 years). These intake data provide the mean, standard deviation and the 5th, 95th and 97.5th percentile amounts, the latter P95 and P97.5 values representing the highest intakes for most of the essential nutrients.

4.2 Allowing for future intakes of vitamins and minerals

To gain a measure of potential changes in consumer food preferences, dietary patterns, food supplement use and the increased fortification of food products that might develop in the future, a comparison was made of dietary surveys undertaken in the United Kingdom (UK) and Ireland over a period of 20 years (Irish Universities Nutrition Alliance (IUNA), 2001; UK Office for National Statistics, NDNS, 1998, 2000, 2003, 2019, 2020); FSAI, 2020). Based on these intake data, the proposed FSE risk management model assumes a precautionary risk management factor of a 50% increase in dietary intake for all the vitamins from foods, including fortified foods, and a 10% precautionary risk management factor for minerals. These precautionary factors represent the biggest changes over the 20-year period, i.e. based on an actual increase in vitamin C intake of 36% rounded up to 50% and 8% for calcium rounded up to 10%. In fact, many of the micronutrient intakes declined over this period, demonstrating the need to monitor suboptimal and inadequate nutrient intakes of (sub)population groups (NDNS, 2020).

These precautionary factors have been used in the FSE (2014) and in this updated FSE risk management model where data are available to estimate proposed maximum levels in food supplements (MLS) using the following equations (see Section 5):

For vitamins: MLS = UL – (MHI x 150%)

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

Reassuringly, Table 7 shows that the FSAI P95 and P97.5 intake data for Groups 2 and 3 risk categories of nutrients for males aged 18–64 years from all sources, including food supplements, are all well below the UL, except for zinc when the P97.5 intake value is used. However, both EFSA (2006) and FSAI (2020) state that if the P97.5 of total zinc is similar to the UL, this would not be considered to be of concern. Pike and Zlotkin (2019) note that population intake data often show zinc intakes above the UL, especially for young children. However, despite these reports of intakes above the UL, there is a lack of any reported zinc toxicity in these populations. The authors comment that current ULs for zinc are likely to be too low. These observed changes in nutrient intakes from dietary surveys used in the FSE risk management model are based on actual survey data over a 20-year period. Table 7 also shows the critical endpoints for adverse effects of excessive exposure.

Table 7 The P95 and P97.5 intakes from all sources compared with the UL for the 3 risk categorisation groups and a summary of the critical endpoints for adverse effects of excessive exposure. The percentage difference between the P95 and P97.5 intakes are also shown.

Nutrient		FSAI nutrient intakes for adults aged 18–64 years			
GROUP 1 No evidence of risk to human health at levels currently consumed (from EVM GL)	UL [a]	P95 ♂ All sources	P97.5 ♂ All sources	% difference rounded	Critical endpoints [a]
Vitamin B1 (Thiamin) (mg)	100	5.3	13.2	149	Thiamin is well tolerated and no adverse effects have been observed.
Vitamin B2 (Riboflavin) (mg)	40	5.6	12.5	123	No toxic or adverse reactions to riboflavin in humans have been identified.
Biotin (µg)	900	128	181	41	Absence of adverse effects at 9 mg per day for 4 years
Vitamin B12 (Cobalamin) (µg)	2000	15.5	22.7	46	Very low adverse effects in humans
Pantothenic acid (mg)	200	17.2	25.0	45	Very high levels in the order of 10 g/day have been associated with diarrhoea and gastrointestinal (GI) disturbances.
Vitamin K (µg)	1000	—	—	—	No evidence of adverse effects to phylloquinone. Antagonistic effects on anticoagulant drugs
Chromium III (mg)	10	—	—	—	No adverse effects observed on trivalent chromium. Hexavalent chromium is toxic.

Nutrient		FSAI nutrient intakes for adults aged 18–64 years			
GROUP 2 Low risk of exceeding UL	UL [a]	P95 ♂ All sources	P97.5 ♂ All sources	% difference rounded	Critical endpoints [a]
Vitamin B6 (Pyridoxine) (mg)	25	7.6	12.4	63	High levels causing irreversible neuropathy
Vitamin C (mg)	2000	310	358	15	GI disturbances that are reversible
Vitamin D (µg)	100	12.8	16.1	25	Hypercalcaemia and hypercalciuria
Vitamin E (mg)	300	23.4	32.3	38	Very low oral toxicity. Effects on blood clotting and blood coagulation resulting in haemorrhage in patients receiving anticoagulant drugs
Nicotinamide (mg) [b]	900	61.5	77.2	26	No adverse effects except GI effects at very high intakes
Molybdenum (µg)	600	—	—	—	GI effects. Diarrhoea; effects on reproduction in rats
Phosphorus (mg)	4000	2435	2677	10	Mild and reversible GI effects, possible effects on calcium-regulating hormone, calcium balance
Selenium (µg)	300	—	—	—	Selenosis, changes to skin, nails and brittle hair
Magnesium (mg)	250	(527) [c]	(589) [c]	12	GI disturbances, osmotic diarrhoea
Folic acid (µg)	1000	(Total 768) [d]	(840) [d]	9	Neurotoxicity, masking of vitamin B12 deficiency mostly in elderly
Potassium (mg)	Not set	—	—	—	GI effects, hyperkalaemia and cardiac effects

Nutrient		FSAI nutrient intakes for adults aged 18–64 years			
GROUP 3 Potential risk at excessive intakes	UL [a]	P95 ♂ All sources	P97.5 ♂ All sources	% difference rounded	Critical endpoints [a]
Vitamin A (preformed retinol) (µg)	3000	1236	1845	49	Teratogenicity, birth defects, hepatotoxicity
Beta-carotene (mg)	15	9.52	11.02	16	No side effects other than reversible yellowing of the skin; risk of lung cancer in smokers
Calcium (mg)	2500	1818	2037	12	Hypercalcaemia, possible risk of kidney stones
Copper (mg)	5	2.9	3.7	28	Mild and reversible GI effects, copper hepatoxicity
Iodine (µg)	600	365	428	17	Elevated thyroid stimulating hormone (TSH)
Iron (mg)	45	26.3	32.8	25	GI effects, iron overload
Manganese (mg)	250	—	—	—	Neurological changes, “manganism”
Zinc (mg)	25	20.6	24.2	17	GI disturbances and copper balance

a The critical endpoint is the adverse effect exhibiting the lowest NOAEL (e.g. the most sensitive indicator of a nutrient’s adverse effects). The derivation of a UL based on the most sensitive endpoint will ensure protection against all other adverse effects (EFSA, 2006)

b For nicotinic acid, the critical endpoints are flushing and vasodilatory effects when used in the treatment of hypercholesterolaemia

c Total from all sources

d Total folate

5. Calculating maximum safe levels (MLS) of vitamins and minerals in food supplements for adults and children aged 4–10 years: examples from the FSE and FSAI risk management models

5.1 Adults

Taking into account the risk categorisation of nutrients using the PSI, the most recent intake data and the quantitative estimates of future potential higher intakes from all other food sources including fortified foods, the updated FSE risk management model has been applied to determine maximum levels of vitamins and minerals in food supplements where possible using MHI from the FSAI survey data according to the following equations:

For vitamins: MLS = UL – (MHI x 150%)

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

Risk for each nutrient has been assessed on a case-by-case basis, taking into account both quantitative and qualitative risk management information, the availability of data and the most appropriate representation of those individuals in the population that are reported to consume the highest amounts of a nutrient. The detailed risk management analyses are shown in Appendices 4 and 5 for Groups 2 and 3, respectively. The proposed maximum safe levels in food supplements for adults and children aged 4–10 years that would not be expected to result in any adverse effects are summarised in Table 8.

Table 8 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 B1 (Thiamin) (mg)	—	—
Vitamin B2 (Riboflavin) (mg)	—	—
Biotin (µg)	—	—
Vitamin B12 (Cobalamin) (µg)	—	—
Pantothenic acid (mg)	—	—
Vitamin K (µg)	—	—
Chromium III (mg)	—	—
GROUP 2 Low risk of exceeding UL		
Vitamin B6 (Pyridoxine) (mg)	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 RE) (µg)	1500	1000
Beta-carotene (mg)	8	8
Calcium (mg)	1000	500
Copper (mg)	2 [b]	1 [b]
Iodine (µg)	200 [b]	150 [b]
Iron (mg) [e]	20 [b]	14 [b]
Manganese (mg)	4 [b]	1.5 [b]
Zinc (mg)	15 [b]	5 [b]

a As described in Section 3.2 and in Table 8 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.

c Higher UL values from 50 µg to 100 µg per day for adults were established by the IOM and EFSA risk assessments in 2010 and 2012, respectively.

d Folic acid: pteroylmonoglutamic acid.

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

As previously mentioned, the proposed model and MLS for food supplements take into account the contributions to total nutrient intake from conventional foods, fortified foods and food supplements, using the best available data for a European context. Interestingly, other theoretical models for setting maximum amounts of vitamins and minerals in fortified foods have also resulted in three categories of risk (Flynn *et al*. 2003, Rasmussen *et al*. 2006, Kloosterman *et al*. 2007), and in a recent French guidance on health recommendations for food supplements (DGCCRF, 2019), this classification was also retained.

