CRN-I Scientific Symposium

Risk analysis approaches for establishing maximum levels of essential nutrients and other bioactive substances in fortified foods and food supplements for adults and children aged 4–10 years

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Outline

- Nutritional risk analysis: principles & guidelines
- Quantification of ULs for relevant age/sex/lifestage subpopulations
- Extrapolation of adult ULs for different lifestage groups
- Reasons for selection of a children's age range of 4–10 years
- Impact of the UL on the selection of NRVs
- Regulatory approaches to the setting of maximum amounts of vitamins and minerals in fortified foods and food supplements
- Proposed risk management model and maximum levels in food supplements (MLS)

The process of nutritional risk analysis is particularly challenging with respect to the essential nutrients and related substances that have favourable physiological effects as there are clearly two types of risk:

RISK OF SUBOPTIMAL INTAKE OR DEFICIENCY

RISK OF ADVERSE EFFECTS ASSOCIATED WITH EXCESSIVE INTAKE

Nutritional risk analysis
Principles and guidelines

Comprises 3 distinct but closely linked components:

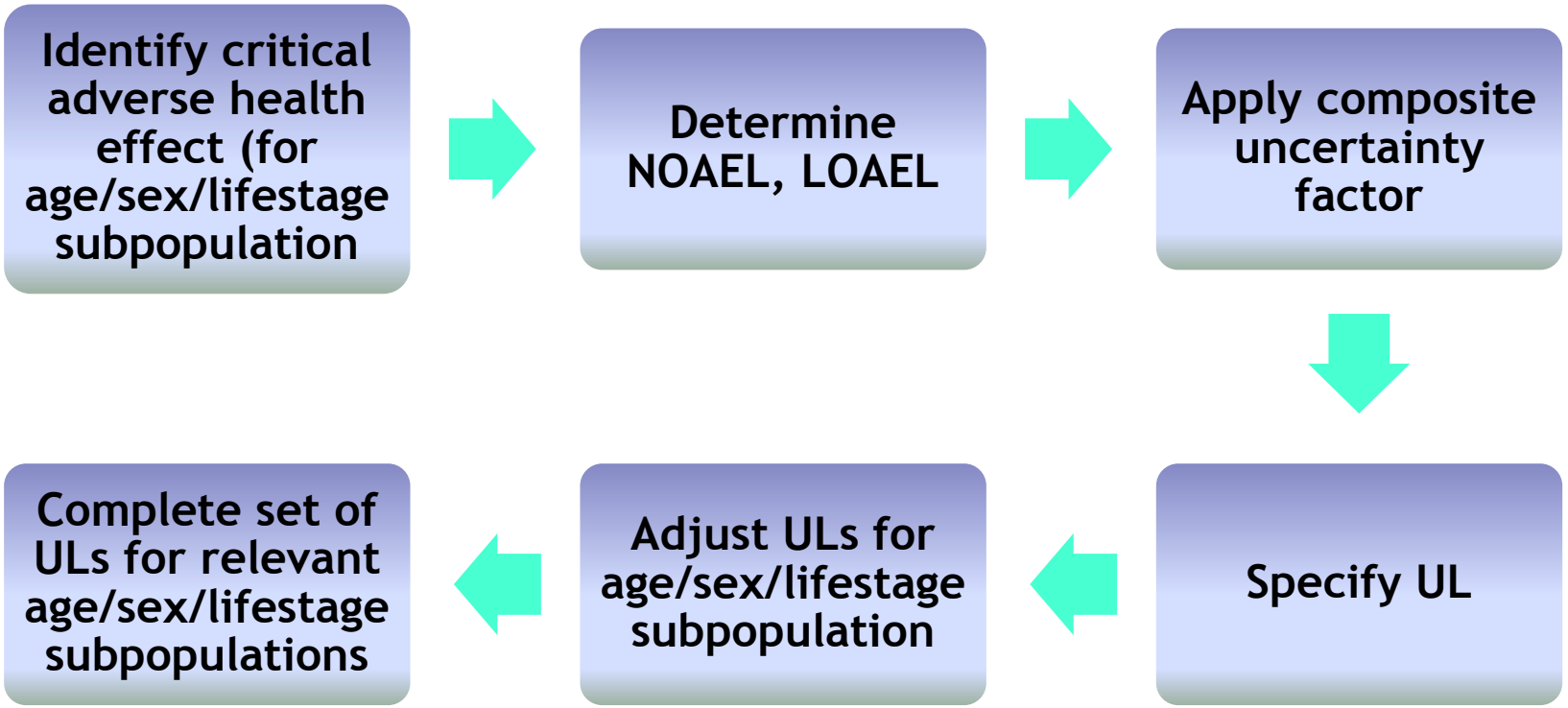
- NUTRITIONAL RISK ASSESSMENT
  - Science-based
- NUTRITIONAL RISK MANAGEMENT
  - Policy-based
- NUTRITIONAL RISK COMMUNICATION
  - Information and judgement about risks

