Food Safety
AUTHORITY OF IRELAND

Report of the Scientific Committee
of the Food Safety Authority of Ireland

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)

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ABBREVIATIONS

µg	Micrograms
AI	Adequate Intake
AMDR	Acceptable Macronutrient Distribution Ranges
BMDL	Lower Limit on the Benchmark Dose
COMA	Committee on Medical Aspects of Food Policy (UK)
DFEs	Dietary Folate Equivalents
DRI	Dietary Reference Intakes
DRVs	Dietary Reference Values
EAR	Estimated Average Requirement
EFSA	European Food Safety Authority
EGMV	Expert Group on Vitamins and Minerals
EU	European Union
FAO	Food and Agricultural Organization (United Nations)
FSAI	Food Safety Authority of Ireland
g	Gram
IARC	International Agency for Research on Cancer
IOM	Institute of Medicine
IU	International Unit
IUNA	Irish University Nutrition Alliance
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Lowest Observed Adverse Effect Level
LTI	Lower Threshold Intake
mg	Milligrams
MKs	Menaquinones
NANS	National Adult Nutrition Survey
NCFS	National Children's Food Survey
NOAEL	No Observed Adverse Effect Level
NPNS	National Pre-School Nutrition Survey
NSIFCS	North/South Ireland Food Consumption Survey
NTD	Neural Tube Defect
NTFS	National Teens' Food Survey
PARNUTs	Foods for Particular Nutritional Uses
PN	Pyridoxine
POM	Prescription Only Medicine
PRI	Population Reference Intake
RDA	Recommended Dietary Allowance
RI	Reference Intake
UF	Uncertainty Factor
UL	Tolerable Upper Intake Level
UV	Ultra Violet
WHO	World Health Organization

FOREWORD

Vitamins and minerals are required in small amounts for normal growth, development and on-going wellbeing. They are found naturally in diet; however, food supplements may be used to augment dietary intakes of vitamins and minerals and are specifically recommended at particular life stages, e.g. folic acid for women of childbearing age, and vitamin D in infancy. European Union (EU) regulation of food supplements containing vitamins and minerals was adopted in 2002 (Directive 2002/46/EC).

Excess of some vitamins and minerals may have detrimental health effects; hence, EU legislation provides for, among others, the setting of maximum safe levels of vitamins and minerals in food supplements by the European Commission. However, these are yet to be established. Currently, maximum levels of vitamins and minerals in food supplements are at the discretion of the manufacturer (provided the supplement is not unsafe). In the absence of official EU maximum levels, there is a need for the Food Safety Authority of Ireland (FSAI) to evaluate the safety of vitamins and minerals in food supplements in Ireland in order to protect consumer health and to provide guidance to the food industry.

The report recommends a standard risk assessment approach for evaluating the safety of vitamins and minerals in food supplements in Ireland. This is on the basis that the daily amount of a micronutrient from a food supplement, added to the usual daily intake from food sources, i.e. from foods, including fortified foods, but excluding supplements, in the highest consumers, i.e. the 95th percentile, should not exceed the tolerable upper intake levels (UL) for the population group(s) for whom the food supplement is intended. A UL is the highest level of long-term daily intake of a nutrient, from all sources, judged to be unlikely to pose a risk of adverse health effects to humans.

Appropriate ULs for Irish population groups are recommended, based on the ULs established by the European Food Safety Authority (EFSA) and the US Institute of Medicine (IOM). Data are also provided on highest intakes (the 95th percentile) of vitamins and minerals from sources other than food supplements estimated for Irish population groups in national food consumption surveys. These data will be updated periodically, as required.

This report provides scientific advice to the FSAI for assessing the safety of vitamins and minerals in food supplements in Ireland and for the development of appropriate guidance for the food industry.

Ita Saul
Chair, Public Health Nutrition Sub-Committee

Albert Flynn
Chair, Scientific Committee

EXECUTIVE SUMMARY

The purpose of this report is threefold:

(1) To provide scientific advice to the FSAI to develop guidance for the food industry on safety of vitamins and minerals in food supplements

(2) To provide ULs and highest intakes of vitamins and minerals for population groups in Ireland to allow risk assessments of food supplements on Irish market, and

(3) To outline the method for assessing the safety of food supplements for population groups in Ireland

Food supplements have been regulated in the EU since 2002 (Directive 2002/46/EC). These regulations provide for, among others, the setting of maximum safe levels of vitamins and minerals in food supplements by the European Commission. However, these are yet to be established. Vitamins and minerals can be used in the manufacture of food supplements to a maximum level at the discretion of the manufacturer (provided there is no unsafe food placed on the market (Regulation 178)). In the absence of EU maximum levels, the FSAI wishes to provide guidance to the food industry on assessing the safety of vitamins and minerals in food supplements in Ireland.

Assessment of the safety of vitamins and minerals in food supplements for different population groups may be carried out using the relevant UL and data on highest intakes from other sources (conventional foods and fortified foods). ULs have been established by international scientific bodies, including EFSA and the IOM. A UL is the highest level of long-term daily intake of a nutrient, from all sources, judged to be unlikely to pose a risk of adverse health effects to humans. ULs vary depending on the sub-group of the population, as the likelihood of adverse effects differs between genders and age groups. This report has reviewed the ULs established by EFSA and the IOM and recommends appropriate ULs for Irish population groups. For some micronutrients, no ULs are recommended as neither EFSA nor the IOM have established a UL, owing to lack of data. However, this does not mean that consuming excess amounts of these nutrients poses no risk(s). Caution is always necessary when consuming large amounts of any micronutrients as the absence of reported adverse effects do not necessarily mean that no adverse effects exist.

Data on highest intakes (the 95th percentile) of vitamins and minerals from sources other than food supplements, i.e. from food sources only, including conventional foods and fortified foods, have been estimated for Irish population groups in national food consumption surveys and are presented in this report. These data are considered to be suitable for assessment of safety of vitamins and minerals in food supplements for different population groups, by reference to ULs.

For assessment of safety of vitamins and minerals in food supplements, the following standard risk assessment approach is recommended:

When consumed according to manufacturer's instructions, the daily amount of a micronutrient from a food supplement (as labelled) added to the usual daily intake from food sources, i.e. from foods, including fortified foods, excluding supplements, of the highest consumers, i.e. the 95th percentile, should not exceed the UL for the population group(s) for whom the food supplement is intended. In line with EU guidance on tolerances around labelled values, the measured amount of micronutrient takes precedence over the declared amount when considering safety of the supplement. The daily amount from the food supplement should be based on the measured amount in the product as purchased, not the amount declared on the label. The intakes of the highest consumers, i.e. the 95th percentile, of micronutrients from food sources in different population groups may be obtained from the Irish national dietary surveys and are presented in this report.

Recommendations

1. It is recommended that the ULs and the 95th percentile intakes presented in this report are used for risk assessment of vitamins and minerals in food supplements on the Irish market.
2. It is recommended that risk assessment be carried out as follows:

   When consumed according to manufacturer's instructions, the daily amount of a micronutrient from a food supplement (as labelled) added to the usual daily intake from food sources (excluding food supplements) of the highest consumers (95th percentile) should not exceed the UL for the population group(s) for whom the food supplement is intended.
3. The FSAI should continue to monitor intakes of vitamins and minerals in population groups, including intakes from food supplements and fortified foods.

Table 1a. Tolerable Upper Intake Levels for Vitamins and Minerals Recommended for Ireland Derived from EFSA

Life Stage Group	Vit A (µg RE/d)[a]	Vit D (µg/day)	Vit E (mg/d)	Niacin (mg/d)		Vit B_6 (mg/d)	Folic Acid (µg/d)	Calcium (mg/d)	Magnesium (mg/d)[b]	Zinc (mg/d)	Copper (mg/d)	Selenium (µg/d)	Iodine (µg/d)	Molybdenum[c] (mg/d)	Fluoride[c] (mg/d)	Boron[c] (mg/d)
				Nicotinamide	Nicotinic Acid											
Infants																
0-6 mo	600[d]	25	*ND*	*ND*	*ND*	*ND*	*ND*	*See IOM*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
7-12 mo	600[d]	25	*ND*	*ND*	*ND*	*ND*	*ND*	*See IOM*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Children																
1-3 y	800	50	100	150	2	5	200	*See IOM*	*ND*	7	1	60	200	0.1	1.5	3
4-6 y	1,100	50	120	220	3	7	300	*See IOM*	250	10	2	90	250	0.2	2.5	4
Males																
7-10 y	1,500	50	160	350	4	10	400	*See IOM*	250	13	3	130	300	0.25	2.5/5[g]	5
11-14 y	2,000	100	220	500	6	15	600	*See IOM*	250	18	4	200	450	0.4	5	7
15-17 y	2,600	100	260	700	8	20	800	2,500	250	22	4	250	500	0.5	8[f]	9
≥ 18 y	3,000	100	300	900	10	25	1,000	2,500	250	25	5	300	600	0.7[f]	8[f]	11[f]
Females																
7-10 y	1,500	50	160	350	4	10	400	*ND*	250	13	3	130	300	0.25	2.5/5[g]	5
11-14 y	2,000	100	220	500	6	15	600	*ND*	250	18	4	200	450	0.4	5	7
15-17 y	2,600	100	260	700	8	20	800	2,500	250	22	4	250	500	0.5	8[f]	9
≥ 18 y	3,000 (1,500[e])	100	300	900	10	25	1,000	2,500	250	25	5	300	600	0.7[f]	8[f]	11[f]
Pregnancy	3,000	100	300	*ND*	*ND*	25	1,000	2,500	250	25	*ND*	300	600	0.7[f]	8[f]	11[f]
Lactation	3,000	100	300	*ND*	*ND*	25	1,000	2,500	250	25	*ND*	300	600	0.7[f]	8[f]	11[f]

Tolerable Upper Intake Level (UL) is the highest average daily nutrient intake level likely to pose no risk of adverse health effects for nearly all people in a particular group. Unless otherwise specified, the UL represents total intake from food, water, and supplements. ULs could not be established for all vitamins. In the absence of a UL, extra caution may be warranted in consuming levels above the recommended intake therefore, sources of intake should only be from food to prevent high levels of intake.

ND = Not Determinable. This value is not determined due to the lack of data of adverse effects in this age group and concern regarding the lack of ability to handle excess amounts.

Vitamins and minerals where no UL has been recommended for Ireland: beta carotene, vitamin K, thiamin, riboflavin, vitamin B_{12}, biotin, pantothenic acid, phosphorus, potassium, chromium, silicon.

[a] As preformed vitamin A only.
[b] The EFSA UL for magnesium represents intake from supplements, water or added to food and beverages. The UL does not include Mg normally present in food and beverages.
[c] Calculation of UL requires a body reference weight and the reference weight used by EFSA was 60kg which is low in an Irish context. Re-calculations were made using a reference body weight of 70kg
[d] The IOM for infants <1 year is recommended.
[e] Because the UL may not adequately address the possible risk of bone fracture in particularly vulnerable groups, it would be advisable for postmenopausal women who are at greater risk of osteoporosis and fracture, to restrict their intake to 1,500 µg RE/day.
[f] Re-calculated EFSA UL for adults using a reference body weight of 70kg
[g] Children aged 4-8 years/adolescents aged 9-14 years

Sources: EFSA (2006) *Tolerable Upper Intake Levels for Vitamins and Minerals, Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies*; EFSA (2012) *Scientific Opinion on the Tolerable Upper Intake Level of vitamin D, Scientific Panel on Dietetic Products, Nutrition and Allergies*

Table 1b. Tolerable Upper Intake Levels for Vitamins and Minerals Recommended for Ireland Derived from the IOM

Life Stage Group	Vitamin C (mg/d)	Sodium (g/d)	Chloride (g/d)	Iron (mg/d)	Manganese (mg/d)	Calcium (mg/d)
Infants						
0-6 mo	ND	ND	ND	40	ND	1,000
7-12 mo	ND	ND	ND	40	ND	1,500
Children						
1-3 y	400	1.5	2.3	40	2	2,500
4-8 y	650	1.9	2.9	40	3	2,500
Males						
9-13 y	1,200	2.2	3.4	40	6	3,000
14-18 y	1,800	2.3	3.6	45	9	3,000
19-30 y	2,000	2.3	3.6	45	11	*See EFSA*
31-50 y	2,000	2.3	3.6	45	11	*See EFSA*
51-70 y	2,000	2.3	3.6	45	11	*See EFSA*
>70 y	2,000	2.3	3.6	45	11	*See EFSA*
Females						
9-13 y	1,200	2.2	3.4	40	6	3,000
14-18 y	1,800	2.3	3.6	45	9	3,000
19-30 y	2,000	2.3	3.6	45	11	*See EFSA*
31-50 y	2,000	2.3	3.6	45	11	*See EFSA*
51-70 y	2,000	2.3	3.6	45	11	*See EFSA*
>70 y	2,000	2.3	3.6	45	11	*See EFSA*
Pregnancy						
14-18 y	1,800	2.3	3.6	45	9	3,000
19-50 y	2,000	2.3	3.6	45	11	*See EFSA*
Lactation						
14-18 y	1,800	2.3	3.6	45	9	3,000
19-50 y	2,000	2.3	3.6	45	11	*See EFSA*

Tolerable Upper Intake Level (UL) is the highest average daily nutrient intake level likely to pose no risk of adverse health effects for nearly all people in a particular group. Unless otherwise specified, the UL represents total intake from food, water, and supplements. ULs could not be established for all vitamins. In the absence of a UL, extra caution may be warranted in consuming levels above the recommended intake, therefore sources of intake should only be from food to prevent high levels of intake.

Vitamins and minerals where no UL has been recommended for Ireland: beta carotene, vitamin K, thiamin, riboflavin, vitamin B_{12}, biotin, pantothenic acid, phosphorus, potassium, chromium, silicon

ND = Not Determinable. This value is not determined due to the lack of data of adverse effects in this age group and concern regarding the lack of ability to handle excess amounts

Sources: IOM (2006) *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*; IOM (2011) *Dietary Reference Intakes for Calcium and Vitamin D. Washington: National Academies Press*

CHAPTER 1. SAFETY OF VITAMINS AND MINERALS IN FOOD SUPPLEMENTS

1.1 Purpose of this Report

This report will serve to:

- Provide scientific advice to the FSAI to develop guidance for the food industry on safety of vitamins and minerals in food supplements
- Provide UL and highest intakes of vitamins and minerals for population groups in Ireland to allow risk assessments of food supplements on Irish market
- Outline the method for assessing the safety of food supplements for population groups in Ireland

1.2 Micronutrients

A healthy diet leading to good nutritional status plays a crucial role in the maintenance of health and wellbeing throughout the life cycle.

Nutrients comprise macronutrients and micronutrients. The macronutrients, fat, carbohydrate and protein are the major constituents of food and serve as fuels for the body. Macronutrients are required in relatively large amounts of grams per day. There is also a requirement for micronutrients (vitamins, minerals and trace elements), but in relatively small quantities (mg or µg per day).

Adverse health effects are associated with over- and under-consumption of macro- and micro-nutrients. This report focuses on the risk posed to consumers from over exposure to micronutrients and the definition of upper safe levels of intake of micronutrients in Ireland. Risk of adverse effects is determined when considering the chronic over-exposure to a micronutrient as opposed to the transient over-exposure to that micronutrient.

1.3 Vitamins

The term vitamin is derived from the words vital and amine because vitamins are required for life and were originally thought chemically to be amines. Although not all vitamins are amines, they are a group of organic compounds required for the maintenance of normal health and are involved in many metabolic processes. Vitamins are required in very small amounts, of the order of milligrams (mg) and micrograms (µg) per day. An organic compound is considered a vitamin if deficiency causes a specific disease which is cured or prevented only by restoring the vitamin to the diet, e.g. vitamin C and scurvy. Most vitamins must be solely provided in the diet. Requirements for some vitamins can be partly met through direct or indirect synthesis in the body, e.g. vitamin D can be formed in the skin on exposure to UVB radiation during the summer, niacin can be synthesised from the amino acid tryptophan and vitamin K can be produced by bacterial fermentation in the gut. However, as biological synthesis of these nutrients is limited for various reasons, dietary intake remains essential to meet physiological requirements.

There are two broad classifications of vitamins relating to the solubility of the vitamin in fat (lipids) or in water:

1. Water soluble vitamins: vitamin C and the B group vitamins (thiamin (B_1), riboflavin (B_2), niacin, vitamin B_6 (pyridoxine), vitamin B_{12} (cobalamin), folate, biotin and pantothenic acid)
2. Fat-soluble vitamins: vitamin A, vitamin D, vitamin E and vitamin K

When vitamins are consumed in amounts surplus to requirements, the body either stores or excretes the excess. Excess water-soluble vitamins are excreted in urine and other bodily fluids while excess fat-soluble vitamins are stored in the liver and fatty tissues. Therefore, in general, fat-soluble vitamins consumed in excess, pose a greater risk of causing toxicity than do water-soluble vitamins.

1.4 Minerals and Trace Elements

Minerals, including trace elements, are inorganic substances that have a physiological function in the body. Elements must be provided in the diet, as they cannot be interconverted. The requirements for minerals and trace elements vary from grams (g) per day, e.g. potassium and sodium, to milligrams (mg) per day, e.g. iron and calcium, and micrograms (µg) per day, e.g. copper and folic acid.

1.5 Dietary Reference Values

To guide the optimal intake of nutrients, dietary reference values (DRVs) have been devised by national and international bodies. DRVs are the complete set of nutrient recommendations and reference values indicating the amount of a nutrient that healthy people need for good health depending on age and gender. DRVs include recommendations for average, upper and lower levels of intake.

The recommended daily amounts (RDAs) for Ireland published by the FSAI in 1999 need to be updated (FSAI, 1999). The FSAI RDAs are based on data from the late 1980s and early 1990s including the EU PRIs derived in 1993, values from the USA derived in 1989 and values from the UK derived in 1991.

EFSA has recently produced DRVs for energy, macronutrients and water. EFSA has also reviewed all relevant micronutrients in terms of establishing ULs and has published other DRVs for the micronutrients. See Appendix IV for tables outlining the IOM-established DRIs and EFSA-established DRVs for micronutrients.

Although similar definitions are used, the terminology to describe the DRVs can vary by jurisdiction. Table 1.1 outlines the different terms used by EFSA, the IOM and Ireland to describe the same DRVs.

The complete set of DRVs and definitions are outlined in Table 1.1 (EFSA, 2010).

Table 1.1. Equivalent Terminology for Dietary Reference Values used by EFSA, the IOM and Ireland

EFSA Dietary Reference Values (DRVs)	**The IOM** Dietary Reference Intakes (DRIs)	**Ireland** Dietary Reference Values (DRVs)
Population reference intake (PRI)	Recommended dietary allowance (RDA; mean requirement + 2 standard deviations (SDs))	Recommended dietary allowance (RDA; mean requirement + 2 SDs)
Average requirement (AR)	Estimated average requirement (EAR)	Average requirement (AR)
Lower threshold intake (LTI; mean requirement - 2 SDs)	No equivalent value	Lower threshold intake (LTI; mean requirement - 2 SDs)
Adequate intake (AI)	Adequate intake (AI)	Adequate intake (AI)
Reference intake range for macronutrients (RI)	Acceptable macronutrient distribution ranges (AMDR)	Reference intake range for macronutrients (RI)
Tolerable upper intake level (UL)	Tolerable upper intake level (UL)	Tolerable upper intake level (UL)

- **Recommended Dietary Allowance**

  The level of (nutrient) intake that is more than enough for virtually all healthy people in a group (The mean requirement plus a notional 2 standard deviations (SDs) -See Figure 1.1). The PRI is the EFSA equivalent term for this DRV. The term PRI is not commonly used in Ireland and therefore, the term RDA is recommended for use in Ireland.

- **Average Requirement**

  The level of (nutrient) intake that is enough for half of the people in a healthy group, given a normal distribution of requirement (the midpoint of the population's requirement – see Figure 1.1).

- **Lower Threshold Intake**

  The level of intake below which, on the basis of current knowledge, almost all individuals will be unlikely to maintain "health and metabolic integrity" (the mean requirement minus a notional 2 SDs – see Figure 1.1).

- **Adequate Intake**

  The value estimated when requirements (PRI, EAR etc.) cannot be determined.