The most recent risk management model, published on 6th August 2020 by FSAI, uses the most comprehensive nutrient intake data and ULs derived from EFSA (2006) and IOM risk assessments (1997,1998,2000,2001). The FSAI report reviewed the literature to ensure that the ULs are appropriate for Ireland, and the model employs the P95 of intake from foods, including fortified foods, to calculate the maximum safe level (MSL) in food supplements.

The general calculation in the FSAI report is:

UL – level of nutrient in diet (P95) = MSL in food supplement

Each nutrient is reviewed on a case-by-case basis in line with the Food Supplements Directive 2002/46/EC, and allowances are made for uncertainties in intake estimates, including possible future changes such as mandatory fortification of certain foods. The UL requires a reference bodyweight (BW), and the FSAI considered an amount of 60 kg for an adult to be too low in an Irish context; hence a 70 kg BW was used. The 70 kg BW is consistent with EFSA Guidance (2019), which states that this amount is a more realistic estimate for the European adult population (aged above 18 years). The vitamins and minerals for which no UL has been recommended for Ireland are: beta-carotene, vitamin K, thiamin, riboflavin, vitamin B12, biotin, pantothenic acid, phosphorus, potassium, chromium and silicon. Several of these nutrients coincide with those nutrients in the FSE Group 1 risk category, which not only have no ULs but are also considered to show no evidence of risk to human health at levels currently consumed.

To date, the FSAI Guidance for Food Businesses (2020) provides maximum safe levels for seven nutrients in food supplements based on their public health importance. With respect to those nutrients for which FSAI has not yet set a MSL, the FSAI scientific report (FSAI, Revision 2, 2020) set out detailed risk assessments. However, a final list of MSLs has not yet been decided. The actual FSAI values for seven nutrients are shown in Table 9, along with the FSE MLS obtained by using the methodology described in this report. The nutrients are arranged according to the FSE categories of risk, and the FSAI and FSE risk management methodologies used are based on P95 and P97.5 intakes, respectively, as well as the TULs/ULs for each nutrient.

For most nutrients, there is an overall consistency between the maximum proposed levels from FSE 2014, FSE 2020 and FSAI (2020). Clearly, there are differences in values relating to changes in intake data. For example, for retinol, in the FSAI report the P95 intake used was for adults aged over 65 years rather than the adult age range 18–64 years as a precautionary measure to protect this higher age cohort on account of higher dietary intake. The folic acid value from the FSAI guidance takes into account the likelihood of future mandatory fortification.

Table 9 A comparison of daily maximum levels in food supplements for adults and children aged 4–10 years in the FSAI and FSE risk management reports.

	Adults		Children [a] aged 4–10 years	
Nutrient	FSE (2021)	FSAI (2020)	FSE (2021)	FSAI (2020)
GROUP 2: Low risk of exceeding UL				
Vitamin B6 (mg)	18	20	2.2	5
Vitamin C (mg)	1700	1800	350	500
Vitamin D (µg)	84.7	75	43.4	35
Magnesium (mg)	250	250	250	250
Folic acid (µg)	600	500	300	200
GROUP 3: Potential risk at excessive intakes				
Vitamin A (retinol) (µg)	1500	1700	1000	Teens, 11–17 years 1300 Children, 4–10 years 650
β-carotene, mg	8	8	8	8

a The selection of the age range 4–10 years by the FSAI is consistent with the FSE risk management model.

For overall changes in nutrient intakes over time, a good example is an analysis of the UK National Diet and Nutrition Survey (NDNS) Years 1 to 9 of the Rolling Programme (RP) 2008/2009–2016/2017, which was conducted on behalf of Public Health England and the Food Standards Agency (2019). This report demonstrated a downward trend in intake of most vitamins and minerals over a nine-year period for many age/sex groups. For vitamin A, a significant average yearly reduction in vitamin A intake was observed for all age/sex groups, with an increasing number of individuals having intakes below the Lower Reference Nutrient Intake (LRNI). As noted in Table 7, the highest intakes of preformed retinol from all sources in the Irish data are well below the UL. Current public health advice is for pregnant women and women trying to conceive to avoid supplements containing retinol, as too much can have harmful effects on the unborn baby. However, the overall development of the baby, and especially lung development and maturation, is dependent on a sufficient supply of vitamin A. The proposed maximum level for preformed retinol of 1500 µg/day is based on qualitative risk/benefit reassessment in the FSE 2021 report, and this amount would not be expected to result in any adverse effects.

5.2 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. The extrapolation of ULs for different life stage groups is described in Table 10.

ULs for different life stage groups are extrapolated on the basis of known differences in body size, physiology, metabolism, absorption and excretion of a nutrient. When data are not available for children and adolescents, extrapolations are made on the basis of bodyweight using the reference weights (EFSA, 2006; IOM, 1997).

Table 10 Extrapolation of ULs for different life stage groups and examples of scaling adjustments used by EFSA and IOM risk assessments to establish ULs for children

Examples of scaling adjustments		
Vitamin/mineral	Basis of scaling	
	Reference bodyweight	$BW^{0.75}$
Vitamin B6	EFSA	IOM
Vitamin E	IOM	EFSA
Folic acid	EFSA	IOM
Nicotinamide	EFSA	IOM
Vitamin A	IOM	EFSA
Iodine	IOM	EFSA
Zinc	IOM	EFSA

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 risk management report 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 are shown in Table 11. In addition, the IOM (1997) described early childhood as ages four through eight years, and determined that the adolescent age group should begin at nine years.

Table 11 Why select a children's age range 4–10 years?

- Reference bodyweights of population groups in Europe (SCF, 1993) refer to 1–3, 4–6, 7–10 and 11–14-year-old children.
- The intake of selected nutrients from foods from fortification and from supplements in various European countries refer to the age group 4–10 years.
- The UK National Diet and Nutrition Survey: Young People aged 4 to 18 Years (2000) also uses age groups 4–6, 7–10 and 11–14 years.
- The UK Dietary Reference Values (DRV) Committee on Medical Aspects (COMA) Report (1991) uses age ranges 4–6, 7–10, 11–14 years.
- EFSA Scientific Opinion on ULs for vitamin D (2012) notes age classifications for intake data are not uniform and selected ULs for 1–10-year olds as 50 µg/day and for 11–17-year olds and adults 100 µg/day, respectively.
- EFSA Scientific Opinion (2013) on DRV for manganese summarises Adequate Intakes (AIs) for age groups 4–6, 7–10, 11–14 years.
- IOM (1997) described early childhood as ages 4 through 8 years and determined that the adolescent age group should begin at 9 years.

The scientific data on nutrient requirements, absorption, metabolism and excretion of nutrients in children are extremely limited. Hence, both 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 [1], $BW^{0.75}$ (EFSA 2006; FAO/WHO 2006, EFSA 2019). The large differences in bodyweights between younger and older children shown in Table 12 can markedly influence the magnitude of the UL.

1 Metabolic body size in kg is the bodyweight to the three-fourths power, $BW^{0.75}$, representative of the active tissue mass or metabolic mass of an individual. Metabolic body size predicts energy requirements. Scaling adjustments in EFSA and IOM risk assessments use either reference bodyweights or $BW^{0.75}$ to establish ULs for children. Examples are shown in Table 10.

Table 12 Reference bodyweights of population groups in Europe (SCF, 1993) [2]

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

The PSI paradigm and calculations for maximum levels for vitamins and minerals in food supplements have been applied to the age group 4–10 years, and the results are shown in Table 13. The MHI intake data are derived from Table 10a in the FSAI Scientific Committee Report (Revision 2, 2020) and the P97.5 for boys (5–12 years) for food sources only. For the IW, the FSAI report provides no data and the amounts from trace elements are small or negligible. The ULs are derived from EFSA risk assessments (2017) using the tolerable upper intake for the age group 4–6 years and the IOM UL for children aged 4–8 years for the Group 2 nutrients vitamin C and phosphorus, and for the Group 3 nutrients calcium, iron and manganese. The PSI values based on nutrient intake data from the FSAI and the FSE 2014 reports show inevitable differences due to changing values for all levels of intake. However, the differences are small and the order of the PSI values results in the same categorisation of the nutrients as for adults and as in the FSE reports of 2014 and 2021. This outcome for the risk categorisation illustrates the robustness of the risk management approach and demonstrates how the PSI methodology can be applied over time and in different contexts. In fact, the PSI methodology for risk categorisation has been applied successfully in India and in the ASEAN countries. Table 9 shows the results for children aged 4–10 years as well as for adults in a comparison of quantitative and qualitative risk management approaches to establishing maximum amounts for seven nutrients based on the FSAI Guidance to Food Businesses 2020 and the FSE reports of 2014 and 2021.

2 A default value for the human bodyweight of 60 kg has been used for the work of WHO, EFSA and EVM, but a more realistic estimate of typical bodyweight for the EU population of 70 kg would support a more proportionate approach to risk assessment. On 23rd September 2019, the EFSA technical report, "Dietary Reference Values for Nutrients Summary Report" contained a table with reference bodyweights for children and adults that was used for scaling. For age groups 4–6 years, 7–10 years and ≥18 years, the reference weights for males were 19.2 kg, 29 kg and 68.1 kg, respectively. This EFSA report is an update of the original version published in 2017.