Codex Alimentarius Commission, 2009

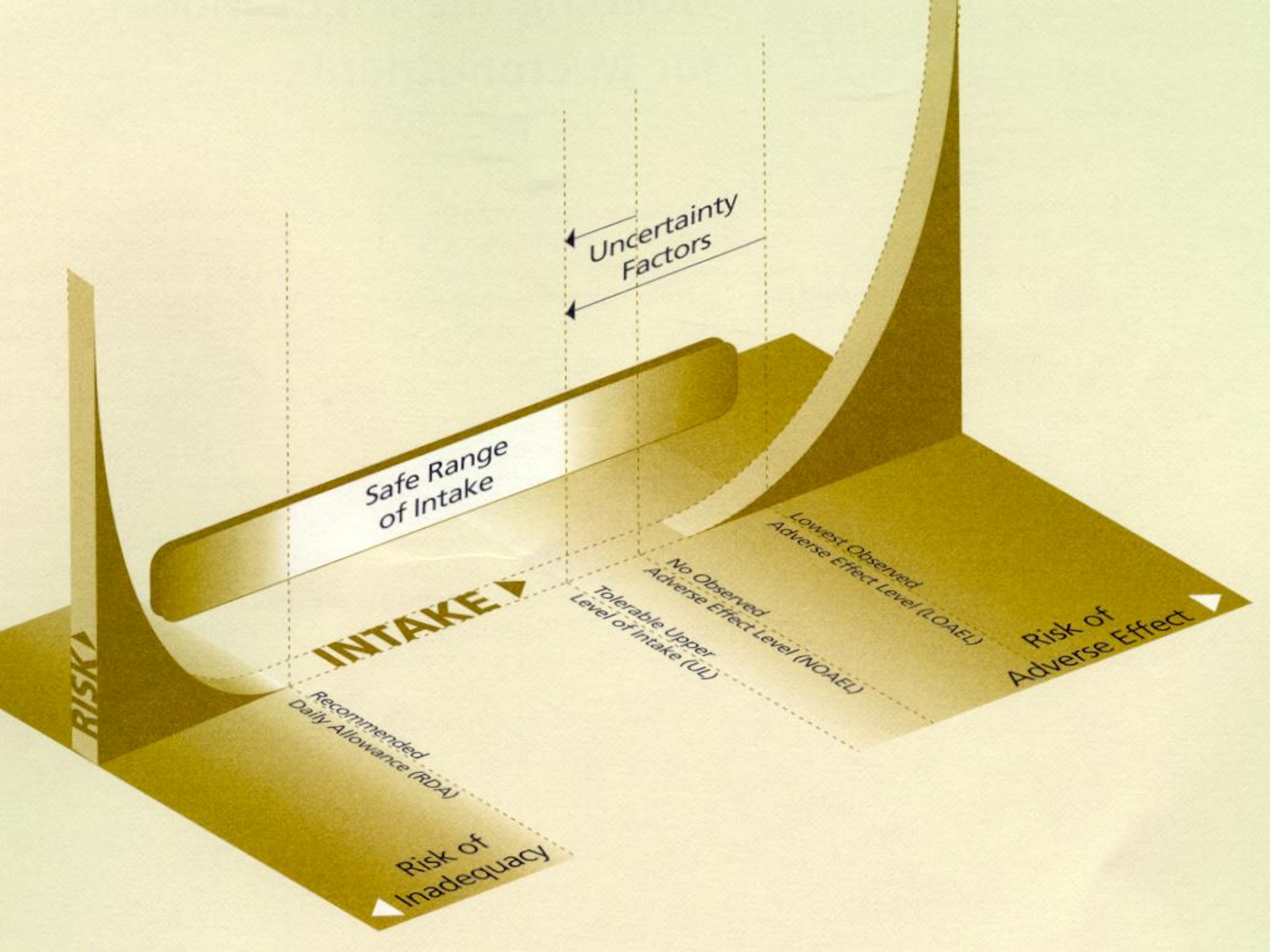
Tolerable upper level of intake (UL) determined by scientific risk assessment