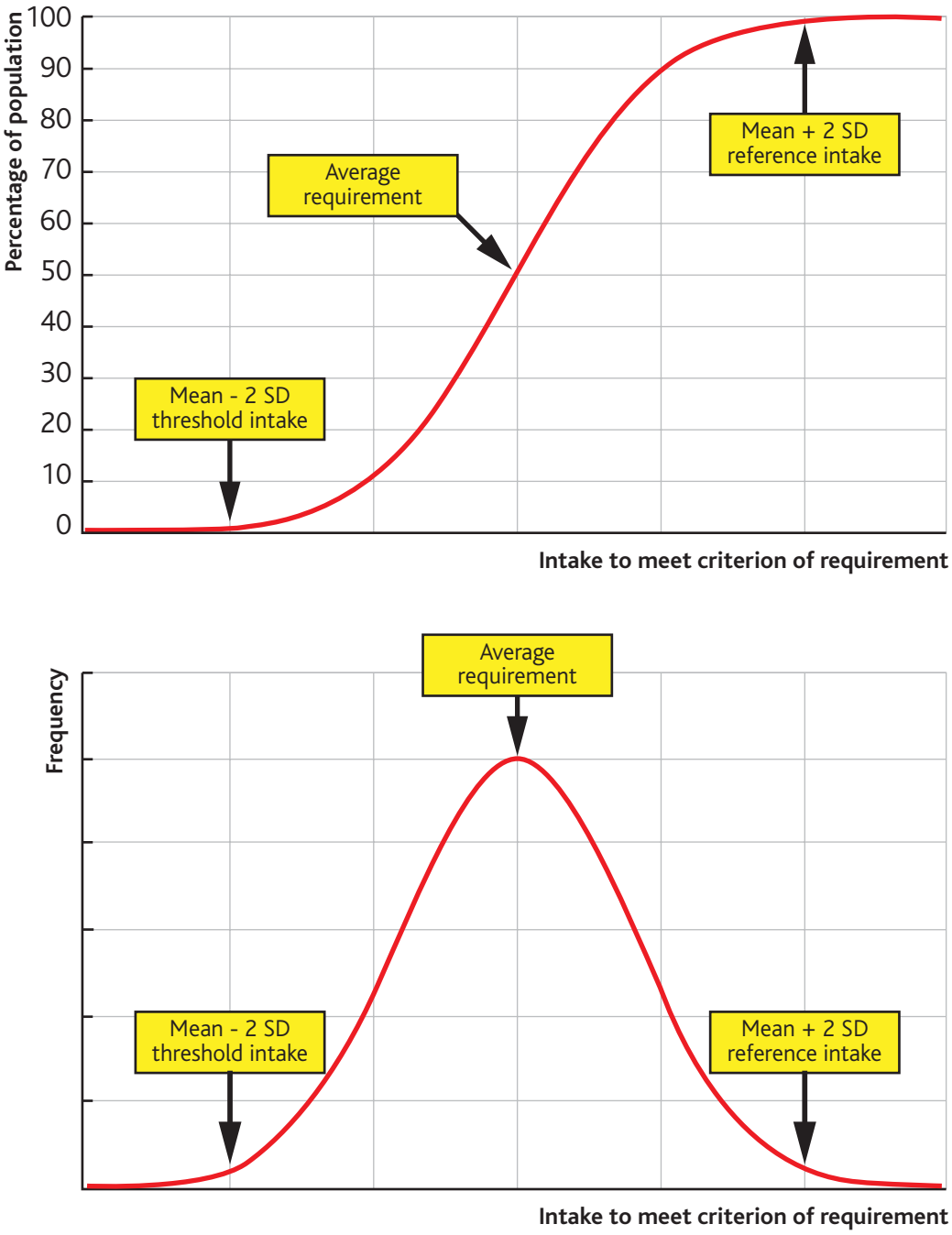
- **Reference Intake Ranges for Macronutrients**

  The reference intake range for macronutrients, expressed as percentage of the daily energy intake, defined by a lower and an upper bound.

- **Tolerable Upper intake Level**

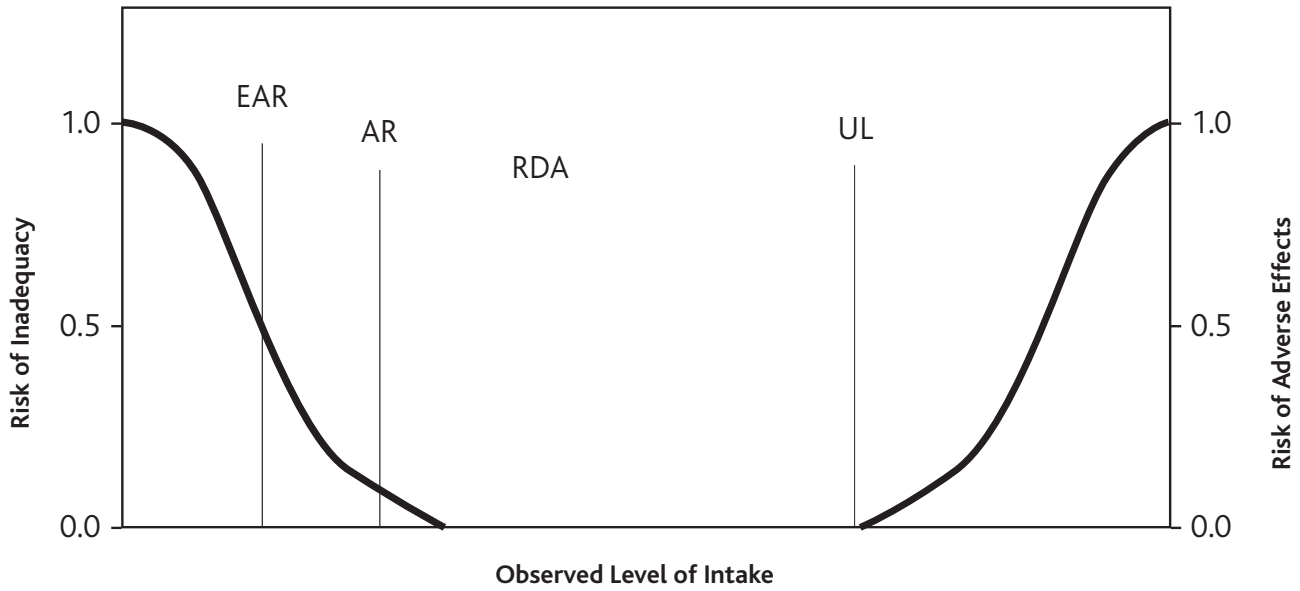
  The highest level of long-term daily intake of a nutrient, ***from all sources***, judged to be unlikely to pose a risk of adverse health effects to humans (Figure 1.2).

Figure 1.1. The Derivation of Reference Intakes of Nutrients from the Distribution around the Observed Mean Requirement; Plotted below as a Cumulative Distribution Curve, Permitting the Estimation of the Probability that a Given Level of Intake is Adequate to Meet an Individual's Requirements.



Source: Bender, D.A. (2014) Introduction to Nutrition and Metabolism. 5th Ed. Boca Raton, Florida. CRC Press

Figure 1.2 Relationships between DRVs



Source: Institute of Medicine (2006) Dietary Reference Intakes: The essential guide to nutrient requirements. The National Academies Press, Washington, D.C., USA

Nutrient reference values on food labels

The nutrient reference values (NRVs) on food labels differ from DRVs. NRVs are generic values for nutrients and are not specific for age and gender. The only exception to this are the labels of certain foods aimed at infants and young children, for which age-appropriate NRVs are used.

Assessing nutrient intakes of individuals and groups

When assessing the adequacy of nutrient intakes of individuals or populations, it is important to compare the intakes with the most appropriate level of requirement. It is also important to consider that when setting recommendations for a particular nutrient, it is assumed that the intake of all other nutrients is adequate, which may not be the case. Body size, activity level or other characteristics, e.g. metabolism, of the individual or group may also need to be considered, since the recommended intakes are designed for 'reference' populations.

The concept of the RDA is commonly misinterpreted as a minimum or average amount of a nutrient needed by an individual. In fact, the RDA by definition, meets the known requirement of 97.5% or almost all, of the population group being considered. The RDA is a suitable individual target intake.

Recommendations are presented as intakes per person per day but in practice, this will usually be achieved as an average over a period of time, owing to daily fluctuations in the diet. Thus, if an individual's nutrient intake can be averaged over a sufficient period, this makes comparison with the recommendation more valid (Younger, 2009).

From the public health perspective, in relation to making nutrient intake recommendations for the population or comparing intakes of groups with recommendations, the AR is the appropriate reference (Carriquiry, 1999). It is assumed that the quality of the diet can be averaged across the group at a given time-point, thus (apparently

healthy) individuals in the group whose intake appears deficient on one day, may make up for it on another day. It is not useful to compare the group intake with the RDA since this overestimates the prevalence of inadequate intakes. It is now considered most appropriate to compare the average intake of the group with the AR in order to estimate dietary adequacy (Younger, 2009). If the average intake of the group is less than the AR, then it is likely that there are people in the group whose intakes are not adequate. Furthermore, the proportion of individuals in the group not meeting the average requirement can be calculated, allowing the size of the problem to be quantified.

The UL is an estimate of the highest level of usual (long-term) intake of a nutrient which carries no appreciable risk of adverse health effects. The UL is meant to apply to all groups of the general population, including sensitive individuals, throughout the life stage. However, it is not meant to apply to individuals receiving the nutrient under medical supervision or to individuals with predisposing conditions that render them especially sensitive to one or more adverse effects of the nutrient, such as those with genetic predisposition or certain disease states (EFSA, 2006). For such individuals, intakes of micronutrients should be guided by medical advice.

The proportion of the population with usual intakes below the UL is likely to be at no appreciable risk of adverse health effects related to overconsumption, while the proportion above the UL is potentially at some risk which may be evaluated by a risk assessment. Risk is considered to be the probability of an adverse effect (and its severity).

The UL can be applied to data derived from intake assessment, e.g. the distribution of usual (long-term) total daily nutrient intakes among members of the general population, to identify population groups that may be at risk and the circumstances in which risk is likely to occur. Risk assessment involves the determination of what is the fraction (if any) of the population whose usual (long-term) intake exceeds the UL, the magnitude of the excess, the dose-response relation of nutrient intake and the adverse effect (if known), and the severity of the adverse effect. The severity of the potential consequences associated with exceeding the UL vary for different nutrients depending on the adverse effect which was used as the criterion for setting the UL, e.g. teratogenicity for retinol, compared to reversible mild diarrhea for magnesium (Carriquiry and Camano-Garcia, 2006; EFSA 2006; IOM 2000, 2006).

1.6 Sources of Intake

All vitamins and essential minerals must be supplied in the diet to prevent deficiency.

Natural food sources of vitamins and minerals

Vitamins and minerals occur naturally in foods. Vitamins and minerals can be found in a variety of foods such as meat, dairy, fish, cereals, grains, nuts, fruit and vegetables. The amount and type of vitamin and/or mineral found varies within each of these food groups. Individuals are encouraged to eat a variety of food from the all the food groups to ensure an adequate intake of micronutrients.

Vitamins and minerals added to foods and food supplements

Vitamins and minerals can also be added to foods, whether or not the foods usually contain them. In addition, they can be added to food supplements in a concentrated form. In the EU, a positive list has been created of vitamin and minerals permitted to be added to foods and used in the manufacture of food supplements (see Table 2.1). The specific vitamin formulations and mineral substances permitted are also listed in the rules (Regulation 1925/2006; Directive 2002/46/EC) (see Appendix I). Only the vitamin formulations and mineral substances listed in these legislative pieces are permitted to be used in these instances. For the purpose of food fortification or the manufacture of food supplements, vitamins and minerals are industrially produced. Vitamins and minerals produced commercially may be derived from natural sources or produced synthetically, e.g. vitamin E can be derived from natural sources such as edible vegetable oil products or synthesised from fossil plant material.

The bioavailability of a nutrient is the proportion of the ingested nutrient that can be absorbed and is available for utilisation by the body for normal metabolic functions. The bioavailability of different forms of vitamins and minerals, natural and synthetic, can vary. Under EU legislation, the vitamin formulations and mineral substances permitted for use in food fortification or food supplements must be bioavailable (Regulation 1925/2006; Directive 2002/46/EC). Therefore, only active forms of vitamins and minerals may be used for food fortification and in the manufacture of food supplements. The bioavailability of such micronutrients added to foods and used in food supplements, can be dissimilar from the forms of vitamins and minerals occurring naturally in foods.

1.7 Dietary Intakes in Ireland

In recent years, the Irish Universities Nutrition Alliance (IUNA) has completed a number of comprehensive national nutrition surveys that record such dietary intake. The surveys conducted to date include:

- **North/South Ireland Food Consumption Survey (NSIFCS) (2001)**

  This survey involved a random sample of 1,379 adults, aged 18-64 years, from the Republic of Ireland and Northern Ireland during 1997-1999. Food and beverage intake data were determined using a seven-day estimated food record.

- **National Children's Food Survey (NCFS) (2005)**

  This survey involved 594 children, aged 5-12 years, from the Republic of Ireland during 2003-2004. A seven-day weighed food record was used to collect food and beverage intake data.

- **National Teens' Food Survey (NTFS) (2008)**

  This survey involved 441 teenagers, aged 13-17 years, from the Republic of Ireland during 2005-2006. A seven-day semi-weighed food diary was used to collect food and beverage intake data.

- **National Adult Nutrition Survey (NANS) (2011)**

  This survey involved 1,500 adults, aged 18-90 years, from the Republic of Ireland during 2008-2010. A four-day semi-weighed food record was used to collect food and beverage data.

- **National Pre-School Nutrition Survey (NPNS) (2012)**

  This survey involved 500 pre-school children, aged 1-4 years, living in the Republic of Ireland during 2010-2011. Food and beverage intake data were collected using a four-day weighed food record.

In general, the survey findings indicate that the intakes of most vitamins and minerals are adequate for the Irish population (see Appendix V). However, there are some exceptions. Across all population groups, the intake of vitamin D is low and calcium and iron intakes are also of concern, particularly in women and children (IUNA, 2001; IUNA, 2005; IUNA, 2008; IUNA, 2011; IUNA, 2012). For women of reproductive age, compliance with the recommendation for daily supplemental intake of folic acid for the prevention of neural tube defects in foetuses is low (IUNA, 2011). Inadequate intake of vitamin A has also been observed among women aged 18-64 years (IUNA, 2011).

All the IUNA dietary surveys take account of the contribution that food supplement use and fortified foods make towards overall intake of micronutrients.

Fortified foods

Data from the IUNA surveys indicate that fortified food is commonly consumed in Ireland. In NANS, 86% of 18-64 year olds consumed a fortified food and out of the total foods consumed by participants, fortified foods accounted for 6.2% (Hennessy *et al.*, 2011). The proportions of other population groups consuming fortified food is also high including teenagers at 90% (Walsh *et al.*, 2010), children at 98% (Hannon *et al.*, 2006) and pre-schoolers at 97% (Hennessy *et al.*, 2013). The main food categories that traditionally undergo fortification in Ireland are ready-to-eat breakfast cereals and beverages, i.e. milks, squashes, fruit juices, carbonated and powdered drinks, (Hannon *et al.*, 2007). However, food fortification is widely practiced and an extensive range of fortified foods can be found on the Irish market (McMenamin *et al.*, 2009). A recent study using intake data from two food consumption surveys (the NSIFCS and the NANS), has shown a greater amount of fortified food on the market in 2008-2010 in comparison with 1997-1999, mainly due to the increase in fortified milk, fat spreads and breads. This was found to result in an increased number of Irish adults consuming fortified food (from 67 to 82%), with women of child-bearing age obtaining the most benefit as a result of voluntary fortification in Ireland (Hennessy *et al.* 2014).

Food supplements

The results from the IUNA surveys indicate that supplement use occurs across all population groups. In the NANS, 22% of men and 33% of women (18-64 year olds) reported the use of a food supplement (Browne *et al.*, 2011). This is a 5% increase in use of supplements as reported in the NSIFCS (Kiely *et al.*, 2001). In NANS, the prevalence of supplement use was highest (37%) in those aged 65 years and over, and in general a greater proportion of women consumed supplements compared with men (IUNA, 2011). Of all the different supplements consumed during NANS, multivitamin/mineral combinations were the most commonly consumed, followed by fish oils supplements and multivitamins (see Table 1.2) (IUNA, 2011). Similar levels of supplement usage were recorded in other population groups. About one fifth of pre-school children (Browne *et al.*, 2013) were regular consumers of nutritional supplements and approximately one quarter of all teenagers (Walsh *et al.*, 2009) and children aged 5-12 years (Walsh *et al.*, 2006).

Food supplements are small amounts of concentrated sources of micronutrients or other substances with a nutritional or physiological effect whose purpose is to supplement the normal diet (Directive 2002/46/EC).

Table 1.2. All Food Supplements used in NANS* 2011 (n211); Proportion (%) of Different Types of Food Supplements

Supplement Type (*n*211)	Proportion
Multivitamin/Mineral combinations	30%
Fish oils	20%
Multivitamins	12%
Single vitamins (*n*18) • Vitamin C (*n*6) • Vitamin B_{12} (*n*4) • Vitamin E (*n*2) • Vitamin B_6 (*n*2) • Folic acid (*n*2) • Vitamin D (*n*1) • β-carotene (*n*1)	11%
Other oils (including evening primrose/starflower oil)	9%
Single minerals (*n*12) • Iron (*n*6) • Zinc (*n*3) • Calcium (*n*1) • Copper (*n*1) • Magnesium (*n*1)	8%
Multi-minerals	5%
Other	5%

*National Adult Nutrition Survey

Food supplementation policy in Ireland

There are two food supplementation policies in Ireland:

1. **400 µg daily folic acid supplement for women of child-bearing age who are sexually active**

   In view of the evidence linking maternal folate status intake with neural tube defects in the foetus, it is recommended that all women of child-bearing age consume daily a 400 µg folic acid food supplement in addition to intake of food folate from a varied diet (FSAI, 2008).

2. **5 µg daily vitamin D_3 supplement for infants (0-12 months)**

   Infants, from birth to 1 year of age, who are being breastfed should be given a daily supplement containing 5 micrograms (µg) of vitamin D. This should be provided by a supplement containing vitamin D exclusively.

   Infants, from birth to 1 year of age, fed infant formula should not be given a daily vitamin D supplement if they are having more than 300ml (about 10 fluid ounces) of infant formula a day. This is because infant formula is fortified with vitamin D and other nutrients (FSAI, 2020).

1.8 Vitamins and Minerals: Relevant Food Legislation in Ireland

European and Irish legislation

Rules for food supplements and fortified foods

Within the EU, vitamin and mineral addition to foods (Regulation 1925/2006) and use in the manufacture of food supplements (Directive 2002/46/EC), are regulated by EU legislation. The legislation outlines rules governing the micronutrients that can be added and labelling requirements. The micronutrients added must be safe and a positive list of vitamin formulations and mineral substances which are permitted to be added is included in the annexes of these rules (see Appendix I). Micronutrients must be in a bioactive form as previously discussed.

Ireland, in compliance with EU legislation, allows the voluntary fortification of foods for general consumption. Micronutrients are permitted to be added to foods at any level (provided there is no unsafe food placed on the market (Regulation 178/2002)). EU legislation also states that Member States can request food manufacturers to notify the competent authority when placing a fortified food on the market or altering the level of fortification in an already fortified food (Regulation (EC) No 1925/2006 (Article 15)). Under current rules in Ireland, the manufacturer does not have to inform the competent authority (in this case, the FSAI) of new foods being fortified and/or levels of fortification changing in existing fortified foods. This is also the case for the majority of the EU Member States. However, some Member States, i.e. Belgium, Denmark, Finland, Norway, Poland and Romania, do require the manufacturer to notify the competent authority of fortified foods being placed on the market and/or the levels of fortification changing in already existing fortified foods.

European rules on food supplements (Directive 2002/46/EC) have been transposed into Irish law. Specified in the Irish food supplement legislation is the legal requirement that all food supplements placed on the market in Ireland must be notified to the competent authority (FSAI) (S.I. No. 506 of 2007 as amended). A copy of the model label used for the product must be provided to the FSAI. This allows the FSAI to monitor compliance with the relevant legislation and enforce rules, as necessary.

Tolerances for nutrition labelling

In December 2012, the European Commission Health and Consumers Directorate General published a guidance document on the setting of tolerances for nutrient values declared on a label in compliance with EU legislation (European Commission, 2012). Tolerances for nutrition labelling purposes refer to the acceptable differences between the nutrient values declared on the label and the actual values found in the food or food supplement upon measurement. This guidance is very important for food businesses to consider when labelling nutrient values in a food or food supplement and authoritative bodies when measuring nutrient levels in a product. The current EU regulations that govern vitamin and mineral addition to foods and use in the manufacture of food supplements allow for the setting of minimum and maximum amounts of these added micronutrients (Article 6 (1) of Regulation 1925/2006 and Art. 5 (1) of Directive 2002/46/EC); maximum safe levels (MSLs) have yet to be established. Establishing maximum safe levels for vitamins and minerals at European level is a complex process, hampered by the absence of detailed dietary intake data in some of the Member States. EU guidance on tolerances around labelled values states that the measured amount of micronutrients takes precedence over the declared amount when considering safety of the supplement and the daily amount of a micronutrient from a food supplement (as measured), taken together with intake from other food sources should be safe for the population group(s) for whom the food supplement is intended. Table 1.3 outlines the acceptable tolerances for vitamins and minerals in foods and food supplements.

Table 1.3. Tolerances for Vitamins and Minerals in Foods and Food Supplements including Measurement Uncertainty

	Tolerances for foods (including uncertainty of measurement)	Tolerances for food supplements (including uncertainty of measurement)
Vitamins	+50%** -35%	+50%** -20%
Minerals	+45% -35%	+45% -20%

**For vitamin C in liquids, higher upper tolerance values could be accepted

Nutrition and health claims legislation

Within the EU, Regulation 1924/2006 outlines specific rules on health and nutrition claims appearing on food including food supplements. The composition of foods and food supplements must meet strict criteria in order to bear a legally authorised claim including the condition that a food must contain the beneficial nutrient for which the claim is made in the final product in a specific minimum quantity. These rules have the potential to influence the minimum levels of vitamin and mineral added to food products or used in the manufacture of food supplements as these nutrients may be added to food or food supplements in order to allow the product to legally bear claims based on the nutrient content.

Other relevant legislation

In Ireland, there is legislation for medicines which encompasses rules governing seven micronutrients at certain doses (see Table 1.4) (Prescription Only Medicine (S.I. No. 540/2003)). Medicinal products which contain levels of vitamin or minerals which exceed those restricted in the medicinal legislation and/or make medicinal claims, require marketing authorisation from the Health Products Regulatory Authority (HPRA) before being placed on the market in Ireland.

Food products are prohibited from bearing medicinal claims.