Table 13 Data used in calculations of Population Safety Indices (PSIs), FSE MLS and FSAI MSL for children aged 4–10 years

Nutrient	UL[a] (4–6 years) EFSA 2006	MHI[b] P97.5 Males (4–10 years)	MHI x 1.5 For vitamins x 1.1 for minerals	RI Regulation (EC) 1169/2011	Population Safety Index PSI		FSE MLS[c]		FSAI[d] MSL Calculated (actual) 2020
					2021	2014	2014 (calculated)	2021 proposed	
Group 2: Low risk of exceeding the UL									
Vitamin B6 (mg)	7 (40)[e]	3.7	5.55	1.4	2.36	2.72 (26.3)[e]	(2.23) 2.23 (35.2)[e]	(1.45) 2.23 (34.4)[e]	3.6 (5)
Vitamin C (mg)	650[e]	187	280.5	80	5.79	5.66	(353.7) 350	(369.5) 350	487 (500)
Vitamin D (μg)	50	4.4	6.6	5	9.12	8.99	(42.4) 42.4	(43.4) 42.4	46.3 (35)
Vitamin E (mg)	120	12.9	19.4	12	8.93	8.81	(98.6) 98.6	(100.6) 98.6	108.1
Niacin equivalent as nicotinamide (mg)	220	31.1	46.65	16	11.81	11.36	(162.7) 162.7	(173.4) 162.7	191.5
Molybdenum (μg)	600			50			50[c]	50[c]	ND
Phosphorus (mg)	3000[e]	1832	2015.2	700	1.67	2.15	(1356.6) 550[c]	(984.8) 550[c]	1395
Selenium (μg)	90			55			55[c]	55[c]	ND
Magnesium (mg)	250[f]	346		375			250[c]	250[c]	(250)
Folic acid (μg)	300	231	346.5	200	0.34		300[c]	300[c]	113 (200)
Potassium (mg)	1233[g]			2000			1200[c]	1200[c]	

Nutrient	UL[a] (4–6 years) EFSA 2006	MHI[b] P97.5 Males (4–10 years)	MHI x 1.5 For vitamins x 1.1 for minerals	RI Regulation (EC) 1169/2011	Population Safety Index PSI		FSE MLS[c]		FSAI[d] MSL Calculated (actual) 2020
					2021	2014	2014 (calculated)	2021 proposed	
Group 3: Potential risk at excessive intake									
Vitamin A (retinol, µg);	1100	652	978	800	0.4	0.5	1000[c]	1000[c]	561 (650)
Beta-carotene (mg)	8	8.4	6.8[h]				7[c]	8[c]	(8)
Calcium (mg)	2500[e]	1578	1735.8	800	1.03 1.78[f]	1.39	500[c]	500[c]	1012
Copper (mg)	2	1.74	1.91	1	0.26	0.66	1[c]	1[c]	0.54
Iodine (µg)	250			150	ND	–0.45	150[c]	150[c]	ND
Iron (mg)	40[e]	17.6	19.36	14	1.6	1.78	7[c]	14[c]	23.8
Manganese (mg)	3.0[e]			2			1.5[c]	1.5[c]	ND
Zinc (mg)	10	12.4	13.64	10	–0.24	0.02	5[c]	5[c]	–0.8

Blank cells or ND denote lack of available data.

a UL as established by SCF/EFSA for 4–6-year-olds where available, otherwise IOM.

b Intake data derived from Table 10a FSAI Scientific Committee Report Revision 2, 2020. P97.5 for boys (5–12 years), food sources only.

c MLS for children show calculated and proposed amounts for 2014 and 2021. For consistency, where the amounts are similar, the 2014 value is retained. For most nutrients, the MLS are based on qualitative risk analysis.

d The FSAI MSL maximum safe level for food supplements for children aged 4–10 years is calculated using the equation in the 2020 FSAI report, TUL – P95 for boys (nutrient intake data from Table 10a) = MSL.

c + d For several nutrients the use of the equations to calculate MLS and MSL results in very low and sometimes negative amounts, e.g. zinc. For iron, the risk assessments by Flynn er al. (2016), FSAI (2020) and FSE calculated MLS exceed the FSE 2014 proposed level of 7 mg. The qualitative risk assessment for the FSE MLS 2020 is raised from 7 mg to 14 mg. In this case, the qualitative risk assessment is used for the proposed maximum safe levels. The heterogeneity of the intake data for quantitative risk assessments are not feasible for determining both MLS and MSL for children. Alternative methods using scaling adjustments based on quantified reference bodyweights and/or based on surface area/metabolic bodyweight also illustrate the complexities of deriving maximum safe levels quantitatively. Pike and Zlotkin (2019) conclude that scientific nutritional risk assessments and appropriate quantitative and qualitative risk management approaches are the best ways of setting not only ULs but also maximum safe levels, MLS and MSL, for nutrients.

e Based on IOM UL.

f Supplemental sources of readily dissociable magnesium salts. MHI intake data refer to total magnesium intake from diet.

g Based on EVM GL for adults of 3700 mg.

h Refers to P95 intake for beta-carotene for boys from Table 10a, FSAI report (2020).

5.3 Scientific challenges to the setting of maximum levels of nutrients in food supplements

The difficulty of providing quantitative data on what individuals should eat and how much of each essential nutrient is required for health and wellbeing remains a scientific challenge, particularly in the light of updated research. The approach to providing guidance on the safe upper levels of vitamins and minerals is no less of a scientific challenge, and it is up to national and international scientific and regulatory bodies to evaluate the safety data. In most cases, scientifically based risk assessments and risk management approaches have resulted in a range of safe intakes between the recommended daily amounts (RDAs/ NRVs or RIs) and upper safe levels (ULs), giving consumers the ability to achieve levels within these ranges without concern over safety risks (see Figure 1, Appendix 2).

It is essential for risk managers to provide guidance on upper safe levels on a case-by-case basis that are scientifically plausible, reliable and nutrient specific. As previously noted, the principles and guidelines for nutritional risk analysis, the steps in scientific risk assessment, the explanation of the derivation of uncertainty factors and upper safe levels for Groups 2 and 3 nutrients are shown in Appendices 2, 4 and 5.

Pike and Zlotkin (2019) have discussed the application of risk assessment models and how different UL-setting organisations have applied various procedures. In addition to the UL documents published by EFSA, IOM, UK EVM and FAO, other international organisations include the Nutrient Reference Values for Australia and New Zealand (ANZ, 2006), the Nordic Nutrition Recommendations (NNR, 2012), the Dietary Reference Intakes for Japan (JAP, 2015), the Dietary Reference Intakes for Koreans (KDRI, 2015) and Dietary Recommended Intakes from the Chinese Nutrition Society (CHI, 2013). All these opinions and approaches to scientific risk analysis that have been published in recent years highlight issues relating to risk assessment methodologies, the establishment of ULs for adults and scaling for children, minimising risk of overconsumption of micronutrients and terminologies used in risk assessments, as well as risk-benefit analyses of micronutrients (Dufour *et al.* 2010; EFSA, 2010,2012a; Flynn *et al.* 2016; Hathcock and Kriengsinyos, 2011; Hathcock, 2014; National Research Council, 2009; Renwick *et al.* 2004, 2008; Rodrick and Levy, 2013; Verkaik-Kloosterman *et al.* 2012; Verkerk and Hickey, 2009).

Differences in all these risk assessments reflect the complexities of selecting critical endpoints to provide the highest degree of public health protection, the identification, for any given nutrient, of a LOAEL or a NOAEL and the magnitude of the UFs applied. This heterogenicity is compounded by differences among organisations on their choices of age category groupings when setting ULs throughout the lifespan. The paper by Pike and Zlotkin (2019) highlights the merits and drawbacks of the risk assessment methodology, the increasing severity of adverse effects for critical endpoint selection and the use of population reference weights for extrapolation of ULs. Nevertheless, there is a general consensus that scientific nutritional risk assessments and appropriate quantitative and qualitative risk management models are the best approaches for setting ULs and safe maximum levels of nutrients, respectively.

In conclusion, nutritional risk analysis draws upon quantitative and qualitative risk-based information, with a view to assessing the probability of an adverse health effect associated with an excessive intake (and inadequate intake) of a nutrient together with the severity of that effect and the potential to cause an adverse effect. An initial step in nutritional risk analysis is also to ensure a common understanding of the nutritional issues between the risk assessors and risk managers, especially with regard to the setting of maximum levels of nutrients in both fortified foods and food supplements.