- EU European Food Safety Authority (EFSA) and Scientific Committee for Food (SCF)
- USA Institute of Medicine (IOM) and Food and Nutrition Board (FNB)
- UK FSA Expert Vitamin and Mineral Group (EVM)

Steps in quantifying an upper safe level



WHO/FAO, 2006


Uncertainty Factors
Safe Range of Intake
INTAKE
RISK
Recommended Daily Allowance (RDA)
Risk of Inadequacy
Tolerable Upper Level of Intake (UL)
No Observed Adverse Effect Level (NOAEL)
Lowest Observed Adverse Effect Level (LOAEL)
Risk of Adverse Effect

$$\text{Upper Safe Level} = \frac{\text{NOAEL or LOAEL}}{\text{Total Product of Uncertainty Factors (UF)}}$$

Selection of UF is critical to consider potential effects for nutritional deficiency and excess.

Nature of Uncertainty Factors (UF) associated with the derivation of an Upper Level for a nutrient substance

- Human variability
- Interspecies differences
- Use of an LOAEL rather than an NOAEL
- Short duration studies to predict chronic adverse effects
- Inferior quality of a study/studies and limitations of the database
- Appropriateness of UL for specific population groups
- Derivation of a composite UF may make adjustment so large to result in a UL that is lower than the required intake of the nutrient (WHO/FAO, 2006)

Vitamin B_6

Adverse effect Sensory neuropathy

FNB Human data 200 mg NOAEL, UF 2 for limitations in data

UL = 200÷2 = 100 mg (Total)

SCF Human data 100 mg UF 2 for long-term exposure

UF 2 for limitations in data

UL = 100÷4 = 25 mg (Total)

FSA EVM Animal (dog) data LOAEL 50 mg/kg BW/day

UF 3 for LOAEL to NOAEL extrapolation

UF 10 for interspecies variation

UF 10 for inter-individual variation

SUL = 50÷300 = 0.17 mg/kg/BW/day (supplemental)

= 10 mg/day for 60 kg adult bodyweight

Upper levels (ULs)

ARE:

- Based on scientific risk assessment's assumptions and uncertainties
- Not only safe, but safe by a comfortable margin
- 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

ULs represent an intake that can be consumed daily over a lifetime without significant risk to health according to available evidence.

Extrapolation of ULs for different lifestage groups

ULs for different lifestage 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) and IOM (1997)

Adjustment of adult ULs to estimate ULs relevant to children

Based on quantified reference bodyweight	Based on surface area/metabolic bodyweight
$UL_{child} = UL_{adult} \times \left[\frac{\text{weight of child}}{\text{weight of adult}}\right]$	$UL_{child} = UL_{adult} \times \left[\frac{\text{weight of child}}{\text{weight of adult}}\right]^{0.75}$
$UL_{child} = UL_{adult} \times \left[\frac{20\ kg}{70\ kg}\right]$	$UL_{child} = UL_{adult} \times \left[\frac{20\ kg}{70\ kg}\right]^{0.75}$
$UL_{child} = UL_{adult} \times 0.29$	$UL_{child} = UL_{adult} \times 0.39$
(WHO/FAO, 2006)	

EFSA Tolerable Upper Intake Level (UL) for IODINE on basis of bodyweight$^{0.75}$