Table 1.4. Prescription Only Medicine Levels as Set Out in S.I. No. 540/2003 for Medicines*

Vitamin	POM level
Vitamin B_6 (Pyridoxine)	>50 mg MDD
Vitamin B_{12} (Cyanocobalamin, hydroxocobalamin, methylcobalamin)	>25 µg MDD
Folic acid	>500 µg MDD
Vitamin A (Retinol – all trans)	>2,250 µg (7,500 IU) retinol equivalent MDD
Vitamin D (Cholecalciferol, ergocalciferol)	>75 µg (3,000 IU) MDD
Vitamin K (Phytomenadione)	No limit; Always POM**
Niacin (Nicotinic acid)	>600 mg MDD

MDD (maximum daily dose)

* POM levels are only applicable to products marketed as medicines

** POM level only applicable to parenteral use of vitamin K

1.9 Issues Arising Due to the Absence of Maximum Limits for Vitamins and Minerals added to Foods and used in Food Supplements

Maximum amounts permitted in foods or food supplements have yet to be set at EU level. In the absence of EU maximum levels, national rules apply. However, Ireland has no such national rules. Therefore, currently there is no maximum specified in EU legislation or Irish rules for vitamins and minerals added to food or food supplements. Vitamins and minerals can be added to foods and used in the manufacture of food supplements to a maximum level at the discretion of the manufacturer (provided there is no unsafe food placed on the market (Regulation 178).

In 2006, the Health and Consumer Protection Directorate-General held a consultation discussing the issues to be considered in the setting of maximum and minimum amounts for vitamins and minerals in foodstuffs. Ireland responded to this consultation in support of the establishment of such levels. Ireland outlined concerns relating to the potential risk posed to health by excessive intakes of micronutrients. However, there have been no maximum levels defined since this consultation was carried out and no time line has been provided to indicate when they will be established (Ireland's full response can be found online at the European Commission website: http://ec.europa.eu/food/safety/docs/labelling_nutrition-supplements-responses-ireland_en.pdf).

Food supplements marketed in Ireland usually provide at least 100% of the NRV per daily amount for vitamins and minerals. Many food supplement products provide vitamins and minerals in excess of NRV, with some approaching or exceeding the UL. These food supplements require risk assessment by the FSAI.

In the absence of EU permitted maximum amounts in food supplements, the FSAI must consider internationally established ULs to support enforcement decisions. The first stage of the risk assessment approach requires selection of the most appropriate UL to use when values differ between international bodies. The ULs are considered in an Irish context taking into consideration Irish dietary intake of vitamins and minerals. This report will provide information to food industry on the UL to be used when carrying out risk assessments on food supplements.

Voluntary food fortification in Ireland – different risk assessment procedures required

As previously noted, the voluntary fortification of all foods for general consumption allowing micronutrients to be added to food at any level (provided there is no unsafe food placed on the market (Regulation 178/2002)) is currently permitted in Ireland. There is no regulatory requirement to notify the authorities of fortified foods being placed on the market or levels of fortification.

The prevalence and level of fortification can affect the overall dietary intake of vitamins and minerals. The mandatory fortification of bread with folic acid was considered for Ireland as a measure to reduce rates of neural tube defects. Preparatory work for this fortification programme included an assessment of the current extent of voluntary folic acid fortification of food on the Irish market and more specifically the analysis of the current level of voluntary folic acid fortification of bread marketed in Ireland. This investigation highlighted some very important issues relating to voluntary fortification. Firstly, the data demonstrated that a wide range of foods were voluntarily fortified with folic acid and there was high variability in the amounts of folic acid added (as described in nutrient content declarations on food labels) between brands. There was also variability within brands, e.g. different breakfast cereals of the same brand providing 166 µg folic acid/100 g cereal v. 334 µg folic acid/100 g cereal, (Flynn *et al.*, 2008). A difference between actual folic acid content and levels declared on food labels was also detected in the fortified bread samples measured. Analysis revealed between 23 and 224% more folic acid than declared on food labels (Flynn *et al.*, 2008). While these findings only relate to folic acid fortified bread products, this level of 'overage' is a matter of concern, particularly if it is evident for other voluntarily-fortified foods.

Additionally, dietary surveys are often analysed in terms of the nutrient content declared on the label and if this 'overage' exists in other products there may be on-going under-estimation of actual nutritional intake, e.g. fortified foods claiming to be a 'source of' a particular vitamin or mineral must contain at least 15% of the NRV for that nutrient per 100g (in the case of beverages, it is 7.5% of the NRV per 100ml). Similarly, fortified foods claiming to be 'high/rich' in vitamins or minerals must contain 30% of the NRV per 100g for that nutrient (in the case of beverages, it is 15% of the NRV per 100ml).

As fortified foods contain much smaller levels of added vitamins and minerals, and consumers may passively consume several foods fortified with the same micronutrients, the risk assessment procedure needed to assess the safety of fortified foods requires a different approach to that needed for food supplements. Therefore, the current report exclusively looks at food supplements. Further work is required to develop an appropriate risk assessment approach that can be applied to establish MSLs for fortified foods in Ireland.

Within the EU, there are a number of health claims allowed for vitamins and minerals in foods, including general health claims, reduction of disease risk claims, and children's development and health claims (Regulation 1924/2006). In April 2014, analysis of the 250 authorised health claims found that 68% relate specifically to micronutrients (Ni Bhriain *et al.*, 2014). In order to bear a claim, the food must provide a minimum amount of the relevant micronutrient, usually equivalent to 15% or 30% of the NRV per 100g and 7.5% or 15% per 100 ml for beverages (Regulation 1169/2011). This legislation applies to nutrition and health claims made in all commercial communications. This legislation may encourage the fortification of foods to these minimum levels to bear claims and could result in increased intakes of vitamins and minerals as there may be a wider range of foods fortified with a wider range of nutrients.

Perhaps an unforeseen consequence of this regulation is that a low proportion of unfortified foods are permitted to bear claims. This was highlighted in a recent study comparing the nutritional composition of unfortified food to the minimum amount of a micronutrient required in in order to bear a claim (Ni Bhriain *et al.*, 2014). Unfortified foods within the fruit and vegetable food group and milk and milk products food group fared particularly poorly in this regard (Ni Bhriain *et al.*, 2014).

Table 1.5. Proportion (%) of Unfortified Foods within a Food Group Permitted to bear a Micronutrient Claim

Food Group (*n* unfortified foods)	Vitamin & Mineral Claim Median[a] (range[b])	Vitamin Claim Median (range)	Mineral Claim Median (range)
Meat, fish & alternatives group (*n*621)	26 (2-75)	13 (2-67)	28 (3-75)
Cereals, breads & potatoes group (*n*128)	14 (0-59)	7 (0-51)	22 (5-59)
Confectionery, biscuits & crisps group (*n*202)	10 (1-49)	9 (1-19)	15 (2-49)
Milk, yoghurt & cheese group (*n*80)	6 (0-81)	2 (0-74)	24 (0-81)
Fruit, vegetables & salads group (*n*404)	4 (0-48)	3 (0-48)	7 (0-29)
Fats, oils & spreads group (*n*53)	0 (0-53)	0 (0-53)	0 (0-34)

[a] The median value represents the mid value of the proportion of foods within a food group with the potential to bear a claim relating to any one of the 12 vitamins or any one of the 11 minerals

[b] The range represents the lowest and highest proportion of foods in a food group with the potential to bear a claim relating to any one of the 12 vitamins or any one of the 11 minerals

This shows that a relatively low proportion of unfortified foods have the potential to bear a claim.

1.10 Vitamin and Mineral Tolerable Upper Limits Suitable for Ireland

In the absence of EU established legal MSLs for vitamins and minerals, scientific recommendations are required to guide enforcement action by FSAI on food supplements and food containing added micronutrients (vitamins and minerals) exceeding levels that can be safely tolerated by the general healthy population (considering age, gender etc.).

A UL is the highest level of long term intake of a nutrient from all sources judged to be unlikely to pose a risk of adverse health effects to humans (IOM, 2006; EFSA, 2006). The UL is not a recommended level of intake but rather the highest level of intake deemed safe. As intake increases above the UL, the potential risk of adverse effects increases. In applying the UL value, it is important to take into consideration the magnitude of intake exceeding the UL and the duration of the excess intake on a case by case basis for each micronutrient. The need for setting ULs has grown out of two major trends: increased fortification of foods with vitamins and minerals and the use of food supplements by more people and at higher doses.

While ULs do not provide maximum levels for micronutrients permitted to be added to foods or used in the manufacture of food supplements, they provide an upper level that can be utilised to provide guidance and support with enforcement decisions when risk assessments are undertaken on vitamin and mineral food supplements. The UL value encompasses intake of the vitamin or mineral from all sources (food, food supplements, water etc.). Any MSLs for vitamin and minerals used in the manufacture of food supplements defined in the legislation in the future will be lower than the UL for the micronutrient to allow for intake of the micronutrient from the diet including fortified food and/or food supplement consumption.

Established international tolerable upper intake levels for vitamins and minerals

ULs for vitamin and minerals have been established by international committees including the EFSA and the IOM (see Appendix III). In this context, EFSA has examined 34 micronutrients and established 15 ULs (six for vitamins and nine for minerals). Similarly, the IOM has examined 34 micronutrients and established 24 ULs (eight for vitamins and 16 for minerals). The values and/or conclusions reached by these two institutions are not always consistent and this is due to a number of factors including differing food legislation and food environments. In addition, the expert panels operating for EFSA and the IOM may have established ULs at different time points, considered different studies and/or applied different uncertainty factors. The ULs established by EFSA may be most appropriate for Ireland given that Ireland is a European country. However, values established by the IOM should be considered to inform opinion and possibly provide a UL for micronutrients in the absence of an EFSA-established UL.

For some micronutrients, there are not enough data available to establish a UL. However, this does not mean that consuming large amounts poses no risks but rather is an indication that caution is necessary when consuming large amounts.

1.11 Risk Assessment of Micronutrients in Food Supplements

When consumed according to manufacturer's instructions, the daily amount of a micronutrient in a food supplement (as labelled) added to the usual daily intake from food sources (from foods including fortified foods, excluding supplements) of the highest consumers, i.e. the 95th percentile, should not exceed the UL for the population group(s) for whom the food supplement is intended.

In line with EU guidance on tolerances around labelled values, the measured amount of micronutrient takes precedence over the declared amount when considering safety of the supplement.

The daily amount from the food supplement should be based on the measured amount in the product as purchased, not the amount declared on the label. The intakes of the highest consumers, i.e. the 95th percentile, of micronutrients from food sources in different population groups may be obtained from the Irish national dietary surveys (see Appendix V), e.g. a supplement providing 10 mg vitamin B_6 as the daily amount declared by the manufacturer with the measured amount of 13 mg in the product as purchased, would be considered safe for adults but should be labelled as not suitable for children.

For adults, the daily amount from the supplement (13 mg) added to the 95th percentile of usual intake from food sources (up to 5.7 mg) gives a total intake of vitamin B_6 up to 18.7 mg which is less than the UL for adults (25 mg). For children aged 7-10 years, the daily amount from the supplement (13 mg) added to the 95th percentile of usual intake from food sources (up to 3.4 mg) gives a total intake of vitamin B_6 up to 16.4 mg which is greater than the UL for this age group (10 mg).

1.12 Recommendations

1. It is recommended that the UL and the 95th percentile intakes presented in this report are used for risk assessment of vitamins and minerals in food supplements on the Irish market.
2. It is recommended that risk assessment is carried out as follows:

   When consumed according to manufacturer's instructions, the daily amount of a micronutrient from a food supplement (as labelled) added to the usual daily intake from food sources (excluding food supplements) of the highest consumers (95th percentile), should not exceed the UL for the population group(s) for whom the food supplement is intended.
3. The FSAI should continue to monitor intakes of vitamins and minerals in population groups, including intakes from food supplements and fortified foods.

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CHAPTER 2. ABOUT THE WORKING GROUP AND METHODS

2.1 Task of the Safe Micronutrient Levels Working Group

The first task assigned to the FSAI Public Health Nutrition (PHN) Sub-committee was to develop scientific recommendations to guide enforcement action by the FSAI on food supplements and food containing added micronutrients (vitamins and minerals) exceeding levels that can be safely tolerated by the general healthy population (considering age, gender and pregnancy). At the first meeting of the PHN Sub-Committee, agreement was reached that a working group of experts should be assigned this task and a work plan for this group was devised. The Working Group was requested by the PHN Sub-Committee to develop recommendations for national ULs for micronutrients by examining those established by EFSA and the IOM in an Irish context.

The terms of reference of the Safe Micronutrient Levels (SML) Expert Working Group were to:

- Review ULs for micronutrients (vitamins and minerals) established by the EFSA and the IOM
- Prepare a report outlining scientific recommendations on national ULs for micronutrients to guide enforcement decisions by the FSAI on food supplements and food containing added micronutrients (vitamins and minerals) exceeding levels that can be safely tolerated by the general healthy population (considering age, gender and pregnancy)

2.2 Membership of the Safe Micronutrient Levels Expert Working Group

The SML Expert Working Group members were mainly drawn from PHN Sub-committee of the FSAI. The membership represented individuals with expert knowledge of vitamins and minerals, and technical ability and experience to develop scientific recommendations for national ULs. Two further external SML Working Group members with nutritional expertise were also nominated to join the group. Toxicology experts were consulted for specialist knowledge of particular micronutrients. The first meeting of the SML Expert Working Group took place in December, 2012.

2.3 Vitamins and Minerals Considered

The SML Expert Working Group agreed to review the upper safe levels of intake of vitamins and minerals permitted to be added to foods and/or used in the manufacture of food supplements under EU rules (Directive 2002/46/EC; Regulation 1925/2006). The micronutrients considered are outlined in Table 2.1 (the full list of all the forms of all the nutrients permitted to be added are outlined in Appendix I).

Table 2.1. Micronutrients Considered by the SML Working Group

Vitamins	Minerals and Trace Elements
Vitamin A	Calcium
β-carotene	Magnesium
Vitamin D	Phosphorus
Vitamin E	Sodium & Chloride
Vitamin K	Potassium
Thiamin (B_1)	Iron
Riboflavin (B_2)	Zinc
Niacin	Copper
Vitamin B_6	Selenium
Folic Acid	Iodine
Vitamin B_{12}	Manganese
Biotin	Molybdenum
Pantothenic Acid	Fluoride
Vitamin C	Chromium
	Boron
	Silicon*

* Permitted to be used in the manufacture of food supplements only under EU legislation (Directive 2002/46/EC).

2.4 Scientific Literature Considered

This report presents an expert review of the ULs established by international bodies in an Irish context. In preparing this report, the Working Group did not attempt to review all of the scientific evidence on which ULs could be based, as this evidence had already been reviewed thoroughly by expert committees including EFSA and the IOM. The Working Group studied such scientific reports and based on the most recent reviews available, made recommendations on ULs for Ireland for most micronutrients. The decisions reached by the Working Group were based on scientific merit and consideration of prevailing Irish conditions.

For the micronutrients, molybdenum, fluoride and boron, EFSA has used reference body weights ranging from 58-72kg when deriving these ULs. These reference body weights are not gender specific and are low compared with current average weights for adult men and women in Ireland (86kg and 70kg respectively). Therefore, both the FSAI and EFSA agree that it would be more appropriate to use a reference body weight of 70kg (for both sexes) when deriving the ULs of these micronutrients for the adult population of Ireland. Table 2.2 outlines the reference body weights used by EFSA to derive the adult ULs for these named micronutrients as well as the re-calculated EFSA ULs using the reference body weight of 70kg for adults.

Table 2.2. EFSA Tolerable Upper Intake Levels Established for Adults using a Variable Reference Body Weight (58-72kg) and a Reference Body Weight of 70kg

Micronutrient (year UL was established)	Upper level of intake per kg body weight per day	EFSA established UL for adults using various reference body weights		EFSA UL for adults recalculated using a reference body weight of 70kg	
		Reference body weight (kg)	UL	Reference body weight (kg)	UL
Molybdenum (2000)	0.01 mg/kg body weight /day	60	0.6 mg/day	70	0.7 mg/day
Fluoride (2005)	0.12 mg/kg body weight/day	58	7 mg/day	70	8 mg/day
Boron (2004)	0.16 mg/kg body weight/day	62.5	10 mg/day	70	11 mg/day

2.5 General Principles for Assessing Micronutrients

The overall format of the report and each of the sections on the individual micronutrients was discussed by the Working Group members in great detail. A template was prepared by members outlining all aspects that need to be considered for each micronutrient in the context of establishing a UL, e.g. function, bioavailability, deficiency etc. This included a section where any UL established by other national, e.g. Nordic, and international organisations such as EFSA or the IOM was examined on the scientific merit of the evidence presented.

The task of preparing a short report on each of the vitamins and minerals under consideration was undertaken by members of the Working Group in conjunction with the FSAI. Each report included a recommendation on which UL, if any, Ireland should adopt for the vitamin or mineral being considered. Each micronutrient report was discussed at a meeting of the Working Group for feedback and comments. All micronutrient reports were amended with feedback during this process.

A decision was made by the Working Group that the inclusion of information on dietary reference values and the prevailing Irish diet was very important to provide context for the ULs.

CHAPTER 3. MICRONUTRIENT TOLERABLE UPPER LIMIT REPORTS

3.1 Vitamins

Vitamin A

Background

a) Description of vitamin A

Vitamin A is a generic term used to designate any compound possessing the biological activity of retinol. Until recently, the term 'retinol equivalents' (REs) was used to convert all sources of preformed retinol and provitamin A carotenoids in the diet into a single unit.

Table 3.1. Inter-conversion of Vitamin A and Carotenoid Units

1 µg retinol equivalents (RE)
=1 µg of all-*trans*-retinol
=2 µg of supplemental (in oil) all-*trans*-β-carotene
=6 µg of dietary all-*trans*-β-carotene
=12 µg of other dietary pro-vitamin A carotenoids

When defining RE, it was assumed that the efficiency of absorption of pro-vitamin A carotenoids was relatively good. Recent studies document however, that absorption of carotenoids is much lower and appears to be quite variable.

Vitamin A, its analogues and its metabolites, function in vision, cell differentiation, embryogenesis, the immune response, reproduction and growth. Carotenoids also have a variety of different actions, including possible antioxidant activity, immune-enhancement, inhibition of mutagenesis and transformation and reduced risk of age-related macular degeneration and cataracts, decreased risks of some cancers, and decreased risk of cardiovascular events.

Vitamin A deficiency is common in the developing world but is rare in developed countries. Severe deficiency causes night blindness and xerophthalmia - Bitot's Spots, xerosis conjunctiva and keratomalacia. Night blindness is just one of the stages where vitamin A deficiency reduces the ability to see. The other deficiency diseases are the result of abnormal functioning of epithelial cells on the surface of the eye. Other consequences of vitamin A deficiency include: impaired cell differentiation and development - replacement of mucus-secreting cells with keratin-secreting cells; reduced immunity to viral infection; impaired reproduction (male and female); abnormal growth; reduced ferritin synthesis; loss of appetite, reduced growth, severe weight loss, death. Individuals following a low-fat diet over prolonged periods are at increased risk of the consequences of vitamin A deficiency.

The hormonal forms of vitamin A (retinoic acid) and vitamin D (calcitriol) interact at the molecular level. Some classes of medications are known to interact with vitamin A such as; tetracycline antibiotics, antacids, anticoagulants, cholesterol-lowering medications.

b) Different forms of vitamin A and clarity on the forms of vitamin A that are relevant to the UL

Dietary vitamin A is absorbed in the upper part of the small intestine, by mechanisms similar to those of lipid absorption. Retinyl esters undergo hydrolysis by pancreatic lipase (short chain esters) and an enzyme in the intestinal brush border (long chain esters). The dietary retinyl esters are hydrolysed in the intestine by pancreatic triglyceride lipase, and the intestinal brush border enzyme, phospholipase B. The unesterified retinol, at physiologic and pharmacologic concentrations, is taken up by the enterocytes, perhaps involving both diffusion and protein-mediated facilitated transport systems. Once in the cell, retinol is complexed with cellular retinol-binding protein type II (CRBPII) and the complex serves as a substrate for re-esterification of the retinol by the enzyme lecithin: retinol acyltransferase (LRAT) and the retinyl esters are incorporated into chylomicrons. The liver is the major storage site for vitamin A, which is mainly localised in lipid droplets of hepatic stellate cells (also known as Ito cells or lipocytes). The liver has a very high, but not unlimited, storage capacity for vitamin A.

Vitamin A is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I. There is no evidence of adverse effects resulting from the consumption of vitamin A naturally occurring in foods.

The toxicity of pharmacological doses of vitamin A does not occur with the intake of high doses of provitamin A carotenoids such as β-carotene, since only the required amount is metabolised to retinol. Therefore, to address the risk of hypervitaminosis A on various health outcomes, only preformed retinol intakes have been investigated. Unequivocal evidence which shows that retinoids are teratogenic in humans who have been inadvertently exposed to prescription drugs containing 13-cis-retinoic acid or etretinate. Of the many malformations observed in infants born to women exposed to 13-cis-retinoic acid, defects of the central nervous system such as hydrocephalus, cerebellar hypoplasia, absence of vermis, and structural malformation of the cerebral cortex were among those reported most often. In addition, craniofacial abnormalities, including cleft palate and either absent or reduced size of the external ears and canals; heart defects; and thymus abnormalities, are also commonly observed in these children. More importantly, human embryos are more sensitive to 13-cis-retinoic acid (1 mg/kg per day) compared to monkeys and rabbits (5 mg/kg per day) and even more than mice and rats (75 mg/kg per day). The observed higher sensitivity to 13-cis-retinoic acid could potentially be explained by differences in plasma half-life and placental transfer rates between species. It is currently recommended that women who are planning to become pregnant or who are pregnant should not consume cooked animal liver or other organ meats which are extremely rich sources of vitamin A. Because the current intakes may exceed the tolerable upper levels, careful consideration should be given to the appropriateness of the enrichment of foods with preformed vitamin A. Excessive vitamin A intake also produces other adverse effects including hepatotoxicity, bulging fontanelle in infants/intracranial pressure, adverse effects on bone and lipid metabolism (discussed below).