6. Quantities of essential nutrients in the diet from fortified foods and food supplements

Current practice in Europe indicates that levels of nutrients in fortified foods and food supplements can safely coexist (see Table 7). An understanding of current practice and the regulatory criteria for setting maximum nutrient levels in food supplements and fortified foods, shown in Table 4 of this report, will contribute to the setting of harmonised maximum levels in food supplements in the European Union. Typically, the amounts of individual nutrients in fortified foods are based on the nutrition claims criteria for "source" and "high" 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/RI) 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/RI 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". These nutrient content claims also serve as quantitative criteria for the use of nutrient function health claims on foods and food supplements in the EU (European Parliament and of the Council (2006b, Regulation (EC) No 1924/2006; Commission Regulation EU No 432/2012). For the most common forticants that are in Groups 1 and 2 of the FSE risk management model (e.g. vitamin C, vitamin B1 (thiamin), vitamin B2 (riboflavin), nicotinamide, folic acid, vitamin B6, vitamin B12, biotin, pantothenic acid, vitamins D and E), the margins of safety and precautionary factors for future fortification above current levels have already been taken into account. These precautionary factors in the risk management model result in amounts for each nutrient that 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). The addition of nutrients such as iron, calcium and magnesium at high levels in foods often presents technological problems (Berry Ottaway, 1993; Richardson, 1993, 1997) with colour, texture and taste as well as having implications for the shelf-life of products and compliance. The risks of excessive intakes of vitamins and minerals from foods is small bearing in mind the constraints related to energy density and satiation aspects of the food or meal.

Overall, about 75% of the foods and drinks consumed in European diets are rarely or never fortified. In 2004, Godfrey *et al*. found that fortified foods were rarely found 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. These authors estimated that high-level consumers of fortified foods were unlikely to obtain more than 10% of their diet in fortified form. In 2013, Hennessy *et al*. 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) across Europe do not exceed the UL set by EFSA. Hennessy *et al*. concluded that there is little risk of adverse effects occurring in the small proportion of individuals exceeding the UL by a modest amount, given the use of adequate safety factors (uncertainty factors, UFs) in establishing ULs in scientific risk assessments.

In addition, the precautionary factors used in the Food Supplements Europe risk management model, the amounts in food supplements and the diet as a whole would not be expected to result in any adverse health effects. In Germany, fortified foods make up only a small proportion of prepacked food (around 4.4%), and the market for fortified foodstuffs as a whole has not recorded any growth in volume over the period 2011–2016. The market share of vitamin-fortified packaged foods was likewise at a constant low level of around 2.5% in 2016, with a slight downward trend. The share of the overall vitamin and mineral intake accounted for by fortified foods tends to be overestimated, especially as a large part of both unpackaged and unprocessed foods is not accessible to additions of nutrients in any way (BfR, 2004a,b, Heinemann *et al*. 2015; Weißenborn *et al*. 2018).

The use of actual market information and real consumption patterns on individual nutrient intakes from fortified foods and food supplements has major implications for the development of scientifically based risk management models.

For example, the use of arbitrary precautionary factors and a generalised, artificial split between amounts of nutrients from fortified foods and food supplements, as well as the application of safety factors for possible multiple use of food supplements are not consistent with the case-by-case methodologies advocated by international principles and guidelines on nutritional risk analysis.

7. Inappropriateness of RDA-based maximum levels for vitamins and minerals in food supplements

Some countries have proposed that the maximum amounts in fortified foods and in food supplements should be based on, or limited to fractions or multiples of the RDA (NRV/RI). However, the FAO/WHO 2006 model for establishing upper safe levels of intake for nutrients and the Codex Alimentarius Commission Principles and Guidelines for Nutritional Risk Analysis, as well as European legislation and subsequent case law, require the establishment of maximum levels based on scientific risk assessment. It should be emphasised that the RDAs/NRVs/RIs and ULs are determined by two completely different scientific conceptual approaches. However, as demonstrated in the FSE risk management model, the two values can be used 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 the UL see Figure 1, Appendix 2).

As previously stated, arbitrary multiples of RDA to set maximum levels of vitamins and minerals in food supplements and fortified foods have no scientific validity. In Europe, the use of nutritional need and an RDA-based approach to setting maximum levels has been rejected by the European Commission and by the Court of Justice of the EU (Judgements of 5 February 2004, Greenham and Abel, C-95/01, EU:C:2004:71, paragraph 46; of 2 December 2004, Commission v Netherlands, C-41/02, EU:C:2004:762, paragraph 69, and of 29 April 2010, Solgar Vitamin's France and Others, C-446/08, EU:C:2010:233, paragraph 60 of 29th April 2004).

In a more recent opinion, the Advocate General (15th December 2016) included a detailed account of the court's judgement of European Commission vs Germany (Judgment of 29 April 2004, C-387/99, EU:C:2004:235). In that judgement, the Commission contested a German rule that automatically classified products that contained three times the recommended daily dose of vitamins as medicinal products. The court condemned what it referred to as the "triple amount rule" because it was not preceded by an evaluation of each vitamin or group of vitamins. In other words, a scientific risk assessment had not been conducted. The reasoning was upheld in the judgement itself (Noria Distribution SARL, Judgement of 27 April 2017, C-672-15, EU:C:2017:310)

This judgement supports the absolute requirement for risk assessments always to be based on science. Case law refers to a "comprehensive assessment of the risk to health based on the most reliable scientific data available and the most recent results of international research". The scientific risk assessments must be undertaken in an independent, objective and transparent manner. Interestingly, the sources of data can be national or international, and the totality of the evidence should be taken into account, even if the scientific evidence is contradictory. The Judgement makes the point that, in practical terms, it is difficult to conceive that, in a highly specialised field of research such as is the impact on human health of vitamins and minerals, all the most up to date and relevant research would be contained within a single Member State. These data could, therefore, be described as "national opinion". The judgement points out that the EU law does not require Member States to align their conclusions and restrictions with those of the most "permissive" Member State. Any restrictions must be justified on the basis of solid science demonstrating real risk or at least the inability to exclude risk, which results from lack of science. This approach stands in contrast to any restrictions based on outdated or partial assessments, or to hypothetical risks.

8. Discussion and conclusions

Today, the process of deriving NRVs, including ULs, and risk management approaches to setting maximum levels of vitamins and minerals in food supplements and fortified foods is becoming more rigorous and transparent. The use of systematic scientific reviews, updated food and nutrient intake databases, and better knowledge about metabolic markers of nutritional status, homeostatic mechanisms and the role of the essential nutrients in health and wellbeing have all contributed to better methodological approaches to nutritional risk analysis.

Recent insights into population micronutrient intakes, such as those from the Food Safety Authority of Ireland (FSAI, 2020) have provided the opportunity to evaluate intakes of vitamins and minerals that are too low or too high, and to determine whether there are potential problems of inadequate or excessive intakes. The need for regulation of specific nutrients depends on the severity of the adverse effects and on the estimates of the prevalence of too low or too high population intakes. Too low population intakes are evaluated against an Estimated Average Requirement (EAR) or more commonly, the Recommended Daily Allowance (RDA) or Reference Intake (RI). Too high population intakes are evaluated against a UL. For the purposes of nutritional risk management, the convenient set points to determine the safe range of intake for each nutrient are for the upper end, the UL, and for the lower end, the labelling RI. The use of these set points are also consistent with the key European legislative criteria set down for establishing maximum amounts of vitamins and minerals in food supplements and fortified foods.

It should be emphasised that the RDAs and ULs are determined by two completely different scientific conceptual approaches, and that the two values are 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 the UL. The PSI calculation in the FSE risk management model, shown in Section 3, describes a process by which nutrients can be allocated into three categories of risk according to the margin between the UL and the RI. The availability of good quality nutrient intake data from FSAI (FSAI, 2020) has enabled a review of the PSI calculations, the risk categorisation and the proposed maximum levels for the vitamins and minerals from both the ERNA 2004 and the FSE 2014 risk management reports. Based on both the updated quantitative and qualitative risk analysis, both the risk categorisations and the proposed maximum levels in Groups 2 and 3 remain essentially unchanged, with the exceptions of preformed retinol and beta-carotene for adults and iron for children aged 4–10 years. The FSE risk management model is therefore considered sufficiently robust, and it provides a transparent, scientifically based methodology for nutritional risk analysis. The quantitative and qualitative approaches are used in the FSE model to propose maximum levels for each nutrient for adults and children aged 4–10 years that would not be expected to result in adverse effects.

Key to the harmonisation of nutritional risk analysis for setting maximum amounts of vitamins and minerals in food supplements and fortified foods is the willingness of the international authorities to support agreed-upon approaches to the derivation process. There is considerable variation in scientific assessments of the safety of the nutrients, as shown in Appendix 1. The ULs/SULs and GLs set tend to be conservative as a consequence of the limited data, the use of different uncertainty factors and the application of the precautionary principle. The setting up of a new EC Expert Working Group and the forthcoming EFSA updates of the scientific risk assessments provide the opportunity to move forward with harmonised methodologies and principles for deriving maximum levels. The provision of a common basis and improvements in objectivity and transparency of the processes used to establish maximum levels in food supplements and fortified foods are vital to harmonise maximum levels for vitamins and minerals across diverse population groups and Member States. Policy coherence and coordination, as well as harmonisation of the principles and guidelines will help achieve the goal of consistency in setting maximum levels, but it does not obviate the need for individual countries or regions to establish amounts based on specific population needs. As FSAI has demonstrated in 2020, having a scientific and harmonised core to setting maximum levels provides a good starting point to facilitate discussion in Europe. There is also a case for standardising terminology to describe maximum levels in the harmonisation process.