Age (years)	UL (µg per day)
1-3	200
4-6	250
7-10	300
11-14	450
15-17	500
Adult	600

Examples of scaling adjustments used by EFSA and IOM risk assessments to establish ULs for children

Vitamin/mineral	Basis of scaling	
	Reference bodyweight	$BW^{0.75}$
Vitamin B_6	EFSA	IOM
Vitamin E	IOM	EFSA
Folic acid	EFSA	IOM
Nicotinamide	EFSA	IOM
Vitamin A	IOM	EFSA
Iodine	IOM	EFSA
Zinc	IOM	EFSA

Risk assessments and adjustment of upper level of intake for lifestage subpopulations

An explanation based on scientific evidence should be provided as to the choice of the scaling method for a particular nutrient substance.

WHO/FAO, 2006

Adjustment of adult ULs to estimate ULs relevant to children

- Scaling on the basis of bodyweight$^{0.75}$ results in higher UL values than scaling on the basis of reference bodyweight.
- The difference in ratios among the scaling methods becomes smaller with increasing age.
- Scaling according to basal metabolic rate, which is a function of metabolically active body mass, appears to be more logical than scaling according to bodyweight, but with notable exceptions of thiamin and niacin, the data showing a relationship between energy intake and nutrient requirement are scarce.
- An adjustment based on BW$^{0.75}$ does not take into account differences in either adaptive and homeostatic mechanisms among nutrient substances or differences in metabolism and in the synthesis of body tissue during growth.

EFSA scaling for UL for children aged 4-6 years for IODINE based on $BW^{0.75}$ and the adult UL of 600 µg/day

UL male child = $600 \times \left[\frac{20\ kg}{74.6\ kg}\right]^{0.75}$ = 223 µg/day	UL female child = $600 \times \left[\frac{19\ kg}{62.1\ kg}\right]^{0.75}$ = 246 µg/day
EFSA UL for ages 4-6 years is rounded to 250 µg/day	
N.B. If UL had been based on reference bodyweight, the children's UL would have been 160 µg for males and 184 µg for females.	
EFSA used $BW^{0.75}$ whereas IOM used BW.	

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 Draft 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.

Outstanding questions: how best to develop a risk management approach for children aged 4-10 years?

- Dietary requirements and ULs are extrapolated from adult values mostly based on reference body weights
- Limited intake data for children from all dietary sources
- Role of vitamins and minerals for children's growth, development and health

Significance of risk to a population consuming a nutrient in excess of the UL is determined by the following:

1. The fraction of the population consistently consuming the nutrient at intake levels in excess of the UL
2. The seriousness of the adverse effects associated with the nutrient
3. The extent to which the effect is reversible when intakes are reduced to levels less than the UL
4. The fraction of the population with consistent intakes above the NOAEL or even the LOAEL

IOM, 2000

Critical issue of the impact of the UL on the selection of nutrient reference values (NRVs). Zlotkin (2006)

- Most NRVs fall well below the ULs.
- Some ULs for children fall very close to the RDA.
- High intakes (P95, P97.5) sometimes approach or exceed the UL (e.g. retinol, iodine, manganese and zinc).
- Narrow range between RDA and UL may be unjustified when the lack of evidence of demonstrable adverse effect/toxicity at current levels above the UL.
- Adverse effects are more often observed with inadequate intakes rather than excessive intakes.
- If intakes exceed the UL, the significant uncertainties about the UL indicate that intake is likely not the problem but rather the application of a UL based on inadequate data.
- CARE IN USE/AVOIDANCE OF MISUSE OF UL AS A BENCHMARK

European regulatory approaches to the setting of maximum amounts of vitamins and minerals in food take due account of:

- Upper safe levels vitamins and minerals by scientific risk assessment based on generally accepted scientific data
- Intake of vitamins and minerals from other dietary sources
- Reference intakes of vitamins and minerals for the population

Objectives of the proposed risk management model

- Evaluation of the risk management options for current and future intakes of nutrients from all sources
- Categorisation of nutrients into 3 groups according to risk using quantitative and qualitative information
- A proposal for a risk management model to address each group of nutrients and to set maximum levels of vitamins & minerals in food supplements and fortified foods for adults and children.