Good dietary sources of vitamin A include milk, cheese, eggs, fortified low-fat spreads, yoghurt and meat and meat products. Liver is a particularly rich source of preformed vitamin A, with concentrations (µg/100 g) in pig, lamb, calf and chicken livers of 25,700 µg, 19,700 µg, 25,100 µg and 10,400 µg, respectively.

c) Usual intakes, RDAs, AIs

Both the IOM and EFSA have set an RDA for vitamin A (see Appendix IV). The average intakes of vitamin A in Ireland are outlined in Appendix V.

ULs established by other organisations

The safety margin (margin between recommended intake and the intake which causes harm) is low (less than five-fold) in the case of preformed vitamin A which makes the derivation of a UL difficult.

Of particular importance in the setting of an upper level, is the role of retinoic acids during morphogenesis and embryonic development. It has long been recognised that abnormal foetal development is associated with either insufficient or excessive intakes of vitamin A and related compounds. A prospective, non-randomised study by Rothman *et al*. (1995) is the only investigation conducted in a large study population (~22.500 persons) in which a link was established between supplementation of moderate retinol amounts (from 3,000 µg/day) prior to the 7th week of pregnancy and a higher risk of malformations in newborn babies. The quantitative conclusion from the Rothman study was that 3,000 µg RE/day of supplemental vitamin A can be considered as a threshold for teratogenicity. Both EFSA and the IOM agree that it seems reasonable to conclude that a daily intake of 3,000 µg RE/day would be associated with a low or negligible risk of teratogenicity. An uncertainty factor is not considered necessary because the data from other studies indicated that the true threshold for an effect could be higher than this value. Based on these studies, a tolerable upper level of 3,000 µg RE/day is suggested for all women of child-bearing age (because the risk occurs very early in pregnancy). This value is 2.5-fold lower than the daily intake that might cause hepatotoxicity in women during chronic intake.

A number of adverse effects have been reported at intakes of preformed vitamin A above the population reference intake (in both EFSA and the IOM reports). The lowest doses reported to produce the different effects, are:

Bulging fontanelle	7,500 µg RE (as a single dose in infants)
Hepatotoxicity	7,500 µg RE/day for six years
Effects on bone metabolism	1,500 µg RE/day (trend analyses do not show a threshold)
Lipid metabolism	7,500 µg RE/day for four years (but a minor change only)
Teratogenicity	>3,000 µg RE/day (based on Rothman *et al*.)

Based on well-founded data on hepatotoxicity (in all adults) and teratogenicity in women of childbearing age, the UL for preformed vitamin A (retinol and retinyl esters) has been set at 3,000 µg RE/day for adults by both EFSA and the IOM. The UL for children and teenagers includes correction for differences in basal metabolic rate compared to adults using scaling according to body surface area (body weight to the power of 0.75). According to EFSA, further recommendations addressing the possible risk of bone fracture in postmenopausal women, who are at greater risk of osteoporosis and fracture, suggested to restrict the intake to 1,500 µg RE/day of preformed vitamin A (retinol and retinyl esters). The findings on bone density and the risk of fracture were reported in some epidemiological studies at lower daily intakes than other adverse effects. However, the accuracy and reliability of dietary assessment methods used to estimate vitamin A intake in some of these studies is questionable as in order to estimate long-term intake of vitamin A with any extend of accuracy, dietary records would have to be kept for a minimum of 15 weeks. EFSA and the IOM concluded that the currently available data on vitamin A intake and bone health do not provide sufficient evidence of causality and are therefore, not appropriate for establishing a tolerable upper level in either report.

EFSA did not determine a UL for infants < one year. The IOM established a UL of 600 µg/day using data from a number of case reports of infants and toddlers who showed toxic effects due to excess vitamin A intakes for months to years. Of particular concern are intracranial (bulging fontanel) and skeletal abnormalities that can result in infants given vitamin A doses of 5,500 to 6,750 µg/day.

However, it is worth noting that some exclusively and predominantly breast-fed infants (generally those that are 'bigger babies' due to their higher milk intake) can exceed the UL of 600 µg/day. This transient exposure to vitamin A levels above the UL occurs around the age of six months, at a time when milk intake is at its peak, as they approach the period when they begin to require solid food and calorie requirements are higher.

Preformed retinol intakes in relation to the UL (UK data only)

There is consensus within Europe that older population groups particularly consume preformed vitamin A up and above the safe upper limit of 3,000 µg/day, and that mostly liver and liver products are solely responsible for the high intake levels. Data from the UK NDNS show that the 97.5 percentile intake in 2000 was 3,659 µg in men and 1,498 µg in all women, with a clear trend of higher 97.5 percentile levels in older men (5,168 µg; 50-64 years) and women (3,190 µg; 50-64 years). The 97.5 percentile level in 2009/10 is lower in men (19-64 years) at 1,928 µg but similar in women (19-64 years) at 2,427 µg. Again, like in 2000, there is a clear trend of higher 97.5 percentile concentrations in men (6,024 µg; 64+ years) and women (3,973 µg; 64+ years). Total liver consumption decreased dramatically from 1986 to 2000 and further to 2009/10 from 30 g/week to 15 g/week and finally to 2 g/week in all men, and in male consumers from 127 g/week to 133 g/week to finally 55 g/week. Similar trends are observed for women with total liver consumption decreasing from 1986 to 2000 and further to 2009/10 from 28 g/week to 6 g/week and finally to 2 g/week, and in female consumers from 114 g/week to 97 g/week to 24 g/week.

The downward trend in liver consumption between 1986 and 2000 is most likely due to a reduction in total liver consumers from 23% to 12% in men and from 24% to 7% in women aged 19-64 years. However, % liver consumers did not change from 2000 to 2009/10, with 12% and 15% for men, and 7% in both years for women. Thus, the change from recording diets from a seven day food diary in 2000 to a four day food diary in 2009/10 is most likely the reason for the strong reduction in weekly liver portions observed in both male and females. Preformed retinol intakes for older males and females were recorded with 5,211 µg/day and 5,446 µg/day at the 97.5 percentile and 6,717 µg/day and 6,940 µg/day at the 97.5 percentile, respectively. Thus, in this dataset, a minimum of 5% of older female and male subjects are above the UL of 3,000 µg/day, whereas this is reduced to a minimum of 2.5% in men and women aged 19-64 years. However, it should also be noted that suboptimal vitamin A intakes have also been described in Western societies. Indeed, a majority of the U.K. population's vitamin A requirements are not met by dietary intake of preformed retinol, and 15% of young individuals aged 19-24 years have a total vitamin A intake below the lower recommended nutrient intake level.

Special considerations

As described above, those most at risk for the toxic effects of excess vitamin A are pregnant women and infants. Thus, pregnant women are advised to avoid any liver or liver-containing products (such as liver pate and liver sausage) during pregnancy. As outlined above, liver consumers are particularly at risk of exceeding the UL but this risk is primarily dependent on the frequency of consumption. People who consume liver at least once a fortnight should not take vitamin A-containing supplements as this will very likely result in vitamin A intakes above the UL.

Conclusions

The EFSA UL values are considered most appropriate for Ireland with the inclusion of the IOM UL for infants under one year of age (EFSA did not set a UL for this age group; the IOM established a UL of 600 µg/day using data from a number of case reports of infants and toddlers who showed toxic effects due to excess vitamin A intakes for months to years). The derivation of a UL for vitamin A is difficult given the low safety margin (margin between recommended intake and the intake which causes harm). Both EFSA and the IOM set a UL for vitamin A of 3,000 µg RE/day for adults based on data on hepatotoxicity (in all adults) and teratogenicity in women of childbearing age.

The UL for children and teenagers includes correction for differences in basal metabolic rate compared to adults using scaling according to body surface area.

Recommendations for Ireland

It is recommended that Ireland adopt the EFSA UL (EFSA, 2006) and it is recommended that Ireland adopt the IOM UL for infants <one year (IOM, 2001) as shown in Table 3.2.

Table 3.2. Tolerable Upper Intake Level for Vitamin A as Preformed Vitamin A (retinol and retinyl esters) only (µg/RE/day) (EFSA, 2006; IOM, 2001)

Age (years)	Vitamin A (µg/day)
<1 year	600*
1-3 y	800
4-8 y	1,100
9-13 y	1,500
14-18 y	2,000 – 2,600
Adults+	3,000

*The IOM value for infants < one year recommended

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β-carotene

Background

a) Description of β-carotene

β-carotene and carotenoids in general, are isoprenoid compounds which are not synthesised in animals but biosynthesised by plants and micro-organisms. They act as precursors to retinol and thus, are considered pro-vitamin A. Vitamin A is a generic term used to designate any compound possessing the biological activity of retinol. Until recently, the term 'retinol equivalents' (REs) was used to convert all sources of preformed retinol and provitamin A carotenoids in the diet into a single unit.

Table 3.3. Inter-conversion of Vitamin A and Carotenoid Units

1 µg retinol equivalents (RE)
=1 µg of all-*trans*-retinol
=2 µg of supplemental (in oil) all-*trans*-β-carotene
=6 µg of dietary all-*trans*-β-carotene
=12 µg of other dietary pro-vitamin A carotenoids

When defining RE, it was assumed that the efficiency of absorption of pro-vitamin A carotenoids was relatively good. However, recent studies document that absorption of carotenoids is much lower and appears to be quite variable.

The best-characterised natural function of β-carotene and its sister carotenoids is to serve as light-absorbing pigments during plant photosynthesis and protection of cells against photosensitisation. Carotenoids including β-carotene have a variety of different actions in humans, including possible antioxidant activity (such as quenching singlet oxygen), immune-enhancement, inhibition of mutagenesis and transformation and reduced risk of age-related macular degeneration and cataracts, decreased risks of some cancers, and decreased risk of cardiovascular events. If plasma carotenoid concentrations are considered as an indicator of adequacy with regard to reducing risk of chronic disease, it becomes apparent that certain subgroups of the population, including adolescents, are known to have notably lower circulating concentrations of carotenoids.

When adequate retinol is provided in the diet, there are no known clinical effects of consuming diets low in carotenes over the short-term. However, carotene-deficient diets were reported to increase various measures of oxidative susceptibility (Dixon *et al.*, 1998; Lin *et al.*, 1998), but this is of uncertain relevance with regard to clinical outcomes.

b) Different forms of β-carotene and clarity on the forms of β-carotene that are relevant to the UL

Competitive interactions among different carotenoids during the absorptive process are known.

The vitamin A-active carotenoids such as β-carotene are considered to have pro-vitamin A activity until they undergo oxidative enzymatic cleavage of the central C15:C15' bond in the intestinal mucosa to yield two molecules of retinal, which can either be reduced to retinol or oxidised to retinoic acid. After the consumption of carotenoid-containing foods, carotenoids are released from their food matrix and, like retinol, are incorporated into mixed micelles. β-carotene is partly converted to vitamin A in the intestinal mucosa. The key step is the oxidative central cleavage of β-carotene at the central 15:15' double bond by β-carotene 15,15'-monooxygenase. The retinal formed from carotenoids is reduced to retinol and further converted to retinyl ester by retinal reductase and lecithin-retinol acyltransferase (LRAT) with the aid of CRBP-II and thereafter incorporated into chylomicrons. The extent of conversion of a highly bioavailable source of β-carotene to vitamin A in humans is considered to be between 60 and 75%, with an additional 15% of β-carotene absorbed intact.

The toxicity of pharmacological doses of vitamin A does not occur with the intake of high doses of β-carotene, since only the required amount is metabolised to retinol. No adverse effects other than carotenodermia, which is characterised by a yellowish discolouration of the skin, have been reported from the consumption of β-carotene or other carotenoids in foods. In addition, long-term supplementation with β-carotene to persons with adequate vitamin A status does not increase the concentration of serum retinol.

β-carotene is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I. There is no evidence of adverse effects resulting from the consumption of β-carotene naturally occurring in foods.

c) Usual intakes, RDAs, AIs

Good dietary sources of β-carotene include carrots, orange juice, oranges, tomatoes and dark green leafy vegetables. In the majority of industrialised countries, fruits and vegetables provide an estimated 2-3 mg/day of pro-vitamin A carotenoids, of which β-carotene is the principal component. However, levels of fruit and vegetable consumption, vary greatly between individuals and β-carotene intake may be much higher than average in people who regularly consume substantial amounts of foods such as carrots. Data from the NSIFCS in 2000 revealed mean daily carotene intakes of 2,543 µg and 2,312 µg, in 18-64 year old men and women, respectively. The primary sources of carotene in the total population were vegetables and vegetable dishes (59.8%) and meat and meat products (14.3%). More recent data from NANS in 2011 show higher carotene intake estimates than the NSIFCS with mean intakes of 3,660 µg and 3,629 µg in 18-64 year-old men and women, respectively. The average intakes of β-carotene in Ireland are outlined in Appendix V.

No recommended intakes have been established by the IOM or EFSA.

ULs established by other organisations and rationale behind values

There is insufficient scientific basis to set a precise figure for an UL of isolated β-carotene as no dose-response relationship for β-carotene effects is available either from the intervention trials in humans or from appropriate animal models.

Therefore, EFSA and the IOM have not set a UL for β-carotene.

Special considerations

There is a concern among heavy smokers and asbestos workers regarding the use of β-carotene supplements. This concern for heavy smokers relates to two independent trials which showed that heavy smokers (at least one package/day for 36 years on average) receiving long-term β-carotene (20 mg/day) supplementation or β-carotene (30 mg/day) + retinol (25,000 IU vitamin A) supplementation, showed increased rather than decreased incidence of lung cancer. A meta-analysis of randomised controlled trials found an increased risk of lung cancers in individuals supplemented with β-carotene at dose levels ≥20mg/d as well as in smokers and asbestos workers supplemented with β-carotene. Epidemiological studies do not support an increased risk of cancer in heavy smokers taking up to 15 mg of supplemental β-carotene daily. EFSA indicates that exposure to 15 mg or less β-carotene from food additives and/or supplements does not give rise to concerns about adverse effects in the general population or in heavy smokers.

Conclusions

The EFSA guidance level for β-carotene supplementation of <15 mg/day is considered most appropriate for Ireland. Neither EFSA nor the IOM have set a UL for β-carotene due to a lack of sufficient data. However, EFSA has concluded that exposure to a level below 15 mg/day of β-carotene from food supplements and/or food additives, does not give rise to concerns about adverse effects in the general population or in heavy smokers.

Recommendations for Ireland

It is recommended that Ireland adopts a guidance level for β-carotene supplementation of <15mg/day.

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- **Statement on the safety of β-carotene in heavy smokers (2012)** *EFSA Journal* 10(12):2953

Vitamin D

Background

a) Description of vitamin D

Vitamin D_3 (cholecalciferol) is produced in skin upon exposure to solar UVB radiation (290–315 nm) as follows: 7-dehydrocholesterol (pro-vitamin D_3) in the epidermis is converted to pre-vitamin D_3, which is then modified to vitamin D_3 at skin temperature. This mechanism is tightly regulated and prolonged exposure to sunlight does not cause toxicity due to photo-degradation of pre-vitamin D_3 and vitamin D_3. Dietary vitamin D (D_2 and D_3) is absorbed with other dietary fats, in the small intestine through lipid micelles by passive diffusion. Due to its hydrophobic structure, the efficiency of absorption of vitamin D is dependent upon the presence of fat in the lumen.

Vitamin D itself is biologically inactive and has a short half-life in circulation as it is either immediately sequestered by adipose tissue or further metabolised. It is transported by vitamin D binding protein (DBP) to the liver where it is metabolised to 25(OH)D, which is the appropriate biochemical marker of vitamin D status, as it reflects total exposure from the dietary supply and dermal production (Seamans and Cashman, 2009). 25(OH)D is then carried by DBP to the kidney where it is further hydroxylated to $1,25(OH)_2D$, the biologically active form. $1,25(OH)_2D$ is transported to target organs bound to DBP but it enters a target cell in its free form. Should increased circulating 25(OH)D and its deactivation product concentrations exceed the binding capacity of DBP, free 25(OH)D and $1,25(OH)_2D$ may enter target cells, bind to the vitamin D receptor (VDR) located in the nucleus and influence gene expression (Bouillon *et al.*, 2008). VDRs are present in most organs in the body, including the brain, heart, skin, gonads, prostate, breast, and mononuclear cells and are therefore associated with multiple physiological functions.

The most extensively documented function of vitamin D is regulation of serum calcium and phosphate homeostasis, a critical component of normal skeletal mineralisation throughout the growing years and during the ageing process. $1,25(OH)_2D$ regulates its own synthesis through a negative feedback system, involving the intestine, kidneys, parathyroid glands and bone, under the regulation of parathyroid hormone (PTH) which responds to changes in circulating $1,25(OH)_2D$, calcium and phosphate levels (Jones *et al.*, 1998). Renal synthesis of $1,25(OH)_2D$ is up-regulated by PTH and down-regulated by fibroblast-like growth factor-23 (FGF23). Low serum phosphate or calcium concentrations stimulate conversion of 25(OH)D to $1,25(OH)_2D$ in the kidney, while high concentrations inhibit it. Increases in $1,25(OH)_2D$ normalise serum calcium by enhancing dietary calcium absorption in the intestine, increasing urinary calcium re-absorption in the kidney, and mobilising calcium from bone (IOM, 2011; EFSA, 2012).

While the major source of vitamin D in humans is cutaneous synthesis of cholecalciferol, there are several environmental factors that impede year-round synthesis, such as latitude and prevailing weather conditions, which determine availability of UVB of sufficient intensity to stimulate skin synthesis. Personal characteristics, such as skin pigmentation, age, attire, sunscreen, working environment, physical activity, and sun exposure behaviour can also prevent or impede vitamin D synthesis. Thus, substantial portions of the world's population, including all who reside at latitudes greater than ~40°, e.g. in Europe all who reside at a latitude above Rome, rely on body stores and dietary sources to maintain adequate vitamin D status all year round. Given that body stores, which have yet to be fully defined, are dependent on sun exposure, the importance of vitamin D intake to overall vitamin D status is a corollary of UVB sunshine deficit (Holick, 2008; Kiely & Black, 2012).

b) Different forms of vitamin D and clarity on the forms of vitamin D that are relevant to the UL

There are very few rich natural sources of vitamin D; the main dietary sources are oily fish, cod liver oil, egg yolk and fortified foods. Ergocalciferol (vitamin D_2) is synthesised by irradiation of plants or plant materials, and found in mushrooms or UV-irradiated yeast. Both vitamin D_2 and D_2 are used in nutritional supplements, which substantially increase intakes in users. As the natural supply of vitamin D in the diet is insufficient to meet vitamin D requirements (Kiely and Black, 2012), careful application of fortification and bio-fortification strategies could safely increase intakes of vitamin D across the distribution and prevent deficiency (Calvo, 2005). A recent systematic review and meta-analysis of the impact of vitamin D fortification in randomised controlled trials showed a consistent effect of fortification on increasing serum 25(OH)D concentrations (Black *et al.*, 2012). Currently in Ireland, vitamin D fortification is on a voluntary basis and fortified foods contribute significantly to total vitamin D intake (Black *et al.*, 2013; 2014).

Concentrations of circulating 25(OH)D increase in response to ingestion of vitamin D and reach a steady state after six to eight weeks. If the dose of vitamin D increases, circulating 25(OH)D will continue to rise. High serum 25(OH)D concentrations (> 220 nmol/L) may lead to hyercalcaemia (Vieth, 1999), defined as a serum calcium > 2.63 - 2.75 mmol/L (as defined by individual laboratory reference ranges) and is mainly related to primary hyperparathyroidism or malignancy, but can also be induced by very high calcium or vitamin D intakes. Vitamin D ingested orally is relatively safe and toxicity is not apparent at doses up to 250 µg/day (IOM, 2011; EFSA 2012). However, the International Agency for Research on Cancer (IARC, 2008) among others, has pointed out that there are no data on the health hazards of maintaining high serum 25(OH)D in healthy persons over long periods, and urged caution in light of past experiences with other compounds, e.g. some anti-oxidants and hormone replacement therapies, that showed serious adverse effects when chronic high dose supplements were used. Over and above the risk of hyercalcaemia, recent reports of U- and reverse J-shaped distributions have emerged for serum 25(OH)D and adverse consequences, including all-cause mortality, cardiovascular disease risk, PTH suppression and intrauterine growth restriction, which deserve serious consideration by both researchers and authoritative agencies.

c) Usual intakes, RDAs, AIs

The IOM and EFSA have set an RDA and AI, respectively, for vitamin D (see Appendix IV). The average intakes of vitamin D in Ireland are outlined in Appendix V.

ULs established by other organisations

The ULs for vitamin D have recently been revised by both the IOM (2011) and EFSA (2012). These ULs were established on the basis of minimising the risk of hyercalcaemia and using evidence from vitamin D supplementation studies. An additional cautionary note was introduced due to the lack of empirical data on the potential adverse effects of chronic high consumption of vitamin D producing a sustained serum 25(OH)D above ~125-150 nmol/L. Thus, to maximise public health protection, an uncertainty factor of 1.2 to 2 was applied and both agencies assigned a UL for vitamin D of 100 µg/day for all adults including pregnant and lactating women (IOM 2011, EFSA 2012). The ULs proposed by both organisations were generally similar with slight variation among children.