The risk management approaches described in this report attempt to address the many difficulties and complexities surrounding the setting of maximum levels. Risk management involves the evaluation of the magnitude of a possible risk, and caution is needed not only in allowing particular levels of vitamins and minerals in food supplements and fortified foods for adults and children, but also in not being overly restrictive in their use. The overall purpose of this updated FSE report is to contribute towards the development of a scientifically based risk management approach to the setting of maximum levels in the EU. Consultation, dialogue and sharing expertise between the interested parties are critical to ensuring that proportionate measures are used to protect consumers and to facilitate informed choice.

Scientists and regulators are encouraged to review the totality of the scientific data and weight of evidence, including scientific publications from industry national and international organisations when undertaking nutritional risk analysis. In addition, whilst there are considerable market data available, more in-depth understanding of consumer use and attitudes towards food supplements is required, including the identification of any emerging risks and also for use in the provision of information for future communications to consumers.

Appendices

Appendix 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 (RE)	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 (B1)	mg	Not set	Not set	100 (G)
Riboflavin (B2)	mg	Not set	Not set	40 (G) (43 T)
Nicotinamide Nicotinic acid	mg mg	900 10	35 [d] –	500 (G) (560 T) 17
Pantothenic acid	mg	Not set	Not set	200 (G) (210 T)
Pyridoxine (B6)	mg	25	100	200 (short term) [e] 10 (long term)
Folic acid	µg	1000 (+dietary folate)	1000 supp. (+200 diet)	1000 (G) (1500 T)
Vitamin B12	µg	Not set	Not set	2000 (G)
Biotin	µg	Not set	Not set	900 (G) S (970 T)
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 (10 T)
Iodine	µg	600	1100	500 (G) (940 T)
Zinc	mg	25	40	25 (42 T)

Nutrient	Unit	SCF/EFSA total intake (UL)	IOM total intake (UL)	EVM for long-term supplementation (SUL) [a]
Manganese	mg	Not set	11	4 (G) (9-12 T) 0.5 (G) for older people
Potassium	mg	Not set	Not set	3700 (G)
Selenium	µg	300	400	350 (450 T)
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) (2400 T)

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.

Appendix 2

Principles and steps used in scientific nutritional risk assessment

The principles for scientific risk assessment are shown in Table A.

Table A Principles for scientific risk assessment

Problem formulation	
STEP 1	**Nutrient Hazard Identification** Review literature to identify potential health problems (e.g. deficiency and excess endpoints).
STEP 2	**Nutrient Hazard Characterisation / Quantitative Evaluation of Critical Effects** Identify, where possible, level at which a nutrient causes adverse effects (e.g. dose response, clinical, epidemiological, metabolic data, case reports). Set acceptable range of oral intake (AROI) or tolerable upper intake level (UL) or safe upper limit (SUL).
STEP 3	**Dietary Intake Assessment** Evaluation of the average intake of various population groups from food, water, supplements. Assess variability of the magnitude of intake using intake percentiles.
STEP 4	**Nutrient Risk Characterisation** Integrate intake information and AROI, UL, SUL data. Evaluate strength and weakness of each step and identify group of greatest concern.

Steps 1 & 2

In Steps 1 and 2, **Nutrient-related Hazard Identification and Hazard Characterisation**, the process begins with the identification of adverse health effects associated with the nutrient substance and makes use of human, animal and in vitro data. Each data source has both advantages and disadvantages. For example, animal data have the advantage of quite extensive and robust datasets and the disadvantage of requiring very uncertain and problematic extrapolation for application to humans. On the other hand, human data are often quite sparse for many nutrients, but they do have the advantage that little or no extrapolation is needed for decisions that are relevant for humans.

A pivotal point in the risk assessment is the identification of the critical adverse health effect upon which the UL is based. The process involves the identification of a No Observed Adverse Effect Level (NOAEL) from human data if possible. If the data cannot support a NOAEL, a Lowest Observed Adverse Effect Level (LOAEL) may be established. Animal data are used only if appropriate human data are not available and also as a guide to search for a hazard that may be identified in human data. The uncertainties in the data are assessed and Uncertainty Factors (UFs) are applied to the identified toxicological thresholds, e.g. NOAEL or LOAEL. The numerical UF accounts for the scientific uncertainties, including inadequacies in the database, interspecies extrapolation, variability and differences in susceptibility of individuals, the nature and severity of the adverse effect and whether there are short-term or long-term effects [3]. Scientific judgement is used in the choice of the UFs, and the UL is derived by dividing the NOAEL or LOAEL by the total product of the UFs. The selection of the UFs is critical when considering the potential effects for nutritional deficiency and excess. These quantitative evaluations of critical effects in the hazard identification and characterisation steps include the key activities shown in Table B.

Table B Key activities in hazard identification and characterisation (FAO/WHO 2006)

- Define data search strategy a priori.
- Identify adverse health effects and related levels of intake.
- Rate and summarise data objectively.
- Determine basis for selection of the critical adverse health effect.
- Clarify intake-response relationship to identify NOAEL or LOAEL.
- Adjust the NOAEL or LOAEL for uncertainty and establish UL.
- As necessary, adjust UL derived for a studied subpopulation to derive ULs for unstudied age/sex/life stage subpopulations.
- Identify vulnerable subgroups
- Characterise the risk overall.

3 Although the factors affecting the selection of UFs are widely accepted, there are no defined criteria for deriving the values themselves. UFs typically range from 1 (signifying great confidence in the NOAEL) to 10 (indicating significant uncertainty or limitations in the data), but they can be as high as 300 when animal data are used (IOM (2000), Pike and Zlotkin (2019)). If the UF is set too high, the resultant UL may be too low, and further extrapolation may suggest erroneously risk at a higher intake, e.g. UL for zinc for young children (Pike and Zlotkin (2019) and Garcia-Casal (2019)

Nutrient-related intake assessment

Step 3

In Step 3, the nutritional 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 intake 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 major challenges. In situations where intake data are limited, mathematical modelling approaches can be used to handle uncertainties in the intake estimates and the potential impact of these uncertainties on risk characterisation.

Scientific committees draw on a wide array of available consumption data, including habitual or average intake of various population groups from conventional food, water, fortified food and food supplements. The variability of the magnitude of intakes can be assessed using intake percentiles, e.g. P5, P50, P95 and P97.5, to represent the spectrum of intakes from deficient up to high intake levels. Consumption data are derived 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). The best intake data is based on the use of four or seven-day weighed dietary records as the sources of the best available data. The objective in the dietary intake assessment is to provide clear, transparent and detailed documentation of the approaches used.

Step 4

In Step 4, **Nutrient-Related Risk Characterisation**, the nutrient intake data assessment and information on the ULs and Acceptable Range of safe intake are fully integrated and applied within the context of the total diet. Wherever feasible, it involves the evaluation of the distribution of habitual total daily intake for the target population(s). The approach recognises that nutrient-related risks are often associated with total intakes from multiple dietary sources including, for example, such conventional foods as dairy products as a major source of calcium, liver as rich sources of vitamin A etc, fortified foods, food supplements and, in the case of certain minerals, water. The nutrient risk characterisation may also take into account the bioavailability and stability of nutrients and related substances in the foods consumed.

The nutrient risk characterisation uses quantitative and qualitative scientific assessment and identifies the proportion of the (sub) population likely to exceed the upper level. It highlights important considerations, including the severity and nature of the adverse effect, a description of the uncertainties, and the identification of any special subpopulation at risk (FAO/WHO 2006; Codex Alimentarius 2010).

Figure 1 illustrates an intake response curve for essential nutrients and Figure 2 summarises the steps in quantifying an upper safe level.