Risk categorisation of vitamins and minerals

Group 1 No evidence of risk within ranges currently consumed; does not represent a risk to human health (no UL established)

Group 2 Low risk of exceeding the UL

Group 3 Potential risk at excessive intakes

Quantitative risk categorisation for nutrients with a UL

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

- UL as set by SCF/EFSA and other risk assessments
- RDA as set by EU Regulation No 1169/2011
- Mean Highest Intake from food (MHI)
  (i.e. the 97.5 percentile intake of the average male adult)
- The estimated intake from water (IW)

NUTRIENT	PSI = $\frac{UL - (MHI + IW)}{RDA}$
Nicotinamide	53.8
Vitamin E	23.9
Vitamin C	22.6
Vitamin B_6	14.4
Vitamin D	8.0
Molybdenum	7.4
Selenium	3.8
Phosphorus	2.5
Iron	1.6
Iodine	1.1
Copper	1.0
Calcium	0.7
Zinc	1.2
Vitamin A (preformed retinol)	0.5

- How to allow for further potential changes in dietary patterns (e.g. changes in food preferences, increases in fortified foods)?

- How to set daily maximum supplement levels (MLS)?

SETTING OF MAXIMUM LEVELS FOR LOW-RISK GROUP 2: warrants use of precautionary risk management factors to account for potential changes in food intake

For vitamins

Maximum Level in Food Supplement (MLS) = UL – (MHI x 150%)

For minerals

Maximum Level in Food Supplement (MLS) = UL –[(MHI x 110%) + IW]

Setting daily maximum levels in food supplements (MLS)

GROUP 1 **No evidence of risk to human health at levels currently consumed**	No further risk management measures required.		
GROUP 2 **Low risk of exceeding UL**	**Nutrient**	**Proposed MLS**	
		Adults	**Children**
	B_6 mg	18 (93)	2 (35)
	C mg	1700	350
	D µg	60	20
	E mg	270 (970)	98 (286)
	Nicotinamide mg	820	163
	Molybdenum µg	350	50
	Phosphorus mg	1250	550
	Selenium µg	200	55
	Magnesium mg	250	250
	Folic acid µg	600	200
	Potassium mg	1500	1200

MLS values in brackets based on IOM ULs

GROUP 3	Case-by-case qualitative risk characterisation		
Potential risk at excessive intakes	Nutrient	Proposed MLS	
		Adults	Children
	Vitamin A µg	1200	1000
	Beta-carotene mg	7	7
	Calcium mg	1000	500
	Copper mg	2	1
	Iodine µg	200	150
	Iron mg	20	7
	Manganese mg	3	1.5
	Zinc mg	15	5

For Group 1: in absence of UL use Highest Observed Intake (HOI)

Defined by WHO/FAO as the highest level of intake observed or administered as reported within a study/studies of acceptable quality. It is derived only when no adverse health effects have been identified.

Ref. Codex Alimentarius Commission 2010: Nutritional Risk Analysis Principles and Guidelines

GROUP 1: no evidence of risk to human health at levels currently consumed

Nutrient GROUP 1	UK EVM Guidance Levels (GLs) for supplementation* Adults
Vitamin B_1 (mg) Thiamin	100
Vitamin B_2 (mg) Riboflavin	40
Biotin (µg)	900
Vitamin B_{12} (µg) Cobalamin	2000
Pantothenic acid (mg)	200
Vitamin K (µg)	1000
Chromium III (mg)	10

* equivalent to WHO/FAO Highest Observed Intake (HOI)

Summary of risk management model

- Categorisation of risk for vitamins and minerals into 3 groups based on quantitative and qualitative information.
- Uses up-to-date actual intake data from ‘mature’ markets.
- Estimations of higher, theoretical intakes from foods including fortified foods to account for potential changes in dietary patterns.
- Proposals for maximum levels in food supplements (MLS) taking due account of the criteria set in the EU Food Supplements Directive and the Regulation on additions of vitamins and minerals to foods.
- Contribution to the ongoing international discussion on approaches to risk management.

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