EFSA (2012) set a UL for vitamin D of 25 µg/day for infants up to one year; 50 µg/day from one to ten years and 100 µg/day for children aged 11 years and over. The IOM (2011) scaled the UL by body size as follows: 25 µg/day for infants aged one to six months, increasing to 38 µg/day up to 12 months, 63 µg/day for one to three year olds and 75 µg/day from four to eight years. The UL for children aged nine years and over is the same as adults, at 100 µg/day. These ULs are much higher than the habitual intakes of vitamin D in Ireland when the contributions from the base diet, fortified foods and supplements, have been considered (Black *et al.*, 2014).

Since the IOM and EFSA published their reports, Gallo *et al.* (2013) reported a randomised controlled trial in infants in Montreal. Briefly, a dose-response study in 132 one-month old infants was conducted to test the efficacy of vitamin D at 10, 20, 30 and 40 µg/day in maintaining 25(OH)D concentrations >75 nmol/L. Infants were followed for eleven months. By three months, 55% of infants in the 10 µg/day group and 80-100% of those in the higher doses had a 25(OH)D ≥ 75 nmol/L. 97% of infants in all groups achieved 50 nmol/L or higher at three months and almost everyone sustained this to 12 months. Growth and bone mineral content did not differ by dosage. The authors discontinued the 40 µg/day dose prematurely because almost all infants on this dose had serum 25(OH) D concentrations ≥ 250 nmol/L by three months of age. In addition to valuable information on the nutritional requirement for vitamin D in infancy, these data provide evidence to justify a more conservative UL in this life stage.

Conclusions

The EFSA ULs for vitamin D are considered most appropriate for Ireland. Both EFSA and the IOM ULs were established on the basis of minimising the risk of hypercalcaemia and using evidence from vitamin D supplementation studies. The IOM has set the similar ULs for vitamin D with slight differences in the age-groups and ULs set for children.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for vitamin D (EFSA, 2012) as shown in Table 3.4.

Table 3.4. Tolerable Upper Intake Level for Vitamin D (EFSA, 2012)

Age (years)	Vitamin D (µg/day)
0-1 y	25
1-10 y	50
11-17 y	100
Adults ≥18 y	100

References:

- **Black LJ, Seamans KM, Cashman KD, Kiely M (2012)** An updated systematic review and meta-analysis of the efficacy of vitamin D food fortification. *Journal of Nutrition*; 142(6):1102-8
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- **Seamans KM and Cashman KD (2009)** Existing and potentially novel functional markers of vitamin D status: a systematic review. *American Journal of Clinical Nutrition*, 89, 1997S-2008S
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Vitamin E

Background

a) Description of vitamin E

The term vitamin E describes a family of eight fat-soluble compounds that are classified as either tocopherols or tocotrienols. The most biologically active compound is the naturally occurring form of α-tocopherol and vitamin E intake is normally expressed in terms of mg α-tocopherol equivalents. Synthetic α-tocopherol does not have the same biological potency as the naturally occurring compound because the stereochemistry of the synthetic compound differs from that of the naturally occurring vitamin.

This fat-soluble nutrient functions as a radical-trapping antioxidant in cell membranes and plasma lipoproteins. Vitamin E is of particular importance in limiting the oxidative radical damage of polyunsaturated fatty acids (PUFAs).

Tocopherols and tocotrienols are absorbed unchanged from the small intestine, in micelles with other dietary lipids, and then incorporated into chylomicrons. The major route of excretion is in bile. Tissue uptake of vitamin E can occur via two mechanisms. Lipoprotein lipase releases the vitamin by hydrolysing the triacylglycerols in chylomicrons and very low-density lipoproteins (VLDLs) while separately, there is uptake of low-density lipoprotein (LDL)-bound vitamin E by means of LDL receptors.

Vitamin E deficiency is rare and generally only occurs as a result of abnormalities of vitamin E metabolism, fat malabsorption syndromes, cystic fibrosis, some forms of chronic liver disease and protein-energy malnutrition. Premature infants are also at risk of vitamin E deficiency. The primary effect of vitamin E deficiency is damage to nerve and muscle membranes. In premature infants the main sign of deficiency is haemolytic anaemia due to fragility of red blood cell membranes.

Vitamin E interacts with a number of other nutrients. The presence of other antioxidants, such as Vitamin C and β-carotene support the antioxidative action of vitamin E. The same is true for selenium. Vitamin E also interacts negatively with iron whereby iron reduces the availability of vitamin E to the body when taken at the same time. Vitamin K deficiency may also be exacerbated by vitamin E. The vitamin E metabolite, tocopherylquinone, is structurally similar to vitamin K and may inhibit vitamin K metabolism and thus coagulation.

b) Different forms of vitamin E and clarity on the forms of vitamin E that are relevant to the UL

Plant oils are the most important dietary sources of vitamin E in addition to nuts, whole grains and wheat germ. Other sources are seeds and green leafy vegetables, with meat and dairy products providing relatively low amounts of vitamin E. There is no evidence of adverse effects resulting from the consumption of vitamin E naturally occurring in foods.

Vitamin E is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

c) Usual intakes, RDAs, AIs

It is difficult to establish vitamin E requirements, particularly as the requirement depends on the intake of PUFAs. It is generally recognised that an acceptable intake of vitamin E is 0.4 mg α-tocopherol equivalent/g dietary PUFA. The IOM and EFSA have set an RDA and AI, respectively, for vitamin E (see Appendix IV). The average intakes of vitamin E in Ireland are outlined in Appendix V.

ULs established by other organisations

In the EFSA report (2004), the term vitamin E is related to α-tocopherol equivalents. EFSA decided that the critical effect on which the UL for vitamin E should be based, is blood clotting in humans. A study investigating the biochemical and physiological effects of vitamin E was used to establish the UL. The findings of this study indicate that supplemental doses of up to 800 IU (540 mg) are without adverse effects. Using these data, a NOAEL of 540 mg/day was chosen and an uncertainty factor of two was used to derive a UL for vitamin E of 270 mg/day for adults, rounded up to 300 mg/day. This UL also applies to 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. The EFSA UL for vitamin E represents total intake from food, water and supplements.

The IOM (2000) used data sets, including studies showing haemorrhagic toxicity in rats, to establish a UL for vitamin E. A LOAEL of 500 mg/kg/day was divided by the overall uncertainty factor of 36 to obtain a UL value of 14 mg/kg/day for adult humans. This was multiplied by the average of the reference body weights for male and female adults (68.5kg). The resulting UL for adults is 959 mg/day, rounded up to 1,000 mg/day. The UL for toddlers, children and adolescents is extrapolated from the adult UL based on body weight difference. The UL for adults also applies to women during pregnancy and lactation. Unlike the EFSA established UL, the IOM UL only applies to any form of supplemental α-tocopherol, i.e. synthetic forms obtained from supplements, fortified foods or a combination of these two forms.

Special considerations

For certain subgroups of the population, the UL for vitamin E may not be applicable. These subgroups include:

- Individuals with vitamin K deficiency caused by:
  - Malabsorption
  - Therapy with anti-coagulants
  - Conditions where the synthesis of vitamin K by the gut microflora might be impaired
- Individuals taking aspirin. There is evidence that aspirin in combination with vitamin E, can increase the risk of haemorrhage

Conclusions

The EFSA ULs for vitamin E are considered most appropriate for Ireland. A study investigating the physiological and biochemical effects of vitamin E was used to establish the UL with blood clotting being the critical effect on which the UL should be based. The EFSA UL for vitamin E is 300 mg/d and represents total intake from food, water and supplements. The IOM has derived a UL of 1,000 mg/d however, this only applies to any form of supplemental Ð-tocopherol, i.e. synthetic forms obtained from supplements, fortified foods or a combination of both.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for vitamin E (EFSA, 2004) as shown in Table 3.5.

Table 3.5. Tolerable Upper Intake Level of Vitamin E (EFSA, 2004)

Age	Vitamin E (mg/d)*
0-12 mo	*ND*
1-3 yrs	100
4-6 yrs	120
7-10 yrs	160
11-14 yrs	220
15-17 yrs	260
≥18 yrs	300
Pregnancy	300
Lactation	300

ND = non determinable

*The term vitamin E is related to α-tocopherol equivalents

References:

- **European Food Safety Authority (EFSA) (2004)** Opinion of the Scientific Committee on food on the tolerable upper intake level of vitamin E
- **Institute of Medicine (IOM) (2000)** Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids

Vitamin K

Background

a) Description of vitamin K

The term 'vitamin K' is a group name for a number of related compounds that have in common a 2-methyl-1,4-naphthoquinone ring system, but differ in the length and degree of saturation of their isoprenoid side chain at the 3-position. Three vitamin K compounds have biological activity: phylloquinone, (vitamin K_1), menaquinones (vitamin K_2) and menadione (vitamin K_3).

Vitamin K acts as a cofactor for a specific carboxylation reaction that transforms selective glutamate (Glu) residues to gamma-carboxyglutamate (Gla) residues. The reaction is catalysed by the microsomal enzyme vitamin K-dependent gamma-glutamyl carboxylase, which, in turn, is linked to a cyclic pathway known as the vitamin K epoxide cycle. The resultant Gla residues are common to all vitamin K-dependent proteins and these have increased affinity for calcium. Prothrombin and other proteins of the blood clotting system, as well as certain bone matrix proteins, contain Gla and thus, require vitamin K for their function.

Newborn infants are at serious risk of haemorrhaging because of poor placental transfer of vitamin K, lack of intestinal bacteria, and the low vitamin K content in breast milk. For this reason, vitamin K is routinely administered prophylactically at birth in many countries. The risk of bleeding is greatest in prematurely born infants, in breast-fed infants, and in those with gastrointestinal conditions that impair vitamin K absorption. In normal infants, plasma prothrombin concentrations and those of the other vitamin K-dependent factors are approximately 20% of adult values at birth. Normal or near-normal blood coagulation is usually maintained in older children and adults and 'clinical' deficiency is rare. Several factors protect adults from a lack of vitamin K and these include widespread distribution of vitamin K in plant and animal tissues, the vitamin K cycle, which conserves the vitamin, and the microbiological flora of the normal gut, which synthesises menaquinones (MKs). However, 'subclinical' vitamin K deficiency in extrahepatic tissues, particularly in bone, is not uncommon in the adult population.

Warfarin produces an anticoagulant effect by interfering with the cyclic conversion of vitamin K to its reduced form (vitamin K hydroquinone). The latter is an essential cofactor for the gamma-carboxylation of the vitamin K–dependent coagulation factors (II, VII, IX, and X), which promotes their calcium binding and activation in the coagulation cascade. The anticoagulant effect of warfarin can be antagonised by vitamin K. The administration of supraphysiological doses of vitamin K orally, intramuscularly or intravenously, is common practice in the reversal of over-anticoagulation with warfarin.

The ability of elevated intakes of vitamin E to antagonise vitamin K action is well established. Vitamin E may exacerbate the effects of vitamin K deficiency. The vitamin E metabolite, tocopherylquinone, is structurally similar to vitamin K and may inhibit vitamin K metabolism and thus coagulation.

b) Different forms of vitamin K and clarity on the forms of vitamin K that are relevant to the UL

Dietary vitamin K, mainly as phylloquinone, is absorbed into the lymphatic system from the proximal intestine after solubilisation into mixed micelles composed of bile salts and the products of pancreatic lipolysis. In healthy adults, the efficiency of absorption of phylloquinone is about 80%. Intestinal bacteria can synthesise a variety of MKs, which are absorbed to a limited extent from the large intestine, transported into the lymphatic system, cleared by the liver, and released in very low-density lipoprotein (VLDL). However, it is not fully clear to what extent intestinal MK contributes to the vitamin K requirement. Approximately 50% of vitamin K is carried in the plasma in the form of VLDL, about 25% in low-density lipoprotein (LDL), and about 25% in high-density lipoprotein (HDL). Once in the circulation, phylloquinone is cleared rapidly at a rate consistent with its continuing association with chylomicrons. Vitamin K is extensively metabolised in the liver and excreted in the urine and bile.

Vitamin K is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I. There is no evidence of adverse effects resulting from the consumption of vitamin K naturally occurring in foods.

Green leafy vegetables are the best dietary source of vitamin K (as phylloquinone). Some plant oils such as soybean oil and rapeseed oil are good dietary sources, containing 173 and 123 µg of phylloquinone per 100 g, respectively. Some vegetable oils, such as peanut, corn, sunflower, and safflower oils, have much lower phylloquinone content (1–10 µg/100 g). In general, meat, cereals, fish, and milk are poor sources of phylloquinone. From NANS in 2008-10, the mean daily intake of phylloquinone among Irish adults was 85 µg/day. Furthermore, 55% of adults had phylloquinone intakes below 1 µg/kg body weight and only 19% of men and 34% of women met the US adequate intakes of 120 and 90 µg/day respectively.

c) Usual intakes, RDAs, AIs

The IOM and EFSA have set an RDA and AI, respectively, for vitamin K (see Appendix IV).

A large review, including elevene different studies, reported that phylloquinone intake ranged from 60 to 210 µg/day with an average intake of approximately 80 µg/day for younger adults (<45 years) and approximately 150 µg/day for older adults (>55 years). Healthy individuals with a phylloquinone intake approaching 80 µg/day have been investigated and showed no signs of deficiency, suggesting that this level is probably adequate for the majority of the adult population. Because dietary assessment methods tend to underestimate the actual daily intake of foods, the highest intake value reported for four adult age groups was used to set the AI for each gender rounding up to the nearest 5 µg. The most recent guideline (AI) for vitamin K intake in the United States for adults (aged 19 years and older) is 120 and 90 µg/day, for men and women, respectively. In Europe, the EC Scientific Committee for Food (SCF) made no recommendation for a PRI for vitamin K but considered that an intake of 1 µg/kg body weight/day appears to be adequate and would be provided by a normal diet.

ULs established by other organisations

In a limited number of human studies, there is no evidence of adverse effects associated with supplementary intakes of vitamin K in the form of phylloquinone of up to 10 mg/day (more than two orders of magnitude higher than the recommended dietary intake of vitamin K) for limited periods of time. These limited data are supported by experimental animal studies in which no adverse effects were observed after daily administration of extremely high doses (2,000 mg/kg body weight) for 30 days.

However, high intakes of phylloquinone can negate the effects of the anticoagulant warfarin. The synthetic form of vitamin K, menadione, can interfere with the function of glutathione, one of the body's natural antioxidants, resulting in oxidative damage to cell membranes. Menadione given by injection has been shown to induce liver toxicity, jaundice, and hemolytic anaemia (due to the rupture of red blood cells) in infants, and is no longer used for the treatment of vitamin K deficiency.

No UL has been established for vitamin K. Data on adverse effects from high vitamin K intake are not sufficient for a quantitative risk assessment and a UL of intake has not been established by the IOM or by EFSA.

Special considerations

Because of the antagonistic interaction of phylloquinone and coumarin anticoagulant drugs, including warfarin, people taking these drugs should not significantly increase their phylloquinone intake by dietary change or by using dietary supplements without medical advice. Owing to the narrow therapeutic range of warfarin and the considerable inter- and intra-individual variability in patients' dose requirement for warfarin, many patients on oral anticoagulant therapy receive phylloquinone supplementation under strict medical supervision which improves the international normalised ratio (INR). Excessive anticoagulation (INR above the therapeutic range) increases the risk of bleeding whilst insufficient anticoagulation (INR below the therapeutic range) leads to therapeutic failure.

Conclusions

Neither EFSA nor the IOM have been able to establish a UL for vitamin K due to a lack of sufficient scientific evidence.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for Vitamin K.

References:

- **Hayes A, Hennessy Á, Walton J, McNulty BA, Lucey AJ, Kiely M, Flynn A, Cashman KD (2016)** Phylloquinone Intakes and Food Sources and Vitamin K Status in a Nationally Representative Sample of Irish Adults. *J Nutr*. 146:2274-2280
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- **Institute of Medicine (IOM) (2001)** Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc
- **Shea MK and Booth SL (2008)** Update on the role of vitamin K in skeletal health. *Nutrition Reviews* 66: 549–557

Thiamin (B_1)

Background

a) Description of thiamin

Thiamin diphosphate (thiamin pyrophosphate) is the coenzyme for four enzymes in carbohydrate and energy-yielding metabolism:

- Pyruvate dehydrogenase, which provides the entry point for carbohydrates into the citric acid cycle
- The branched-chain oxo-acid decarboxylase involved in metabolism of leucine, isoleucine and valine
- Alpha-ketoglutarate dehydrogenase in the citric acid cycle
- Transketolase in the pentose phosphate pathway of carbohydrate metabolism.
  In addition, thiamin triphosphate has a role in nerve conduction, acting as the phosphate donor to phosphorylate, a chloride ion channel and to other proteins in the nerve membrane

Thiamin is unstable in light, and although bread and flour contain significant amounts of thiamin, much or all of this can be lost when baked goods are exposed to sunlight in a shop window. It is also destroyed by sulphites, and in potato products that have been blanched by immersion in sulphite solution, there is little or no thiamin remaining. Polyphenols, including tannic acid in tea and betel nuts, also destroy thiamin, and have been associated with thiamin deficiency. Fermented raw fish is devoid of thiamin, because of the action of thiaminases that cleave the vitamin.

Historically, thiamin deficiency affecting the peripheral nervous system (beriberi) was a major public health problem in south-east Asia following the introduction of the steam-powered mill that made highly polished (thiamin depleted) rice widely available. There are still sporadic outbreaks of deficiency among people whose diet is rich in carbohydrate and poor in thiamin. More commonly, thiamin deficiency affecting the heart and central nervous system, is a problem in people with an excessive consumption of alcohol.

Thiamin deficiency can result in three distinct syndromes:

- A chronic peripheral neuritis, beriberi, which may or may not be associated with heart failure and oedema
- Acute pernicious (fulminating) beriberi (shoshin beriberi), in which heart failure and metabolic abnormalities predominate, with little evidence of peripheral neuritis
- Wernicke's encephalopathy with Korsakoff's psychosis, a thiamin-responsive condition associated especially with alcohol and narcotic abuse. Those at risk of refeeding syndrome have depleted thiamin stores and upon refeeding, micronutrients such as thiamin are rapidly consumed as a result of the switch to anabolism induced by feeding. This, in turn, can contribute to the onset of Wernicke's encephalopathy or Korsakoff's psychosis due to the thiamin depletion. In addition to a deficient diet, alcohol inhibits the active transport of thiamin from intestinal mucosal cells into the blood stream, and so inhibits absorption of the vitamin

In general, a relatively acute deficiency is involved in the central nervous system lesions of the Wernicke-Korsakoff Syndrome, and a high energy intake, as in alcoholics, is also a predisposing factor. Dry beriberi (neuritis without oedema) is associated with a more prolonged, less severe deficiency, with a generally low food intake, while higher carbohydrate intake and physical activity predispose to oedema and wet beriberi. Acute beriberi has been reported in anorectics and hunger strikers provided with intravenous glucose solution without the addition of the vitamin.

b) Usual intakes, RDAs, AIs

Because thiamin has a central role in energy-yielding, and especially carbohydrate, metabolism, requirements depend mainly on carbohydrate intake, and have been related to non-fat energy intake. In practice, requirements and reference intakes are calculated on the basis of total energy intake, assuming that the average diet provides 40% of energy from fat. For diets that are lower in fat content, and hence higher in carbohydrate and protein, thiamin requirements may be somewhat higher. RDAs for thiamin set by different authorities range between 1 – 1.2 mg / day.

The IOM and EFSA have set RDAs for thiamin (see Appendix IV). The average intakes of thiamin in Ireland are outlined in Appendix V.

ULs established by other organisations

There have been occasional reports of anaphylactic reactions to intravenous and intramuscular administration of relatively large amounts of thiamin. However, there is no evidence of adverse effects of even high oral doses of the vitamin. This is mainly because the intestinal absorption of thiamin is by saturable active transport, and at high levels of intake a smaller proportion of the intake is absorbed. Because of this, neither the IOM nor EFSA has set an upper level.

At high intakes, a proportion of thiamin is excreted in sweat, giving it a yeasty odour. There is some (limited) evidence that this acts as an insect repellent, and some people travelling to tropical regions take thiamin supplements (or consume yeast extract) to minimise attack by mosquitoes.

Conclusions

Neither EFSA nor the IOM has established a UL for thiamin due to a lack of sufficient evidence. There has been no reported evidence of adverse effects even with high oral doses of thiamin.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for thiamin.

References

- **Bender DA (2003)** Chapter 6 Thiamin in *Nutritional Biochemistry of the Vitamins*, 2nd edition, Cambridge University Press, Cambridge
- **European Food Safety Authority (EFSA) (2001)** Opinion of the scientific committee on food on the tolerable upper intake level of vitamin B_1
- **Institute of Medicine (IOM) (1998)** Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline

Riboflavin (B_2)

Background

a) Description of riboflavin

Riboflavin forms the coenzymes flavin mononucleotide (riboflavin phosphate) and flavin adenine dinucleotide, which act in a wide variety of enzymes involved in oxidation and reduction reactions and energy-yielding metabolism. Some enzymes also contain covalently-bound riboflavin.