Figure 1. Intake response curve for essential nutrients

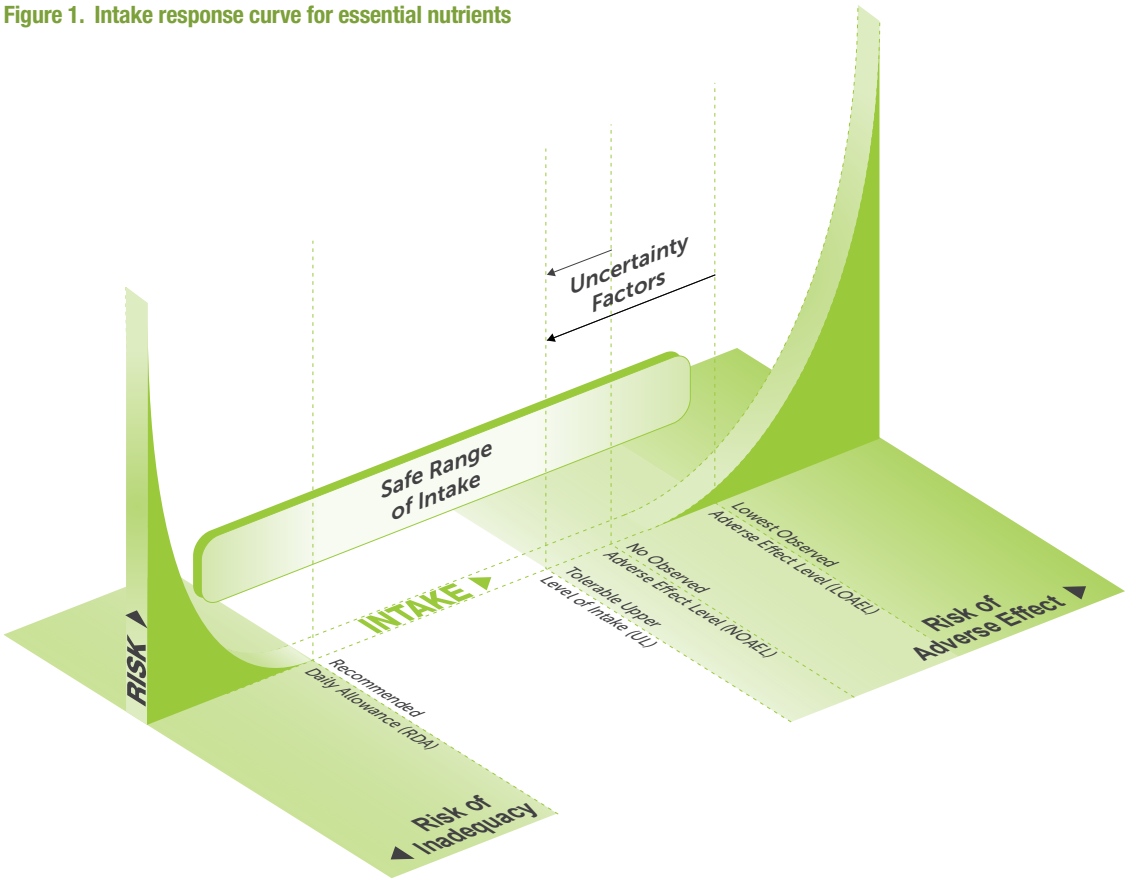
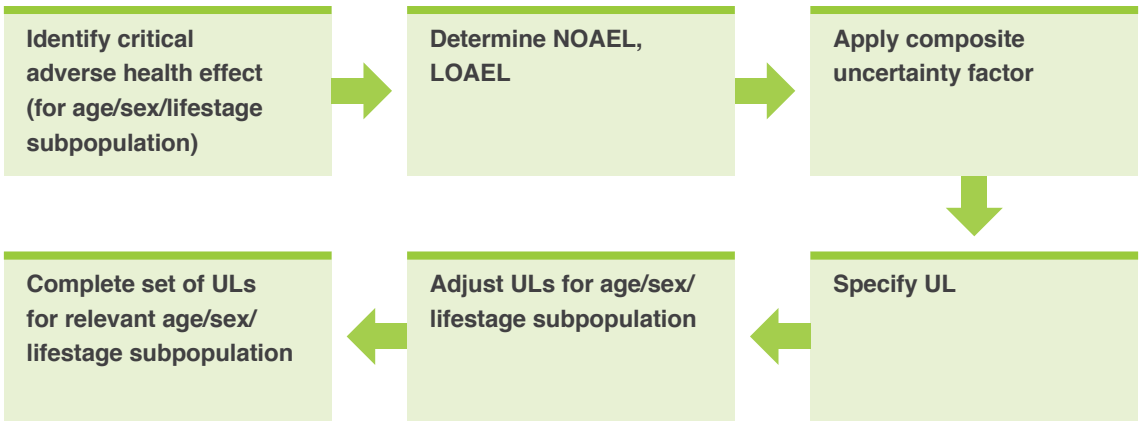


Figure 2. Steps in quantifying an upper safe level



WHO/FAO 2006

Appendix 3

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 EVM and upper safe levels for supplements from Hathcock (2014)

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. • Because of the lack of evidence of adverse effects of high intakes of this vitamin, the FSAI (2020) decided not to recommend a UL.
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. • Typical levels of chromium in food supplements range from 125 to 250 µg per day. In the FSAI 2020 report, a WHO guidance level of 250 µg per day is considered most appropriate for Ireland.

Nutrient	Qualitative risk characterisation
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. • IOM also stated that there is no evidence of adverse effects at high levels of pantothenic acid because the intestinal absorption of panthothenic acid takes place by saturable active transport, and at high levels of intake, a smaller proportion of intake is absorbed. • 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 (2014) noted the EVM provided evidence that supplemental intakes of 2000 mg did not produce adverse effects, 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. • Because neither EFSA nor IOM established a UL for pantothenic acid because of lack of evidence of adverse effects at high levels of intake, FSAI (2020) recommended that Ireland did not adopt a UL for this nutrient.
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. • Neither EFSA nor IOM established a UL for riboflavin due to lack of scientific evidence of adverse effects even with high doses of the vitamin. Hence, FSAI (2020) decided not to adopt a UL for riboflavin for Ireland.

Nutrient	Qualitative risk characterisation
Thiamin	• Systematic data on adverse effects with oral intake of vitamin B1 in humans are very limited. However, from the available literature it can be concluded that orally ingested vitamin B1 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 B1 as a nutrient with no adverse effects. • The SCF (2001) concluded that it is not possible to derive a numerical UL for vitamin B1. However, existing evidence from clinical studies as well as the long history of therapeutic use, at levels up to 200 mg/day for months, indicates that current levels of intake from vitamin B1 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. • In 2020, FSAI concluded that there has been no reported evidence of adverse effects even with high oral doses of thiamin. Ireland decided not to adopt a UL for this vitamin.
Vitamin B12	• There are no adverse effects known for vitamin B12 from foods or from food supplements. There are no clearly defined adverse effects produced by vitamin B12 that can be used to define a LOAEL or NOAEL, which can be used as a basis for deriving a UL. The SCF (2000) concluded that there is no evidence that the current levels of intake from food and food supplements represent a health risk. Adverse effects have not been reported in the treatment of patients with compromised B12 absorption who received amounts up to 1000 µg/day orally for prolonged periods. • The EVM found no evidence of adverse effects of vitamin B12 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 B12 dosages of up to 1000 µg in pernicious anaemia patients, and considerable clinical experience and evidence of safe oral intakes of 3000 µg/day. • Neither EFSA nor IOM established a UL for vitamin B12 due to lack of adverse effects even at high doses. Hence, FSAI (2020) decided not to adopt a UL for vitamin B12 for Ireland.

Nutrient	Qualitative risk characterisation
Vitamin K	• Vitamin K1 (phylloquinone), which is the form occurring naturally in food, is not associated with adverse effects in animal and human studies. A quantitative risk assessment cannot be carried out and a UL cannot be derived. 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, based on the same clinical data as the EVM (Cracium *et al.* 1998). • FSAI (2020) noted that data on adverse effects from high vitamin K intakes are not sufficient for a quantitative risk assessment, and, as neither IOM nor EFSA had established a UL, it recommended that Ireland did not adopt a UL for this vitamin.

Appendix 4

Risk management of GROUP 2 nutrients

Nutrient	Qualitative risk characterisation
Vitamin B6	• 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 B6 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 B6 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. • Using P95 intake data, FSAI (2020) established MSLs for adults and children aged 4–10 years of 20 mg and 5 mg, respectively, as shown in Table 9. The FSAI calculated amounts are 20.1 mg for adults, as shown in Table 5, and 3.6 mg for children aged 4–7 years, as shown in Table 13. Similarly, the FSE MLS calculated and proposed amounts for adults are 15.1 mg and 18 mg, respectively. For children aged 4–10 years, the FSE calculated and proposed amounts are 1.45 mg and 2.23 mg, respectively, as shown in Table 13. • The calculated MLS using the risk management model (Food Supplements Europe, 2014; Richardson, 2015) 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 for 2014 and 2021 are shown in Table 8 with the IOM values referred to in footnote b. • The EFSA UL for vitamin B6 of 25 mg was considered more appropriate for Ireland than the higher UL set by IOM of 100 mg/day (FSAI 2020). However, because of the large differences in scientific opinions on the derivation of the ULs for vitamin B6, a thorough reassessment of its safety and the determination of the validity and use of different levels of this nutrient in different circumstances is required.

Nutrient	Qualitative risk characterisation
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. FSAI (2020) recommended that Ireland adopts critical endpoints of osmotic diarrhoea and gastrointestinal disturbances. • 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 information in Section 5.2 and Table 13 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. The calculated and proposed MLS for adults for 2021 is 1700 mg/day rounded from the 2014 mean of 1686.5 mg/day for males and 1719.5 for females.

Nutrient	Qualitative risk characterisation
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 D3 (cholecalciferol). Some higher fungi such as mushrooms are a natural source of vitamin D2 (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 increases 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.