Many reactions involving flavin coenzymes proceed by way of single-electron reactions, forming the half-reduced flavin radical, which is stabilised by binding to the enzyme protein. Although the flavin radical proceeds to form the fully oxidised or fully reduced (non-radical) coenzyme, radicals are, by definition, unstable, and it has been estimated that reoxidation of reduced flavins in the mitochondrial electron transport chain leads to the formation of potentially damaging oxygen radicals from 3 – 5% of the 30 mol of oxygen consumed per day.

Riboflavin and riboflavin phosphate that are not bound to plasma proteins are filtered in the kidney, and renal tubular reabsorption of riboflavin is saturated at normal plasma concentrations. There is also active tubular secretion of the vitamin; urinary excretion of riboflavin after high doses can be two to three fold greater than the glomerular filtration rate.

Riboflavin deficiency is a significant public health problem in many areas of the world, characterised by skin and oral lesions, and some impairment of fatty acid metabolism. Deficiency is rarely, if ever, fatal, because there is very efficient conservation and recycling of riboflavin in deficiency.

b) Different forms of riboflavin and clarity on the forms of riboflavin that are relevant to the UL

The main dietary sources of riboflavin are milk and dairy products, providing 25% or more of the total intake in most diets, and to a considerable extent average riboflavin status in different countries reflects milk consumption. In addition, because of its intense yellow colour, riboflavin is widely used as a food colour. Apart from milk and eggs, which contain relatively large amounts of free riboflavin, most of the vitamin in foods is as flavin coenzymes bound to enzymes, which are released when the protein is hydrolysed, and cleaved to free riboflavin in the intestinal lumen. Riboflavin is absorbed from the intestinal tract by saturable active transport.

c) Usual intakes, RDAs, AIs

RDAs for riboflavin set by different authorities range between 1.3 – 1.6 mg /day. The IOM and EFSA have set RDAs for riboflavin (see Appendix IV). The average intakes of riboflavin in Ireland are outlined in Appendix V.

ULs established by other organisations

There is no evidence of adverse effects of even high oral doses of the vitamin. This is because the intestinal absorption of riboflavin is by saturable active transport, and at high levels of intake, a smaller proportion of the intake is absorbed. In addition, as the plasma concentration rises, the capacity to reabsorb it from the glomerular filtrate is exceeded, and the vitamin is excreted in the urine. At higher blood concentrations, there is active renal secretion of riboflavin. Because of this, neither the IOM nor EFSA have set an upper level.

Conclusions

Neither EFSA nor the IOM have established a UL for riboflavin due to a lack of sufficient scientific evidence. There have been no reported effects of adverse effects even with high oral doses of the vitamin.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for riboflavin.

References

- **Bender DA (2003)** Chapter 7 Riboflavin in *Nutritional Biochemistry of the Vitamins*, 2nd edition, Cambridge University Press, Cambridge
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Niacin

Background

a) Description of niacin

Two compounds have the biological activity of niacin: nicotinic acid and nicotinamide. In the USA, niacin is commonly used specifically to mean nicotinic acid, with niacinamide for nicotinamide.

Both nicotinic acid and nicotinamide are used to form the nicotinamide nucleotide coenzymes NAD and NADP, which act in a wide variety of oxidation and reduction reactions in the body. In addition, NAD is the donor of ADP-ribose for the modification of tissue proteins, with a role in the repair mechanism after accidental damage to DNA. Derivatives of NAD are also involved in cell signalling in response to hormone action.

b) Different forms of niacin and clarity on the forms of niacin that are relevant to the UL

There is little, if any, free nicotinic acid in foods; most niacin is present as the nicotinamide nucleotide coenzymes. Cereals contain nicotinic acid, but this is almost entirely present as niacytin, esters with complex carbohydrates. Normally less than 10% of niacytin is biologically available, except in the case of maize meal that has been treated with alkali, as in the traditional preparation of tortillas.

The nicotinamide ring of the coenzymes can also be synthesised in the body from the amino acid tryptophan; it is conventional to express total niacin intake as the sum of preformed nicotinic acid and nicotinamide plus 1/60 x tryptophan.

Pellagra, the disease caused by niacin deficiency, leads to a scaly sunburn-like dermatitis, diarrhoea, a depressive psychosis, and may be fatal. It was a major problem of public health in the southern USA until the middle of the 20th century, and was eradicated mainly by mandatory fortification of flour with niacin. In parts of southern Africa and India, pellagra continued to be a problem until near the end of the century. In the USA and Africa, pellagra was associated with maize-based diets that provide very little free niacin or tryptophan. In India, it was associated with sorghum-based diets, and the problem may have been an excessive amount of branched-chain amino acids, which compete with tryptophan for absorption and tissue uptake, in the proteins of sorghum.

Good dietary sources of niacin include meat, poultry, fish, legumes, cereals and seeds. While a small amount of niacin can be found in tea, coffee, milk and green leafy vegetables.

c) Usual intakes, RDAs, AIs

RDAs for niacin set by different authorities range between 12 – 18 mg /day for adults. In most diets (except those based largely on maize), the intake of tryptophan is more than adequate to meet niacin requirements without the need for preformed niacin. Both the IOM and EFSA have set RDAs for niacin (see Appendix IV). The average intakes of niacin in Ireland are outlined in Appendix V.

In considering ULs, only preformed niacin is relevant, not tryptophan in dietary proteins. It is important to distinguish between nicotinic acid and nicotinamide. The formulation of supplements is also important. Sustained release preparations lead to a more prolonged high level of the vitamin and lead to liver damage at lower total doses.

ULs established by other organisations

The IOM set a UL of 35 mg/d based on a LOAEL of 50 mg that causes transient flushing, with an uncertainty factor of 1.5 to account for the transient nature of the flushing response. Although the IOM report states that niacin is the generic descriptor for nicotinic acid and nicotinamide, it later notes that "*The generic term niacin may be considered to be interchangeable with nicotinic acid*". This is not correct when considering flushing, which only occurs in response to nicotinic acid, and not nicotinamide.

EFSA considered nicotinic acid and nicotinamide separately. At pharmacological doses, the two vitamers, i.e. one of two or more related chemical substances that carry out the same vitamin function, are metabolised by different pathways to a considerable extent.

Using the same data from studies in the 1930s as the IOM, EFSA noted that some people showed vasodilatation and flushing after a dose of 30 mg nicotinic acid. It considered that vasodilatation poses a potential hazard to the elderly, possibly leading to hypotensive episodes, and set a UL for nicotinic acid of 10 mg /d.

For nicotinamide, EFSA used data from recent studies of high dose nicotinamide for prevention of Type I Diabetes mellitus, in which doses up to 3 g /day were used. The NOAEL was 25 mg /kg bw /d, but since the clinical trials were largely conducted in young people, and they considered that there may be age-related differences in nicotinamide metabolism, it used a safety factor of x 0.5 to set a UL of 12.5 mg /kg bw /d, equivalent to ~900 mg /day for an adult.

Conclusions

The EFSA concept of separating niacin into nicotinic acid and nicotinamide for the purpose of setting ULs is considered to be most appropriate for Ireland. EFSA considers nicotinic acid and nicotinamide separately as, at pharmacological doses, they are metabolised by different pathways. EFSA has set a UL of 10 mg/d for nicotinic acid based on studies which observed vasodilatation and flushing after a dose of 30 mg nicotinic acid. The UL for nicotinamide of 900mg/d was derived from studies which investigated high dose nicotinamide for the prevention of Type I Diabetes mellitus.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA ULs for nicotinic acid and nicotinamide (EFSA, 2002) as shown in Table 3.6.

Table 3.6. Tolerable Upper Intake Level of Niacin (EFSA, 2002)

Age	Nicotinamide (mg/day)	Nicotinic acid (mg/day)
0-12 mo	*ND*	*ND*
1-3 yrs	150	2
4-6 yrs	220	3
7-10 yrs	350	4
11-14 yrs	500	6
15-17 yrs	700	8
> 17 yrs	900	10
Pregnancy	*ND*	*ND*
Lactation	*ND*	*ND*

ND = non determinable

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Vitamin B_6

Background

a) Description of vitamin B_6

Six compounds have the biological activity of vitamin B_6: pyridoxine, pyridoxal and pyridoxamine, and their phosphates. The phosphorylated compounds are dephosphorylated in the intestinal mucosa, and tissues take up the unphosphorylated vitamers and phosphorylate them. The vitamers are readily interconvertible in the body; the metabolically active compound is pyridoxal phosphate.

Pyridoxal phosphate functions in three main areas of metabolism: as the coenzyme for a wide variety of enzymes involved in the metabolism of amino acids; as the coenzyme for glycogen phosphorylase (and hence, the release of glucose from glycogen reserves in liver and muscle); and to attenuate the actions of steroid hormones by displacing hormone receptors from DNA binding.

b) Different forms of vitamin B_6 and clarity on the forms of vitamin B_6 that are relevant to the UL

Dietary sources of vitamin B_6 include fish, poultry, nuts, potatoes, legumes and bananas. A small proportion of the vitamin B_6 in foods may be unavailable because of reaction with lysine in proteins.

Dietary deficiency of vitamin B_6 is unknown, apart from an outbreak among bottle-fed infants in the 1950s. Here the problem was that the infant formula had been over-heated, so that the vitamin reacted with lysine in proteins. This rendered the vitamin unavailable, and pyridoxal-lysine has antivitamin metabolic activity. The affected infants developed a number of neurological signs, including convulsions.

There is however, evidence from enzyme activation assays and measurement of plasma concentrations of the vitamin that about 10% of the population in developed countries may be marginally inadequately supplied with vitamin B_6.

c) Usual intakes, RDAs, AIs

Because of the role of pyridoxal phosphate in amino acid metabolism, vitamin B_6 requirements are calculated on the basis of 15 – 16 µg per gram of dietary protein. RDAs for vitamin B_6 set by different authorities range between 1.4 – 1.7 mg /day. The IOM and EFSA have set RDAs for vitamin B_6 (see Appendix IV). The average intakes of vitamin B_6 in Ireland are outlined in Appendix V.

ULs established by other organisations

There is clear evidence that doses of vitamin B_6 (as pyridoxine hydrochloride) in excess of 500 mg /day are neurotoxic. There is less evidence for intakes below 500 mg /day, but the IOM set a UL of 100 mg /day, based on a NOAEL of 200 mg /day, in a relatively small number of relatively short-term trials. The IOM UL for vitamin B_6 represents total intake from food, water and supplements.

There is one study that reports neurological symptoms in women taking an average of 100 mg pyridoxine (PN)/day (Dalton & Dalton, 1987). This was not a clinical trial, but involved women attending a premenstrual tension clinic who, if they said they were taking PN supplements, were asked about specific symptoms, such as tingling in the fingers and toes, etc. There was no neurological examination of these women, but they did report cessation of their symptoms when the PN supplements were withdrawn. Because of the methodology, the IOM excluded the Dalton and Dalton data from its consideration of NOAEL.

EFSA took a more precautionary approach, noting that the trials used to determine the The IOM NOAEL were of short duration, while neurological damage develops slowly. It also considered it inappropriate to exclude the data. EFSA set a UL of 25 mg /day based on the average intake of 100 mg /day in the Dalton and Dalton study, with a safety factor of x 0.5 to allow for long-term intakes and the slow development of neurological damage, and a further factor of x 0.5 to allow for "deficiencies in the [Dalton and Dalton] database".

The advice from the UK Committee on Toxicology is that people should not take supplements providing more than 10 mg PN /day except under medical supervision. However, doses of 50mg/day are commonly prescribed (and self-prescribed) for the treatment of premenstrual tension, albeit with little evidence of efficacy from double-blind placebo-controlled trials. The most commonly available supplements provide 50 mg pyridoxine hydrochloride /day.

Conclusions

The EFSA UL for vitamin B_6 of 25 mg/day is considered more appropriate for Ireland than the higher UL set by the IOM of 100 mg/day. The IOM higher UL was based on a NOAEL of 200 mg/day from a small number of trials of short duration but which excluded a key study carried out by Dalton and Dalton that reported neurological symptoms in women taking an average of 100 mg PN /day.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for vitamin B_6 (EFSA, 2000) as shown in Table 3.7.

Table 3.7. Tolerable Upper Intake Level of Vitamin B_6 (EFSA, 2000)

Age	Vitamin B_6 (mg/d)
0-12 mo	*ND*
1-3 yrs	5
4-6 yrs	7
7-10 yrs	10
11-14 yrs	15
15-17 yrs	20
> 17 yrs	25
Pregnancy	25
Lactation	25

ND = non determinable

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Folic Acid

Background

a) Description of folate/folic acid

The terms folic acid and folate are often used interchangeably. However, there are important differences. Folic acid refers to the synthetic form of the B vitamin known as folate. Natural folates (occurring in human tissue and in plant and animal foods) are a mixture of reduced folates (most predominantly 5-methyltetrahydrofolate) and are usually found in the polyglutamylated form containing a variable number of glutamate residues. Folic acid, in contrast to natural folates, is fully oxidised and is a monoglutamate containing just one glutamate moiety. These chemical differences mean that folic acid is inherently more stable and more bioavailable compared with naturally occurring food folates at equivalent intake levels. Folic acid, the synthetic vitamin form, is found in the human diet only in fortified foods and supplements but is readily converted to the natural cofactor forms after ingestion. It is a yellow-orange crystalline solid, tasteless, odourless and moderately soluble in pure water. Total folic acid refers to folic acid from both fortified foods and supplements, excluding any folate from natural sources, i.e. total folic acid = µg folic acid as fortified food + µg folic acid as supplements.

Folate is required for one-carbon metabolism. This involves the transfer and utilisation of one-carbon units in pathways involving amino acid metabolism, methylation processes and in DNA and RNA biosynthesis.

Folate is metabolically closely linked with vitamin B_{12}, and the latter vitamin is required for normal folate recycling. These two vitamins are intrinsically linked via the enzyme methionine synthase (involved in the conversion of homocysteine to methionine) which requires both vitamins for its activity; a deficiency of either leads to an identical anaemia, i.e. megaloblastic anaemia. In vitamin B_{12} depletion, methionine synthase activity will be decreased resulting in folate co-factors essentially becoming trapped as 5-methyl-tetrahydrofolate, 5-methyl-THF, i.e. the so-called methyl-trap hypothesis, thus impairing folate recycling.

Folate also has an important, albeit less well recognised, metabolic interaction with riboflavin (vitamin B_2). Riboflavin in the form of FAD serves as a cofactor for the folate-metabolising enzyme methylenetetrahydrofolate reductase (MTHFR) which is required to generate the active folate form 5-methyl-THF in cells. The effects of riboflavin on folate metabolism appear to be greatest in individuals homozygous for the common C677T polymorphism, i.e. TT genotype, in MTHFR. These individuals, i.e. just over 10% of Irish adults, typically present with low serum and red cell folate, along with elevated homocysteine concentrations, particularly when folate and/or riboflavin intake is sub-optimal. More recently, this common polymorphism has been linked with higher blood pressure. The elevated homocysteine and the less well recognised phenotype, elevated blood pressure, are both highly responsive to lowering with riboflavin supplementation at dietary levels in people with the TT genotype, confirming the importance of the riboflavin-MTHFR interaction.

Clinical folate deficiency leads to megaloblastic anaemia (characterised by immature, enlarged blood cells reflecting impaired DNA synthesis) which is reversible with treatment. Low folate status i.e. sub-clinical deficiency is typically detected by measurement of folate concentrations in serum/plasma or in red blood cells. Red cell folate is considered to represent folate stores and is the best index of longer term status, i.e. over the previous three to four months, whereas serum folate reflects recent dietary intake. Folate deficiency is not uncommon even in otherwise well-nourished populations. A low or deficient status of folate can arise in any situation where requirements are increased or availability is decreased, or both; with the clinical manifestation of folate deficiency, i.e. megaloblastic anaemia, more likely to be present when both occur simultaneously.

Pregnancy is a time when folate requirement is greatly increased to sustain the demand for rapid cell replication and growth of foetal, placental and maternal tissue. Likewise folate requirement is increased during lactation in order to meet both maternal and neonatal folate needs. Folate deficiency is common in chronic alcoholism, which causes intestinal folate malabsorption, decreased hepatic uptake and increased urinary folate excretion. Several commonly used drugs can increase folate requirements or have been linked with folate depletion through various mechanisms. These include: sulphasalazine (used in the treatment of inflammatory bowel disease), pyrimethamine (an antimalarial), triamterene (a diuretic), metformin (used in Type 2 Diabetes) and phenytoin/primidone (anticonvulsants used to treat epilepsy).

Low dietary intake is in fact the most common cause of folate inadequacy, even in developed countries. Dietary folate intakes can be considered suboptimal in the diets of many people in that, although they may be adequate in preventing clinical deficiency, i.e. megaloblastic anaemia, they are often insufficient in achieving a biomarker status of folate that is associated with the lowest risk of neural tube defects (NTD). This widespread under-provision of folate is generally attributed to the poor stability and incomplete bioavailability of natural food folates when compared with synthetic folic acid. Apart from having an established role in preventing NTDs, emerging evidence supports a number of roles for folate in maintaining health, from maternal and foetal health in pregnancy through childhood, to preventing chronic disease in middle and old age.

b) Different forms of folic acid and clarity on the forms of folic acid that are relevant to UL

The intestinal absorption of dietary folates is a two-step process which involves the hydrolysis of folate polyglutamates to the corresponding monoglutamyl derivatives followed by their transport through the intestinal membranes into the enterocyte. The hydrolysis of polyglutamyl folates occurs in the proximal part of the jejunum with the involvement of a brush border enzyme that has an optimal pH of 6.5; studies have shown that the maintenance of this optimal pH is critical for the complete deconjugation of polyglutamyl folates in the jejunum.

i. Bioavailability

The bioavailability of naturally occurring folates is inherently limited and variable. There is much variability in the ease with which folates are released from different food matrices and the removal of the polyglutamyl "tail" (deconjugation) before uptake by intestinal cells. Also, other dietary constituents can contribute to instability of labile folates during the processes of digestion. As a result, naturally occurring folates show incomplete bioavailability compared with folic acid. The bioavailability of folic acid is assumed to be 100% when ingested as a supplement.

Table 3.8 compares folate bioavailability among the three forms of folate/folic acid namely; natural food folate, folic acid present as fortified food and supplemental folic acid.

Table 3.8. Relative Folate Bioavailability: A Comparison of the Three Intake Forms of Folate/Folic Acid

Route of Intake of Folate/Folic Acid	% Bioavailability
Supplemental folic acid	100
Fortified food containing folic acid	85
Natural food folate	50

ii. Folate intake and status

The folic acid content of food can be expressed in terms of dietary folate equivalents (DFE). Dietary folate equivalents are based on differences in bioavailability between natural food folates and folic acid added to foods. Therefore, DFE = µg natural food folate + 1.7 times µg folic acid from fortified foods (Table 3.9).

Table 3.9. Folate/Folic Acid Content of Food in Terms of Dietary Folate Equivalents

Folate/Folic Acid (µg/day)	DFE (µg/day)
1 µg of natural food folate	1 µg of DFE
1 µg of folic acid added as a fortificant, i.e. consumed as a fortified food	1.7 µg of DFE

The major sources of natural food folates are green leafy vegetables, asparagus, liver, beans and legumes, egg yolk, wheat germ and yeast. Folic acid is found in the human diet only in fortified foods and supplements but is readily converted to the natural co-factor forms after ingestion.

Folate status is known to vary considerably within and between countries depending primarily on the level of exposure to folic acid through fortified food. This is because unlike natural food folates which are inherently unstable outside living cells, folic acid provides a highly stable and bioavailable form of the vitamin.

c) Usual intakes, RDAs, AIs

Population-based data on folate status (both dietary intakes and biomarker concentrations) for Irish adults have just become available, with the completion in 2012 of NANS of 1,500 adults aged 18+ years, the first representative dietary survey in Ireland to provide corresponding biomarker data. Early results show that non-consumers of folic acid (from either fortified food or supplements) had the lowest concentrations of serum and red cell folate, whilst consumers of folic acid from both sources had the highest biomarker concentrations (Hopkins *et al.* 2015). Thus, the distribution of folate biomarker concentrations across population subgroups was highly dependent on folic acid intake and this was predominantly provided through fortified foods (with 68% of the population consuming folic acid from fortified foods only, a further 11% consuming folic acid from the combination of fortified foods and supplements, while only 3% consumed folic acid through supplements only). The results showed that non-consumers of folic acid, i.e. from either fortified food or supplements, represented by 18% of the population, were at greatest risk of suboptimal folate status. The average intakes of folate in Ireland are outlined in Appendix V.

In the US, folate recommendations are expressed as DFEs which take into account, differences in bioavailability between synthetic folic acid in fortified foods and naturally occurring dietary folate (IOM, 1998). DFEs are defined as the micrograms of naturally occurring food folate plus 1.7 times the micrograms of synthetic folate, i.e. any folic acid from fortified food. The IOM (1998) recommends 400 µg/d as DFE for adult females and males. To cover increased needs during pregnancy and lactation, it recommends 600 µg/day and 500 µg/day respectively (Appendix IV). EFSA (2014) recommends 330 µg/d as DFE for adult females and males. To cover increased needs during pregnancy and lactation, it recommends 600 µg/day and 500 µg/day, respectively (Appendix IV).

In most European countries however, this conversion factor is not applied and folate intakes are typically expressed simply as total folate in µg/d (rather than as DFEs), thus disregarding the known differences in bioavailability between the natural food forms and folic acid. In Europe, folate recommendations vary between 200-400 µg/day for adults in different countries. Generally, those countries/organisations with more recently generated recommendations based on newer evidence, estimate higher folate requirements than those countries (including the UK) with older recommendations still in place. In most countries, except France, the average requirement (AR) is established based on the concentration of folate in blood or tissues which is associated with no deficiency symptoms. Red cell folate and serum/plasma folate are the biomarkers of folate status which are most often used as primary health indicators for establishing an AR, albeit cut-off values for adequacy vary across different official reports.