Nutrient	Qualitative risk characterisation
Vitamin D continued	• 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 P95 intake data, Flynn *et al.* (2016) estimated safe maximum levels for vitamin D with and without overages of 25% in fortified foods and food supplements for vitamin D for adults aged 18–64 years and for children aged 7–10 years. The amounts including the overages were 92.0 µg for adults and 46.1 µg for children aged 7–10 years. • The FSAI 2020 report states that the ULs are much higher than the habitual intakes of vitamin D for adults and children in Ireland when the contributions from the base diet, fortified foods and food supplements are considered. Based on the EFSA adult UL of 100 µg/day minus the 95th percentile of dietary intake of 7.9 µg = 92 µg, and taking into account the likelihood of increased future fortification, a risk management assessment resulted in an MSL of 75 mg for adults. For children, based on the EFSA UL for 4–6 year-olds of 50 µg minus the 95th percentile dietary intake of 5–12 year-olds of 7 µg, the calculated amount is 43 µg/day. The FSAI risk management assessment took into account the likelihood of increased future fortification, and this resulted in an MSL of 35 µg/day for children aged 4–10 years. • On 31st July 2020, the German Bundesinstitut für Rizikobewertung (BfR) published an opinion entitled “Vitamin D: consumption of high-dose food supplements is unnecessary”. The opinion highlighted concerns about food supplements containing 100 µg and 50 µg/day of cholecalciferol. BfR pointed out that the amount of 100 µg/day is the same as the ULs established by EFSA and IOM, and that the UL is not a figure for recommended consumption but corresponds to the chronic intake quantity for a nutrient from all sources that does not lead to impairments to human health. The BfR opinion states that even without exposure to sunlight, a daily consumption of 20 µg of vitamin D is adequate to meet the body’s needs for this vitamin for the vast majority (97.5%) of the population. On the other hand, BfR considered it unlikely that impairments to health would result from the occasional consumption of higher-dose preparations, and that long-term (chronic) use of products could lead to a long-term intake of vitamin D above the UL. In the context of an expanding market for foodstuffs enriched with vitamin D, BfR is concerned that there is a potential risk to health by a chronically elevated intake of vitamin D.

Nutrient	Qualitative risk characterisation
Vitamin D continued	• In December 2017, the Dutch authorities notified the European Commission and EU Member States of their intention to change the Commodities Act Order on food supplements. For vitamin D, the draft order states in Article 4.3, "Food supplements shall contain an upper daily intake of 75 µg vitamin D, as per instructions". The same amount was included in the Belgium Royal Decree on maximum levels in food supplements published in the Belgium Official Journal on 31st October 2017. • In the UK, the food supplements trade associations set out a rationale for a maximum safe level of 75 µg/day. This amount took into account: – The EFSA end IOM ULs of 100 µg vitamin D – Low intakes of vitamin D from food sources – Intakes from food including fortified food as well as future increases resulting from increases in fortification practices, changing food habits and food choices – The establishment of 75 µg/day by FSAI • 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 for 2014 and 2021 are 83.2 µg/day and 42.4 µg/day, respectively.

Nutrient	Qualitative risk characterisation
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 (bodyweight $^{0.75}$). 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. • The EFSA UL of 300 mg/day from all sources is based on human studies, whereas the IOM UL of 1000 mg/day is based on studies of haemorrhagic toxicity in rats. Using P95 intake data, Flynn *et al.* (2016) estimated safe maximum levels with and without overages of 25% in fortified foods and food supplements for vitamin E for adults aged 18–64 years and for children aged 7–10 years. The amounts including the overages were 282.5 mg for adults and 150 mg for children aged 7–10 years. • FSAI (2020) concluded that the EFSA ULs for vitamin E are most appropriate for Ireland. • Based on EFSA ULs, the calculated and proposed MLS for adults and children are shown in Tables 5 and 13 and are 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.

Nutrient	Qualitative risk characterisation
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. FSAI (2020) stated that nicotinic acid and nicotinamide should be assessed separately, and that the use of the generic term “niacin” is not correct when considering flushing. • 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 and proposed MLS for nicotinamide in food supplements are 820 mg/day and 162.7 mg/day for adults and children, respectively. These values are shown in Tables 5 and 13.

Nutrient	Qualitative risk characterisation
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. • The EFSA UL of 600 µg/day was considered most appropriate for Ireland (FSAI 2020). However, both FSAI and EFSA agreed that a bodyweight of 70 kg rather than a reference bodyweight of 60 kg would be more representative of the adult population of Ireland. Hence, for Ireland, the Tolerable Upper Intake level for adults (>17 years) is 700 µg/day and for children aged 4–6 years and 7–10 years, 200 µg/day and 250 µg/day, respectively. • 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 based on qualitative analyses are 350 µg/day and 50 µg/day for adults and children, respectively, as shown in Tables 5 and 13. • Both EFSA and IOM ULs are based on reproduction and development in rats and mice as the critical endpoints, and the same NOAEL. However, FSAI (2020) noted that different UFs were applied, resulting in a three-fold differences in their ULs. • 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.

Nutrient	Qualitative risk characterisation
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). • FSAI (2020) did not recommend that Ireland adopt a UL for phosphorus, and that emerging evidence should be reviewed regularly in order to ensure consumers in Ireland are not at risk of overexposure. • The proposed MLS of 1250 mg/day shown in Tables 5 and 8 for adults is based on the IOM UL. 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, as shown in Table 13.. Values for MLS are based on qualitative risk analyses.

Nutrient	Qualitative risk characterisation
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). • FSAI (2020) recommended that Ireland adopts the EFSA ULs for adults and children and the IOM UL for infants <1 year of age. • Bearing in mind the risks of deficiencies and excess for adults and children, the MLS of 200 µg/day and 55 µg/day, respectively, based on qualitative analyses, 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 based on qualitative analyses. • FSAI (2020) considered the EFSA UL of 250 mg/day for easily dissociable magnesium salts for persons over the age of four years, noting that, other than in individuals with impaired renal function, diarrhoea is completely reversible within one or two days, and magnesium salts do not represent a significant health risk.

Nutrient	Qualitative risk characterisation
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 2004b). • 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 B12-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 B12 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 B12 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 appropriate or relevant for setting ULs for children and adolescents (Flynn *et al*. 2016, Pike and Zlotkin 2019). 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 B12 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 B12 deficiency and does not interfere with the timely diagnosis of vitamin B12 deficiency. Details of the metabolism of L-methylfolate and folic acid in vitamin B12 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).

Nutrient	Qualitative risk characterisation
Folic acid/ folate continued	• The safety of long-term intake of folic acid above the EFSA, IOM and EVM of 1000 µg/ day has been questioned by Reynolds (2016). He postulated that excess folic acid may increase demand for vitamin B12, thereby causing relapse of neurological and/ or haematological symptoms. Reynolds called for a downward revision of the UL. However, Wald *et al*. (2018) examined all the original IOM data on levels of folic acid and prevalence of neuropathy and found no evidence of neuropathy. They concluded that it was time to abandon the tolerable upper intake of 1000 µg/day. This scientific debate continues with a review of clinical studies on folic acid adverse effects in subjects with low vitamin B12 status. Although the delay in the diagnosis of neuropathy by the masking of macrocytic megaloblastic anaemia in subjects with undiagnosed vitamin B12 deficiency is still assumed to be a risk factor of a high folic acid intake, Van Gool *et al*. (2020) concluded that proof of increased cognitive impairment is untenable, and their review fully supports the safety of 1000 µg/day as the upper level for folic acid. • 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. • FSAI (2020) stated that the UL applies only to folic acid and not to naturally occurring food folates. The report addresses concerns about chronic exposures associated with consumption of excess folic acid from fortified foods or food supplements, or a combination of both. The FSAI report (2016), "Folic acid fortification for the prevention of birth defects" reviewed the evidence for adverse effects. This report concluded that the available evidence shows that programmes of mandatory fortification of foods with folic acid at levels sufficient to provide significant protection to women of childbearing age against NTD-affected pregnancies do not increase the risk of adverse health effects in the population.

Nutrient	Qualitative risk characterisation
Folic acid/ folate continued	• The mandatory fortification of bread and flour continues to raise many scientific, technical, legal and consumer behaviour questions. Richardson (2015) reviewed the need to establish the right public health strategies for folic acid and reduction of risk on NTDs in the UK. These strategies include dietary interventions with folic acid combined with vitamin B12 within the context of a nutritional impact on all segments of the population, as well as targeted use of mandatory fortification of certain foods and folic acid food supplements or a combination of both. • 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. Food Supplements are also specifically formulated for pregnant women. • 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 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 (Flynn *et al*. 2009). • Most food supplements available in Europe contain 400 to 500 µg folic acid (pteroylmonoglutamic acid). • Using P95 intake data, Flynn *et al*. (2016) estimated safe maximum levels for folic acid with and without overages of 25% in fortified foods and food supplements. The amounts for adults aged 18–64 years and for children aged 7–10 years were 698 µg and 205 µg, respectively.. • The FSAI (2020) calculated and actual MSL amounts for adults are 771 µg and 500 µg, respectively, as shown in Table 5. For children aged 4–10 years, the calculated and actual MSL are 113 µg and 200 µg. respectively, as shown in Table 13. • The FSE calculated and proposed amounts for adults are 535 µg and 600 µg, respectively, as shown in Table 5. The proposed amount for children aged 4–10 years is 300 µg, as shown in Table 13.. Both these amounts are based on qualitative risk analyses. • These amounts would not be expected to result in any adverse effects, based on the UL for folic acid of 1000 µg/day.