ULs established by other organisations

No adverse effects have been associated with the consumption of excess folate from foods therefore, there is no UL for naturally occurring food folates. The UL applies only to folic acid intakes, i.e. folic acid fortified food or supplemental folic acid, or a combination of both.

ULs for folic acid have been set for the US (IOM), for Australia/New Zealand, for Europe (EFSA), and for a number of specific European countries: the Nordic and DACH countries (Germany, Austria and Switzerland), France and the Netherlands. These ULs are remarkably similar across the various jurisdictions.

The close metabolic interrelationship between folate and vitamin B_{12} provides the basis for the UL as set by the IOM and organisations worldwide. Historical evidence shows that large doses of folic acid given to an individual with undiagnosed vitamin B_{12} deficiency can potentially correct the megaloblastic anaemia (found in both B_{12} and folate deficiencies) thereby, delaying the diagnosis of B_{12} deficiency and leaving the individual at risk of developing the irreversible neurological damage associated with B_{12} deficiency. In this way, high dose folic acid is seen to mask vitamin B_{12} deficiency.

In the USA, the IOM (1998) estimated a UL for adults (≥ 19 years) for folic acid at 1,000 µg/day. The basis for the UL is case reports from patients with vitamin B_{12} deficiency. When erroneously treated with high doses of folic acid (≥5 mg/day in most cases), the anaemia was reversed in the majority of patients, but not the neurological symptoms, thus delaying or masking the diagnosis of vitamin B_{12} deficiency. Because no data were available for children, the IOM used the UL for adults adjusted by weight: 300-800 µg per day, depending on the age group except for infants for whom no UL was set. In the EU, a similar approach was used to set UL for adults and children (EFSA, 2006).

Special considerations

Anticonvulsant drugs (phenytoin, primidone) are a well-established cause of folate deficiency. This interaction is complex however, and concurrent administration of high-dose folic acid is reported to reverse the therapeutic effectiveness of the anticonvulsant drug resulting in increased seizures in treated epileptic patients. Methotrexate is a folate antagonist used to treat a number of diseases including cancer, rheumatoid arthritis and psoriasis; supplementation with folic acid or folinic acid is used to reduce the antifolate toxicity and signs of severe folate deficiency arising in treated patients. Folic acid supplementation in children with sickle cell disease is controversial; it has been both widely prescribed and hotly debated over many years. On one hand, folate deficiency is commonly reported in paediatric sickle cell patients and there is good evidence of clinical benefits of folic acid supplementation; on the other, some remain unconvinced of the need for or benefit of folic acid supplementation in these patients and are concerned about potential harmful side effects.

As explained previously, historical evidence shows that large doses of folic acid, i.e. 5 mg/d and above, administered to patients with undiagnosed vitamin B_{12} deficiency can correct the associated megaloblastic anaemia without correcting the underlying deficiency. This in turn, could potentially delay the diagnosis of vitamin B_{12} deficiency and leave the individual at risk of developing the other clinical sign of B_{12} deficiency – the irreversible neurologic damage. This adverse effect is not considered to occur in children (Zlotkin, 2006; FDA, 2016).

Concerns that such adverse effects could occur as a result of population-wide chronic exposure to folic acid through food fortification among those most at risk of B_{12} deficiency, i.e. older people, have been the primary reason for delaying the introduction of mandatory folic acid fortification in many European countries. However, a recent risk assessment in Ireland has shown that the effect of mandatory fortification of bread or flour on the risk of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults in Ireland would be negligible (FSAI, 2016). The FSAI Report 'Folic Acid Fortification for the Prevention of Birth Defects' (FSAI, 2016) reviewed the evidence for other possible adverse health effects of folic acid fortification related to cognitive impairment, unmetabolised folic acid in the circulation, promotion of cancers, diabetes and glucose/insulin metabolism, epilepsy, multiple births and embryo selection, and asthma. The 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 child-bearing age against NTD-affected pregnancies do not increase the risk of adverse health effects in the population. Nevertheless, it is prudent to avoid population-wide long-term intakes of folic acid at levels higher than are necessary for beneficial effects.

Conclusions

The EFSA ULs for folic acid are considered to be most appropriate for Ireland. Both EFSA and the IOM have set ULs for folic acid intakes, i.e. folic acid fortified food or supplemental folic acid, or a combination of both, with no UL for the naturally occurring food folate as no adverse effects have been associated with the consumption of excess folate from foods.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for folic acid for adults (EFSA, 2006) as shown in Table 3.10.

Table 3.10. Tolerable Upper Intake Level of Folic Acid (EFSA, 2006)

Age	Folic Acid (µg/day)
1-3 years	200
4-6 years	300
7-10 years	400
11-14 years	600
15-17 years	800
> 18 years	1,000
Pregnancy	1,000
Lactation	1,000

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Vitamin B_{12}

Background

a) Description of vitamin B_{12}

Vitamin B_{12} has the largest and most complex chemical structure of all the vitamins. Vitamin B_{12} refers to a group of cobalt-containing compounds known as cobalamins. There are a number of different forms of the vitamin including the two metabolically active forms methylcobalamin and deoxyadenosylcobalamin; other dietary cobalamins are readily converted to these forms. Vitamin B_{12} is required for normal recycling of folate. Along with folate, it is required for numerous methylation reactions, including the methylation of DNA, RNA, myelin basic protein, neurotransmitters and amines. It is also required in the metabolism of branched chain amino acids and odd-chain length fatty acids.

Vitamin B_{12} is metabolically closely linked with folate and is required for normal folate recycling. The haematological sign of vitamin B_{12} deficiency, megaloblastic anaemia, is identical to the anaemia which arises with folate deficiency because these two vitamins are intrinsically linked via the enzyme methionine synthase. In vitamin B_{12} depletion, methionine synthase activity is reduced, resulting in folate co-factors essentially becoming trapped as 5-methyltetrahydrofolate, i.e. the so-called methyl-trap, thus folate recycling is inhibited. Vitamin B_{12} and folate are important for homocysteine metabolism; with low status of either vitamin, homocysteine concentrations in blood will invariably be elevated.

Vitamin B_{12} deficiency leads to megaloblastic anaemia (characterised by immature, enlarged blood cells reflecting impaired DNA synthesis) which is reversible with treatment, and neuropathy which is irreversible and potentially fatal if left untreated. Inadequate intake of B_{12} is very rarely the cause of deficiency apart from in those following vegan diets (see Occurrence in Foods). Intestinal malabsorption, rather than inadequate dietary intake, explains most cases of vitamin B_{12} deficiency. Vitamin B_{12} deficiency is uncommon in younger adults because total body stores can reach 5,000 µg (5 mg) and daily turnover is slow, with dietary intakes of only about 2 µg/day considered as being sufficient to maintain adequate B_{12} status. In older people, deficiency can commonly occur mainly because of impaired intestinal absorption.

Classical deficiency of vitamin B_{12} arises as a result of an autoimmune condition known as pernicious anaemia, i.e. intrinsic factor deficiency. Antibodies to intrinsic factor (IF) bind to IF preventing formation of the IF- B_{12} complex, thus inhibiting vitamin B_{12} absorption and leading to severe B_{12} depletion. Treatment of pernicious anaemia generally requires injections of vitamin B_{12} to bypass intestinal absorption. Pernicious anaemia is estimated to be present in approximately 2% of adults over 60 years of age.

Far more commonly, low status of B_{12} arises as a result of malabsorption of food-bound B_{12}. This is the major cause of poor vitamin B_{12} status in otherwise healthy older adults. Food-bound vitamin B_{12} malabsorption is usually associated with atrophic gastritis, a chronic inflammation of the lining of the stomach that ultimately results in the loss of glands in the stomach (atrophy) and decreased gastric acid production; because gastric acid is required for the release of vitamin B_{12} from food proteins, vitamin B_{12} absorption is diminished. Atrophic gastritis is thought to affect up to 30% of people over 60 years of age and is frequently associated with infection by Helicobacter pylori (H. pylori) which induces chronic inflammation of the stomach. Food bound B_{12} malabsorption leads to a more subtle depletion, i.e. subclinical deficiency, of vitamin B_{12} that is not associated with the classical deficiency signs and may therefore remain undetected for years. Emerging evidence indicates that subclinical deficiency, as indicated by low concentrations of B_{12} biomarkers in blood, may be implicated in the development of several chronic age-related diseases, such as cognitive dysfunction, cardiovascular disease and osteoporosis.

Other causes of vitamin B_{12} deficiency include surgical resection of the stomach or area of the small intestine where receptors for the IF- B_{12} complex are located. The long-term use of acid-reducing drugs (such as proton pump inhibitors) has also been implicated in the development of deficient/low status of vitamin B_{12} (see Special Considerations following).

b) Different forms of vitamin B_{12} and clarity on the forms of vitamin B_{12} that are relevant to the UL

The absorption of vitamin B_{12} is a highly complex process that is dependent on normal functioning of the gastrointestinal tract; consequently, it often becomes less efficient with age. Vitamin B_{12} is tightly bound to protein in food and must be released by hydrochloric acid and pepsin in the stomach in order for B_{12} to be absorbed. The synthetic form of vitamin B_{12}, found in fortified foods and supplements, is however, already free and thus, there is no requirement for gastric acid. Free vitamin B_{12} immediately binds with R-binding proteins and then with intrinsic factor (IF) in the duodenum forming the IF- B_{12}complex which travels to the terminal ileum where it is absorbed via specific receptors by calcium dependent endocytosis. There is a limit to the amount of vitamin B_{12} that can be absorbed at any given time via the IF-related pathway, and the receptors are reported to become saturated with B_{12} intakes greater than 1.5-2.0 µg of vitamin B_{12}. In addition, an alternative pathway exists whereby vitamin B_{12} can be absorbed by passive diffusion, i.e. even in the absence of IF, but this process is very inefficient—only about 1% of the vitamin B_{12} dose will be absorbed passively.

Once absorbed, vitamin B_{12} then binds to one of two transport proteins, transcobalamin or haptocorrin. The majority of vitamin B_{12} binds to haptocorrin, a glycoprotein with an unknown function, whilst 20-30% is bound to transcobalamin, forming holo-transcobalamin (holoTC), the metabolically active fraction of the vitamin. Total body stores of vitamin B_{12} can reach 5mg, with the majority stored in the liver. The liver excretes around 1-10 µg/d of vitamin B_{12} into bile; however, up to 90% of this is reabsorbed via a highly efficient enterohepatic cycle while the rest is excreted in faeces. The daily requirement for vitamin B_{12} is so small in comparison to body stores that it is considered to take years for clinical deficiency to develop, even when there is a complete halt in B_{12} absorption.

Vitamin B_{12} is synthesised only by microorganisms and is present in animal products such as meat, poultry, fish (including shellfish) and to a lesser extent milk and dairy products only because those animals consume the microorganisms, i.e. rumen, corophagy, soil bacteria. Because it is not present in (clean) plant foods, vegetarians will generally have lower B_{12} intakes than meat eaters but their dietary intakes are invariably found to be more than adequate when compared with current RDAs. Vegans, who eat no animal products, will need supplemental vitamin B_{12} to meet their requirements. Certain novel plant foods, e.g. Spirulina, claiming to provide a rich source of B_{12} may be particularly misleading for consumers because these foods do not have any vitamin B_{12} activity; indeed they may have anti-vitamin activity. The confusion has arisen because of an artifact of the microbiological assay typically used to determine the B_{12} content of foods which can erroneously 'pick up' and thus, detect as B_{12} components in certain plants that are similar in structure to vitamin B_{12} but do not have vitamin activity.

Cyanocobalamin is the synthetic form of the vitamin that is typically used in supplements and fortified foods because of its stability. It is tasteless, dark red, crystalline hygroscopic powder. There are no reported adverse effects.

c) Usual intakes, RDAs, AIs

The average intakes of vitamin B_{12} in Ireland are outlined in Appendix V. The average western diet supplies approximately 3-15 µg/day, thus dietary intakes in most countries greatly exceeds current recommended intakes of vitamin B_{12} (ranging 1 to 2.4 µg/day in adults). Despite this, low vitamin B_{12} status is commonly found in older adults because of food-bound B_{12} malabsorption (owing to hypochlorhydria). In order to address this problem in older adults, the IOM recommends that adults over 50 years should consume most of their vitamin B_{12} from fortified foods or supplements. Surprisingly, no European country has addressed this issue in setting B_{12} recommendations.

EFSA have set an AI for B_{12} of 4 µg/day for adults, increasing to 4.5 µg/day during pregnancy and 5 µg/day for lactation (see Appendix IV). In the US, the RDA for B_{12} is 2.4 µg/day for adults, with an increase to 2.6 µg/day recommended during pregnancy and to 2.8 µg/day for lactation to cover the additional requirements of the foetus/ infant (see Appendix IV). The Committee on Nutrition of the American Academy of Paediatrics recommends a daily vitamin B_{12} intake of 0.15 µg/100 kcal energy intake for infants and pre-adolescent children. Other authorities have suggested intakes of 0.4-0.5 µg (0-1 year of age), 0.9-1.8 µg (1-10 years of age) and 2.4 µg (> 10 years).

ULs established by other organisations

Vitamin B_{12} is not known to cause adverse toxic effects. Doses as high as 1 mg (1,000 µg) daily by mouth or 1 mg monthly by intramuscular (IM) injection have been used to treat pernicious anaemia without significant side effects. When high doses of vitamin B_{12} are given orally, only a small percentage, i.e. 1%, can be absorbed, which probably explains the low toxicity.

For this reason, no UL has been established for vitamin B_{12}, either by the IOM in the US or by EFSA.

Special considerations

Historical evidence shows that large doses of folic acid, i.e. 5 - 15 mg/day, administered to patients with undiagnosed vitamin B_{12} deficiency can correct the associated megaloblastic anaemia without correcting the underlying deficiency. This in turn, could potentially delay the diagnosis of vitamin B_{12} deficiency and leave the individual at risk of developing the other clinical sign of B_{12} deficiency – the irreversible neurologic damage. Concerns that such adverse effects could occur as a result of population-wide chronic exposure to folic acid through food fortification among those most at risk of B_{12} deficiency, i.e. older people, have been the primary reason for delaying the introduction of mandatory folic acid fortification in many European countries similar to the policies in place in North America and in many countries worldwide.

A number of drugs can reduce the absorption of vitamin B_{12} from food. Chronic use of proton pump inhibitors, e.g. omeprazole and lansoprazole, widely used to treat gastroesophageal reflux (and less commonly Zollinger-Ellison syndrome) is a concern in relation to food-bound vitamin B_{12} malabsorption because these drugs act by suppressing the production of gastric acid (required for normal B_{12} absorption from food). Similarly, another class of gastric inhibitor drugs, histamine$_2$ (H_2)-receptor antagonists, have been found to reduce the absorption of B_{12} from foods. Thus, individuals taking drugs that inhibit gastric acid secretion may need to consider taking vitamin B_{12} in the free form, i.e. as a supplement or fortified food, because gastric acid is not required for its absorption.

Other drugs reported to inhibit B_{12} absorption from food include cholestyramine (a bile acid-binding resin used in the treatment of high cholesterol), chloramphenicol and neomycin (antibiotics), and colchicine (anti-gout medication). Some (limited) evidence links metformin (used in the treatment of Type 2 Diabetes) with low vitamin B_{12} status. However, this requires further investigation.

Conclusions

Neither EFSA nor the IOM have established a UL for vitamin B_{12} due to its lack of adverse effects even at high doses.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for Vitamin B_{12}.

References

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Biotin

Background

a) Description of biotin

Biotin is a water-soluble vitamin which occurs in eight isomeric forms of which only one, D(+)-biotin, occurs in nature. It binds to four carboxylase enzymes and functions as a coenzyme in reactions which catalyse the addition of bicarbonate into a substrate. It is essential for energy, carbohydrate, lipid and amino acid metabolism.

Biotin deficiency is very rare; the symptoms are dermatitis (around the eyes, nose and mouth), conjunctivitis, alopecia (hair loss), abnormalities of the central nervous system, including depression, lethargy, hallucinations and paraesthesia (tingling/burning sensation) of the extremities.

b) Different forms of biotin and clarity on the forms of biotin that are relevant to the UL

Bioavailability data for biotin are lacking; biotinidase enzyme in the gut of mammals cleaves biotin that is covalently bound to lysine (biocytin) and to oligopeptides prior to uptake. Absorption is reduced by raw egg white which contains the protein avidin; this binds four moles biotin per mole of avidin, thereby making the biotin unavailable.

Biotin occurs in many foods in very variable amounts; it is also synthesised by gut bacteria. The amounts in food are generally not documented; liver, kidney, egg yolk and certain vegetables (soybeans, nuts, lentils, spinach and mushrooms) are rich sources whereas fruits, cereals and most lean meats, are poor sources.

The form of biotin permitted under EU legislation in the manufacture of foods and supplements is D-biotin.

c) Usual intakes, RDAs, AIs

Average dietary intakes in three EU countries (Germany, UK and Ireland) have been reported and range from 34 µg/day (Ireland) to 40 µg/d (Ireland); the 97th percentiles range from 43 µg/d (Germany) to 103 µg/day (Ireland). Biotin intakes from supplements are very variable, ranging from 0.1 to 130 µg/d (UK); maximal doses up to 5 mg/d have been reported (Germany). The average intakes of biotin in Ireland are outlined in Appendix V.

Biotin requirements have not been estimated due to lack of data; however, there are EU reference values for adults from 15 up to 100 µg per day, COMA set safe and adequate intakes of 10 to 200 µg/d and the IOM has defined AIs of 5 µg/d (infants) up to 35 µg/d (lactating women) (Appendix IV). Both the IOM and EFSA have set AIs for biotin (see Appendix IV).

ULs established by other organisations

Toxicity studies in animals have been limited, and cannot readily be translated into the human context. There are few data on the effects of biotin in healthy humans, though EFSA reports a recent study showing a decrease in mitogen-stimulated proliferation of peripheral blood mononuclear cells, and reduced release of interleukin-1β and interleukin-2.

The EFSA considers that since there are no systematic dose-response studies, a quantitative risk assessment is not possible, thus ULs cannot be derived. It concludes that the risk of human toxicity from food and supplements is low, but that there are insufficient data to allow conclusions as to the safety of very high intakes from supplements.

The IOM also set no ULs for biotin, merely stating that there have been no reported adverse effects in patients given up to 200 mg orally and up to 20 mg intravenously to treat biotin-responsive inborn errors of metabolism and acquired biotin deficiency.

In conclusion, there is currently little evidence of dietary deficiency of biotin, nor any evidence of benefit or ill effect from high intakes.

Special considerations

People who receive dialysis or peritoneal dialysis may have an increased requirement for biotin (to replace that lost during dialysis).

People with genetic biotinidase deficiency (in whom absorption is impaired) require increased dietary biotin, as do people with genetic holocarboxylase sythetase deficiency.

Conclusions

Neither EFSA nor the IOM have established a UL for biotin due to a lack of evidence of adverse effects of high intakes of this vitamin.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for biotin.

References

- **European Food Safety Authority (EFSA) (2001)** Opinion of the scientific committee on food on the tolerable upper intake level of biotin
- **Institute of Medicine (IOM) (1998)** Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline

Pantothenic Acid

Background

a) Description of pantothenic acid

Pantothenic acid (sometimes known as vitamin B_5) is used to form coenzyme A (CoA), which is involved in fatty acid metabolism, entry of the products of carbohydrate and amino acid metabolism into the citric acid cycle as acetyl CoA, and a wide variety of metabolic reactions involving transfer of acetyl or other acyl groups, e.g. in cholesterol and steroid hormone synthesis, and the formation of the neurotransmitter acetyl choline. It also forms the prosthetic group of the fatty acid synthase multi-enzyme complex.

Pantothenic acid is widely distributed in foods; indeed the name comes from the Greek for "from everywhere". Dietary deficiency is unknown except in experimental studies, which have frequently used the antimetabolite omega-methyl pantothenic acid as well as dietary depletion. During such depletion studies, there is development of neuromotor disorders and depression, presumably as a result of impaired formation of acetyl choline, gastrointestinal complaints, decreased serum cholesterol, reflecting the impairment of steroidogenesis, and decreased acetylation of a number of drugs, reflecting reduced availability of acetyl CoA for these reactions.

Prisoners of war in the Far East in the 1940s, who were severely malnourished, showed, among other signs and symptoms of, vitamin deficiency diseases, a new condition of paraesthesia and severe pain in the feet and toes, which was called the 'burning foot syndrome' or nutritional melalgia. Although it was tentatively attributed to pantothenic acid deficiency, no specific trials of pantothenic acid were carried out; rather the subjects were given yeast extract and other rich sources of all vitamins as part of an urgent programme of nutritional rehabilitation.

In early studies of pantothenic acid deficiency in animals, it was found that black rats developed grey fur; at one time the vitamin was known as the anti-grey-hair factor. There is no evidence that greying of hair in human beings is associated with low pantothenic acid status, nor that supplements of the vitamin have any effect on hair pigmentation. Nevertheless, pantothenic acid or a metabolic precursor is often added to shampoos (as 'provitamin B_5'), with no evidence of efficacy.

b) Usual intakes, RDAs, AIs

There is no evidence on which to estimate pantothenic acid requirements. Average intakes are between 3 – 7 mg / day, and since deficiency does not occur, such intakes are obviously more than adequate to meet requirements and form the basis of adequate intake figures in lieu of RDA. The IOM and EFSA have established AIs for pantothenic acid (see Appendix IV). The average intakes of pantothenic acid in Ireland are outlined in Appendix V.