Nutrient	Qualitative risk characterisation
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 a 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.

Nutrient	Qualitative risk characterisation
Potassium continued	• 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. • Because neither EFSA nor IOM have established a UL for potassium, FSAI (2020) recommended that Ireland does not adopt a UL, and that emerging evidence should be reviewed regularly to ensure that consumers in Ireland are not at risk of overexposure. • The proposed MLS for adults of 1500 mg/day and for children of 1200 mg/day, based on qualitative risk analyses, 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 5

Risk management of GROUP 3 nutrients

Nutrient	Qualitative risk characterisation
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 P95 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). 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.

Nutrient	Qualitative risk characterisation
Preformed retinol continued	• 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. Clearly, a critical endpoint of teratogenicity specifically for pregnant women would not be appropriate for other life stages (Pyke and Zlotkin (2019). • 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. FSAI (2020) noted that liver is a particularly rich source of preformed vitamin A, and that mostly, liver and liver products are solely responsible for high intake levels. However, there has been a substantial decrease in liver consumption over the last two decades, and this downward trend is continuing for both males and females. 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.

Nutrient	Qualitative risk characterisation
Preformed retinol continued	• 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 and 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. • Using P95 intake data, Flynn *et al.* (2016) estimated safe maximum levels with and without overages of 25% in fortified foods and food supplements for retinol for adults aged 18–64 years and for children aged 7–10 years. The amounts including the overages were 2123 µg for adults and 980 µg for children aged 7–10 years. • In 2020 FSAI stated that the derivation of ULs for vitamin A is difficult, given the low safety margin (the margin between recommended intake and the intake that causes harm). The EFSA ULs are considered to be most appropriate for Ireland for adults and children from age groups 1–3 years to 14–18 years. FSAI decided on a maximum level permitted in a food supplement for adults (over 18 years of age) as 1700 µg/day. This amount was based on the EFSA UL for adults of 3000 µg/day minus the 95th percentile of dietary intake of 1275 µg for adults older than 65 years (as a precautionary measure to protect this age cohort with higher dietary intake than the 18–64-year-olds The value of 1725 µg/day was then rounded down to 1700 µg/day for adults. • 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 assessment of food safety from Norway, the FSAI (2020) MSL and the EVM GL, as well as 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 1500 µg/day and 1000 µg/day, respectively.

Nutrient	Qualitative risk characterisation
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 is 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 erythropoietic protoporphyria (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.

Nutrient	Qualitative risk characterisation
Beta-carotene continued	• 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 2020 FSAI concluded that the EFSA ANS guidance level of less than 15 mg/day from food supplements and/or food additives is appropriate for adults and children aged 4–10 years in Ireland. The FSAI MSL for food supplements is based on the EFSA ANS guidance level minus the estimates from European dietary studies of 3–7 mg/person/day = 8 mg. This amount of 8 mg supersedes the UK EVM 2003 supplemental level of 7 mg. There are concerns about the use of beta-carotene food supplements among heavy smokers. EFSA (2006) stated that there may be a very small difference between levels that may confer health benefits and those that may produce adverse effects in smokers in the general population. EFSA concluded that the use of beta-carotene as a supplement should be regarded cautiously. FSAI in 2020 concluded that exposure to a level of beta-carotene below 15 mg/day from food supplements and/or food additives does not give rise to concerns about adverse effects in the general population or in heavy smokers. Based on these more recent safety assessments, the MLS is 8 mg/day for adults and children aged 4–10 years.
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.

Nutrient	Qualitative risk characterisation
Calcium continued	• 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 12, footnote 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. • FSAI (2020) concluded that Ireland adopts the EFSA UL of 2500 mg/day for adults aged 19 years and over and the IOM ULs of 2500 mg/day for ages 1–8 years and 3000 mg/day for 9–18-year-olds. The amount for 14–18-year-olds allows for rapid bone accretion during the adolescent growth spurt. • Whereas Flynn *et al*. (2016), using P95 intake data, estimated safe maximum levels including overages for food supplements of 969 mg for adults and 1142 mg for children aged 7–10 years, the FSAI (2020) calculated amounts for adults and children aged 4–10 years are 880 mg and 1012 mg, as shown in Tables 5 and 13, respectively. • MLS of 1000 mg/day for adults and 500 mg/day for children are proposed by FSE and are shown in Tables 5 and 13, based on a qualitative safety assessment.

Nutrient	Qualitative risk characterisation
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 a 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). In 2020 FSAI concluded that the EFSA ULs for copper were appropriate for Ireland. The UL for adults >17 years is 5 mg/day and for children, 2 mg/day for 4–6-year-olds and 3 mg/day for 7–10-year-olds. • 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 and shown in Tables 5 and 13. • 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.

Nutrient	Qualitative risk characterisation
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 11000 µg, 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. • FSAI (2020) noted that both EFSA and IOM established ULs for iodine based on the same studies, which observed changes in TSH levels, but applied different UFs. The choice of UFs accounts for the large differences in ULs. FSAI recommended the adoption of the EFSA ULs of 600 µg/day for adults aged 18 years and over, and 250 µg/day for children aged 4–6 years and 300 µg/day for 7–10-year-olds.

Nutrient	Qualitative risk characterisation
Iodine continued	• MLS of 200 µg/day for adults and 150 µg/day for children are proposed and are shown in Table 8. These MLS values are based on the qualitative safety assessment above and are shown in Tables 5 and 13. • 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. • FSAI (2020) concluded that the IOM ULs for iron are the most appropriate for Ireland due to the high incidence of hereditary haemochromatosis. The recommendations for Ireland for the Tolerable Upper Intake Levels are 40 mg/day for children aged 1–13 years and 45 mg/day for ages 14 years to >70 years. • 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).

Nutrient	Qualitative risk characterisation
Iron continued	• 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 (WHO, 2012b). 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, 2012a). • 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, which is regarded as the critical adverse effect (Pyke and Zlotkin 2019) • 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. 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. • Using P95 intake data, Flynn *et al.* (2016) estimated safe maximum levels with overages of 25% in fortified foods and food supplements for iron for adults aged 18–64 years and for children aged 7–10 years. The amounts were 23.5 mg for adults and 24.5 mg for children aged 7–10 years. The FSAI (2020) calculated amount for iron for adults is 23.2 mg and for children aged 4–10 years is 23.8 mg, as shown in Tables 5 and 13, respectively. • Taking into account the quantitative and qualitative assessments, the P2.5, P5, mean, P95 and P97.5 intakes of iron from the available intake data, the FSE MLS of 20 mg/day for adults and 14 mg/day for children are proposed, as shown in Tables 8 and 13.

Nutrient	Qualitative risk characterisation
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. • 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. • There is very limited information on dietary intakes of manganese. Typically, 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.

Nutrient	Qualitative risk characterisation
Manganese continued	• 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. • FSAI (2020) concluded that the IOM ULs are the most appropriate for Ireland, based on the critical adverse effect of elevated blood manganese and neurotoxicity. The Tolerable Upper Intake Levels were set at 11 mg/day for 19 years to over 70 years, 3 mg/day for 4–8-year-olds, 6 mg/day for 9–13-year-olds and 9 mg/day for 14–18-year-olds. • 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, as shown in Tables 5 and 13. These amounts are 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.

Nutrient	Qualitative risk characterisation
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. • 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 a SUL of 25 mg for supplemental zinc. The ULs for children and adolescents are calculated on the basis of reference bodyweights $^{0.75}$. 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.

Nutrient	Qualitative risk characterisation
Zinc continued	• FSAI (2020) concluded that the EFSA ULs for zinc were the most appropriate for Ireland, and recommended ULs of 25 mg/day for those over 17 years of age, 10 mg/day for 4–6-year-olds, 13 mg/day for 7–10-year-olds, 18 mg/day for 11–14-year-olds and 22 mg/day for 15–17-year-olds. • MLS of 15 mg/day for adults and 5 mg/day for children are proposed and are shown in Tables 5 and 13. 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 6

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

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 of 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 a SUL for daily consumption over a lifetime of 9.6 mg boron/day for a 60 kg adult. • EFSA used a reference bodyweight of 62.5 kg to derive the UL for boron at 10 mg/day. FSAI (2020) came to an agreement with EFSA that a bodyweight of 70 kg was more representative of the adult population in Ireland, and recalculated the UL to be 11 mg/day. • 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.

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. • FSAI (2020) considered the critical endpoints to be moderate dental fluorosis (for 1–8-year-olds and bone fracture (>8 years), and used the EFSA ULs. However, FSAI (2020) came to an agreement that a bodyweight of 70 kg was more representative of the adult population in Ireland and recalculated a value for adults of 8 mg/day. • 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.

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 was 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 a 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.
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 a 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. • IOM (2005) established ULs of 2.3 g/day for total sodium and 3.6 g/day for chloride based on the impact of sodium on blood pressure. FSAI (2020) adopted these ULs and a salt equivalent of 5.75 g/day for adults (14 years to >70 years), 4.75 g/day for 4–8-year-olds and 5.5 g/day for 9–13-year-olds.

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 2004a). 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).

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