ULs established by other organisations

There is no evidence of adverse effects of high levels of pantothenic acid intake. This is because the intestinal absorption of pantothenic acid is by saturable active transport, and at high levels of intake, a smaller proportion of the intake is absorbed. Because of this, neither the IOM nor EFSA have set an upper level.

[2] The IOM has stressed the interdependence of calcium and vitamin D especially when considering levels of adequacy. A high calcium intake (within the dietary reference range) can compensate for low vitamin D intake much better than a high vitamin D intake can for a low calcium intake. The IOM UL for calcium was adopted so that there would be a statement of concern about the interdependence of calcium and vitamin D with respect to toxicity.

Conclusions

Neither EFSA nor the IOM have established a UL for pantothenic acid due to a lack of evidence of adverse effects of high levels of intake.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for pantothenic acid.

References

- **Bender DA (2003)** Chapter 12 Pantothenic acid in *Nutritional Biochemistry of the Vitamins*, 2nd edition, Cambridge University Press, Cambridge
- **European Food Safety Authority (EFSA) (2002)** Opinion of the scientific committee on food on the tolerable upper intake level of pantothenic acid
- **Institute of Medicine (IOM) (1998)** Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline

Vitamin C

Background

a) Description of vitamin C

Vitamin C, also known as ascorbic acid, is a water-soluble nutrient. Vitamin C functions biologically as a strong reducing agent and as an antioxidant involved in the prevention of the damaging effects of free radicals. Vitamin C is also a co-factor in enzymatic and hormonal processes and increases the absorption of non-haem iron. Vitamin C also plays a role in the biosynthesis of neurotransmitters, carnitine, collagen and other components of connective tissue.

Vitamin C deficiency in humans leads to the clinical symptoms of scurvy. Scurvy is characterised by defects of collagen formation.

Vitamin C may alter the absorption of metal ions.

b) Different forms of vitamin C and clarity on the forms of vitamin C that are relevant to the UL

Vitamin C is absorbed in the intestine via a sodium-dependant active transport process that is a saturable and dose-dependent relationship. The absorption efficiency decreases with increasing doses of the vitamin. Vitamin C is widely distributed in the body, with higher levels found in the adrenal glands, pituitary and retina. Vitamin C is oxidised to dehydroascorbic acid, which can be reduced back to ascorbic acid or hydrolysed to diketogulonic acid and then oxidised to oxalic and threonic acid, xylose, xylonic acid and lyxonic acid. There is some oxidation to carbon dioxide at high doses. Unmetabolised vitamin C and its metabolites are largely excreted in the urine with approximately 3% of a 60 mg oral dose excreted in the faeces. With high intakes, unabsorbed vitamin C is a substrate of intestinal bacterial fermentation in the intestine, which may account for the diarrhoea and gastrointestinal upset sometimes reported by individuals taking large doses of this vitamin.

Vitamin C is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I. Foods of plant origin, particularly citrus and soft fruits and green leafy vegetables are a major source of vitamin C. Liver and kidney are good animal-derived sources. There is no evidence of adverse effects resulting from the consumption of vitamin C naturally occurring in foods.

c) Usual intakes, RDAs, AIs

EFSA has derived an AR for vitamin C and the IOM has set an RDA for vitamin C based on intakes required to saturate leukocytes with vitamin C (see Appendix IV). The average intakes of vitamin C in Ireland are outlined in Appendix V.

ULs established by other organisations

The EFSA panel (2004) concluded that there were insufficient data to establish a UL for vitamin C. It noted that the vitamin was of low toxicity and based on limited data, acute gastrointestinal (GI) intolerance is the most clearly defined adverse effect at high intakes. EFSA concluded that there were insufficient data on the dose-response relationship. In characterising the risk, EFSA recognised that supplemental daily doses of vitamin C up to about 1,000 mg, in addition to normal dietary intakes, are not associated with adverse gastrointestinal effects, but noted that acute GI effects may occur at higher intakes (3,000-4,000 mg/day).

The IOM (2000) established a UL for vitamin C. Osmotic diarrhoea and gastrointestinal disturbances are the critical endpoints upon which the UL for vitamin C is based. The IOM noted that the effects are generally not serious and are self-limiting, i.e. individuals experiencing such effects may easily eliminate them by reducing supplemental vitamin C intake. The IOM UL is based on a study whereby the vitamin C intake of healthy human volunteers was increased by increments of 1,000 mg/day. At supplemental dose levels of 3,000-4,000 mg/day, effects such as abdominal distension, flatulence, diarrhoea and transient colic were described by volunteers. In deriving the UL, a LOAEL of 3,000 mg/day was selected and an uncertainty factor of 1.5 was applied. A NOAEL of 2,000 mg/day is estimated for adults (19 yrs and older). The UL values for toddlers, children and adolescents are extrapolated based on body weight difference from those established for adults. The UL for adults is applicable to pregnant and lactating women. The UL represents total intake from food, water and supplements.

Special considerations

Potentially vulnerable groups to the adverse effects of intake of vitamin C at the UL include:

- Individuals who are unable to regulate iron absorption, e.g. individuals genetically pre-disposed to haemochromatosis (a disorder causing the body to absorb an excessive amount of iron from the diet) or thalassaemia (a disorder that affects the body's ability to create red blood cells) due to the enhanced absorption of iron that may be caused by vitamin C intake
- Individuals with a pre-disposition to urinary or renal stones. Some reports have suggested high intakes of vitamin C increase oxalate excretion; however, to date, human studies have not revealed a substantial increase in excretion and no pathway for the formation of oxalate from ascorbate is known
- Individuals on medication. Gastrointestinal disturbances, induced by over-high intakes of supplemental vitamin C may result in the loss of medication
- Sports people. Some reports have suggested that supplemental doses of vitamin C (1 g/day) may delay the recovery process following muscle-damaging exercise and decrease mitochondrial biogenesis in endurance performance (Close *et al.*, 2006; Gomez-Cabrera *et al.*, 2008)

Conclusions

The IOM ULs for vitamin C are considered most appropriate for Ireland. The IOM has set ULs for vitamin C based on the critical endpoints of osmotic diarrhoea and gastrointestinal disturbances. The UL represents total intake from food, water and supplements. Due to a lack of sufficient data, EFSA has not established a UL for vitamin C.

Recommendations for Ireland

It is recommended that Ireland adopts the IOM UL for vitamin C (IOM, 2000), as shown in Table 3.11.

Table 3.11. Tolerable Upper Intake Level of Vitamin C (IOM, 2000)

Life Stage Group		Vitamin C (mg/d)
Infants	0-6 mo	*ND*
	7-12 mo	*ND*
Children	1-3 y	400
	4-8 y	650
Males	9-13 y	1,200
	14-18 y	1,800
	19-70 y	2,000
	>70 y	2,000
Females	9-13 y	1,200
	14-18 y	1,800
	19-70 y	2,000
	>70 y	2,000
Pregnancy	14-18 y	1,800
	19-50 y	2,000
Lactation	14-18 y	1,800
	19-50 y	2,000

References

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- **European Food Safety Authority (EFSA) (2004)** Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on request from the Commission related to tolerable upper intake level of vitamin C
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- **Institute of Medicine (IOM) (2000)** Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids

3.2 Minerals and Trace Elements

Calcium

Background

a) Description of calcium

Calcium is important for the maintenance of healthy teeth and bones, cell signalling, coagulation, muscle contraction, neural transmission and many other functions. Calcium is the fifth most abundant element in the human body. Almost all (99%) of the calcium in the body is located in bones and teeth, mostly as calcium hydroxyapatite. Bone mineral provides structure and strength, and a reservoir of calcium that helps to regulate blood serum calcium concentrations at about 2.5 mmol/L (range 2.3 - 2.62 mmol/L) (EFSA, 2012; IOM, 2011). Calcium is obtained in the diet mainly in dairy foods, with small but significant amounts in some plant foods, certain mineral waters and tap water in some areas with very 'hard' water, and nutritional supplements.

Hypercalcaemia is defined as a serum calcium > 2.63 - 2.75 mmol/L (as defined by individual laboratory reference ranges) and is mainly related to primary hyperparathyroidism or malignancy, but can also be induced by very high calcium or vitamin D intakes. Clinical symptoms of hypercalcaemia are fatigue, muscle weakness, anorexia, nausea, vomiting, constipation, tachycardic arrhythmia, soft tissue calcification, failure to thrive and weight loss.

b) Different forms of calcium and clarity on the forms of calcium that are relevant to the UL

The concentration of ionised calcium (Ca^{2+}) is controlled at a range of 1.1-1.4 mmol/L by circulating parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25$(OH)_2$D or calcitriol) and calcitonin. When serum Ca^{2+} concentrations decrease, the calcium-sensing receptor (CaSR) stimulates PTH, which induces hydroxylation of the circulating metabolite of vitamin D (25-hydroxyvitamin D (25(OH)D)) in the kidney to its active form, 1,25$(OH)_2$D. The actions of 1,25$(OH)_2$D restore serum Ca^{2+} concentrations by promoting calcium absorption from the gut, renal reabsorption and bone resorption. When serum Ca^{2+} concentrations increase, PTH secretion is inhibited and calcitonin is produced by the parafollicular C cells of the thyroid, thereby inhibiting osteoclast-mediated bone resorption and increasing urinary excretion of Ca^{2+}. Hypercalciuria is defined as a urinary calcium excretion in excess of about 250 mg/day in women or 275-300 mg/day in men (or >0.3 mg/mg creatinine), which can result in nephrolithiasis (kidney stones) and renal impairment.

c) Usual intakes, RDAs, AIs

The IOM and EFSA have set RDAs for calcium (see Appendix IV). The average intakes of calcium in Ireland are outlined in Appendix V.

ULs established by other organisations

The ULs for calcium were recently revised by both the IOM (2011) and EFSA (2012) and although there is some variability between them, both stated that excessive calcium intakes are primarily associated with supplementation and that it is difficult to attain the high chronic intakes of calcium associated with adverse consequences, particularly among older adults, from dietary sources.

Taking adults first, both EFSA and the IOM expert panels evaluated data on the potential adverse effects of excess calcium intakes on hypercalciuria, the milk-alkali syndrome (or calcium-alkali syndrome), vascular calcification and cardiovascular disease, prostate cancer and kidney function among the general population and selected kidney stones as the adverse effect indicator, based on the available data.

The EFSA panel noted that calcium supplementation in excess of 1,000 mg/day could increase the risk for calcium-alkali syndrome, depending on the duration of supplementation and the pre-existing risk.

The IOM took particular note of the Jackson *et al*. (2006) report of the three-year follow-up of the Women's Health Initiative (WHI). The WHI study randomised 36,282 healthy post-menopausal women aged 50 to 79 years to 1,000 mg of elemental calcium (as calcium carbonate) plus 10 µg of vitamin D_3 or placebo per day. Prior history of hypercalcaemia or kidney stones were exclusion criteria and the average follow-up was about seven years. Jackson *et al*. (2006) reported a 17% increased risk of kidney stones among the women randomised to the active arm of the study, which was not associated with hypercalcaemia or hypercalciuria. Therefore, the committee concluded that a total calcium intake around 2,000 mg/day, from supplementation and food sources, represented the LOAEL in adults over 50 years of age. No uncertainty factor was applied due to the proximity of the LOAEL to the upper end of the distribution of intakes, so the IOM established a UL for calcium at 2,000 mg/day among adults over 50 years. Although the risk of kidney stones in younger adults is higher than in older adults, it appears to be unrelated to calcium intake and it was deemed that calcium supplementation per se is less prevalent in younger adults than older adults. The IOM set the UL for calcium among adults aged 19-50 years (including pregnant and lactating women) at 2,500 mg/day. This is less than the value of 3,000 mg/day set for adolescents (including pregnant and lactating adolescents) from 14-18 years of age, which was established on the basis of a higher tolerated intake to accommodate rapid bone accretion during the adolescent growth spurt, and no evidence of an adverse effect of an intake higher than the UL.

To assist its deliberations, the EFSA panel had access to a further follow-up report on the WHI (Wallace, 2011), which was available after the publication of the IOM report. The Wallace paper used a compliance-based approach, as opposed to the intention-to-treat analysis by Jackson *et al*. (2006) and found that the statistical significance of the risk was attenuated (hazard ration of 1.21; 95% CI 0.98-1.34). Thus, the EFSA panel assigned a UL of 2,500 mg for all adults age 19 years and over, on the basis of a lack of evidence that calcium intakes up to 3,000 mg/day have been associated with kidney stones in the general adult population.

With regard to infants, children and adolescents, the EFSA panel found no evidence of risk of calcium intakes at the highest current intake estimates in these groups and noted data from a three-month randomised controlled trial (RCT) by Markowitz *et al*. (2004) that demonstrated no adverse effects of 1,800 mg/day in children aged one to six years. Therefore, EFSA has not set a UL for calcium in infants, children or adolescents, on the basis of insufficient evidence. The IOM, on the other hand, elected to adopt a more cautious approach and selected a UL of 1,000 mg for infants aged zero to six months, which increased to 1,500 mg for infants aged 6-12 months. These values are precautionary and based on an analysis by Sargent *et al*. (1999) of a small RCT in infants to assess tolerance to calcium-supplemented formula, which showed no adverse effect on calcium excretion at 1,750 mg/day. The IOM took this value as the NOAEL and adjusted downwards and upwards from six months to the age range of three to none months in the Sargent *et al*. (1999) report, and associated changes in body weight, to achieve the values of 1,000 and 1,500 mg/day for infants younger and older than six months, respectively. The IOM maintained the 1997 UL of 2,500 mg/day in 1-8 year olds and increased the value by 500 mg/day to 3,000 mg in 9-18 year olds to account for increased body size and requirements for adolescent growth.

With regard to infants, children and adolescents, intakes from the national food consumption surveys at the 95th percentile of the distribution range from ~1,300 mg/day in one to four year olds to a maximum of ~1,900 mg in teenage boys, both well below the IOM ULs for these age groups of 2,500 mg for 1-8 year olds and 3,000 mg/d in 9-18 year olds.

Special Considerations

The risk of adverse effects associated with calcium may be greater for some people, such as individuals who take thiazide diuretics, those with impaired renal function, and those with low intakes of minerals that interact with calcium.

Conclusions

A combination of both the IOM and EFSA ULs for calcium is considered most appropriate for Ireland. It has been noted by both EFSA and the IOM that excessive calcium intakes are primarily associated with supplementation, and chronic excessive calcium intake from dietary sources is difficult to achieve. The IOM has set a UL for infants, children and adolescents based on analysis of a small RCT in infants. However, EFSA did not set a UL in infants, children or adolescents for calcium in view of the lack of evidence for adverse effects.

Recommendations for Ireland

It is recommended that Ireland adopts the IOM recommendation for 0 to 18 years (IOM, 2011)[2], and adopts the EFSA recommendation for adults aged 19 years and over (EFSA, 2012) as shown in Table 3.12.

Table 3.12. Tolerable Upper Intake Level of Calcium (EFSA, 2012; IOM, 2011)

Age	Calcium (mg/d)
0-6 mo	1,000
6-12 mo	1,500
1-8 yrs	2,500
9-18 yrs	3,000
≥19 yrs	2,500

References

- **EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA) (2012)** Scientific Opinion on the Tolerable Upper Intake Level of calcium. *EFSA Journal*; 10(7):2814. [44 pp.] doi:10.2903/j.efsa.2012.2814
- **Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D (2011)** Washington, DC: The National Academies Press
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- **Markowitz ME, Sinnett M and Rosen JF, (2004)** A randomized trial of calcium supplementation for childhood lead poisoning. *Pediatrics*, 113, e34-39
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- **Wallace RB, Wactawski-Wende J, O'Sullivan MJ, *et al.* (2011)** Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. *American Journal of Clinical Nutrition*, 94, 270-277

[2] The IOM has stressed the interdependence of calcium and vitamin D especially when considering levels of adequacy. A high calcium intake (within the dietary reference range) can compensate for low vitamin D intake much better than a high vitamin D intake can for a low calcium intake. The IOM UL for calcium was adopted so that there would be a statement of concern about the interdependence of calcium and vitamin D with respect to toxicity.

Magnesium

Background

a) Description of magnesium

Total body magnesium (Mg) content is approximately 25 g (1,000 mmol), of which 50 to 60% is present in bone (IOM, 1997). Mg is a cofactor in more than 300 enzyme systems that regulate diverse biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation. It also plays an important role in protein and nucleic acid synthesis and has a stabilising and protecting effect on membranes. Finally, Mg is considered essential in maintaining Ca, K and Na homeostasis and has a role in the structural development of bone. Mg deficiency may occur in plants (chlorosis, low crop yields, forest damage), livestock (grass staggers, or grass tetany in ruminants) and man. Depending on the degree of the deficiency, symptoms are latent, moderate or even life threatening (SCF, 2001). Less than 1% of total Mg is in blood, and serum Mg levels are kept under tight homeostatic control by the kidney, which typically excretes about 120 mg Mg into urine each day. Normal serum Mg concentrations range from 0.75 to 0.95 mmol/L and hypomagnesaemia is defined as a serum Mg below 0.75 mmol/L.

b) Different forms of magnesium and clarity on the forms of magnesium that are relevant to the UL

The Mg content of food varies substantially. It is generally accepted that fats, refined sugars and pure alcohol are more or less free of Mg. Green leafy vegetables, such as spinach, legumes, nuts, seeds, and whole grains, are good sources. Cocoa, shrimps, soybeans and some other beans are rich sources. In general, foods containing dietary fibre provide Mg. Some types of food processing, such as refining grains in ways that remove the nutrient-rich germ and bran, lower Mg content substantially. Tap, mineral, and bottled waters can also be sources, but the amount of Mg in water varies by source and brand (ranging from 1 - 120 mg/L). Mg salts, especially the sulphate (epsom salt) are used as laxatives. Approximately one-third to one-half of the dietary magnesium consumed is typically absorbed by the body.

It is important to note that in food derived from plant and animal sources, Mg is mostly bound or chelated, e.g. to phytic acid, phosphates, chlorophylls or it is included in the skeleton. In aqueous solutions, Mg salts, e.g. sulphate, chloride, phosphate, citrate, and carbonate, are mostly dissociated depending on the concentration, pH and temperature. Mg in foods does not induce diarrhoea or other adverse effects in healthy persons, probably as Mg is bound to matrices and hence, is mostly not easily dissociable. On the other hand, Mg salts, e.g. chloride or sulphate, become readily dissociable after the reaction with gastric hydrochloric acid and exert dose-dependent laxative effects (IOM, 1997; SCF, 2001).

c) Usual intakes, RDAs, AIs

The IOM and EFSA have set an RDA and AI, respectively, for magnesium (see Appendix IV). The average intakes of magnesium in Ireland are outlined in Appendix V.

ULs established by other organisations

Unless a laxation effect is desired by consumers, mild diarrhoea is the most sensitive non-desirable effect of orally administered easily dissociable Mg salts. The SCF (2001) concluded that mild diarrhoea occurs in a small percentage of adult subjects at oral doses of about 360-365 mg Mg per day, hence setting the no-observed-adverse-effect level (LOAEL). No laxative effects have been observed in adult men and women (including during pregnancy and lactation) at doses up to 250 mg Mg per day. Therefore, this dose is considered as being the NOAEL.

Based on a NOAEL of 250 mg Mg per day and an uncertainty factor of 1.0, an UL of 250 mg Mg per day was be established for readily dissociable Mg salts such as chloride, sulphate, aspartate, lactate and compounds like MgO in nutritional supplements, water, or added to food and beverages. This UL does not include Mg normally present in foods and beverages and is for adults, including pregnant and lactating women, and children from four years on. As no data were available for children from one to three years, and since it was considered that extrapolation of the UL for older children and adults on the basis of body weight was inappropriate, no UL could be established for this age group. Similarly, the IOM established ULs that apply only to supplemental Mg for adults and children over none years at a higher level of 350 mg/d but also stipulated ULs for healthy children over 12 months of age at 65 mg from one to three years and 110 mg from four to eight years.

Special Considerations

A greater risk of magnesium toxicity (from nonfood sources) is associated with individuals with impaired renal function. For individuals with intact renal function, diarrhoea induced by easily dissociable Mg-salts or compounds like Mg-oxide is completely reversible within one to two days and does not represent a significant health risk.

Conclusions

The EFSA UL for magnesium is considered most appropriate for Ireland. However, due to a lack of data, a UL for children under four years of age could not be established. Therefore, a UL of 250 mg/day for persons over four years of age was set with no UL for children under four years.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for magnesium (EFSA, 2001) as shown in Table 3.13.

Table 3.13. Tolerable Upper Intake Level of Magnesium* (EFSA, 2001)

Age	Magnesium (mg/d)
0-12 mo	*ND*
1-3 yrs	*ND*
4-17 yrs	250
≥18 yrs	250

ND = non determinable

*Applies to supplemental magnesium only

References

- **European Commission Scientific Committee on Food (2001)** Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Magnesium
- **Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (IOM) (1997)** Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride

Phosphorus

Background

a) Description of phosphorus

Phosphorus as phosphate is an essential nutrient involved in many physiological processes, such as cellular energy cycle, regulation of acid-base balance, as a component of cell membranes (phospholipids), in cell regulation and signalling, and in the mineralisation of bones and teeth (EFSA, 2005). Approximately 80% of the body's phosphorus is present in the skeleton and teeth bound in solid form (hydroxyapatite), with the remainder distributed in soft tissues and extracellular fluid. Phosphorus homeostasis is determined by dietary intake, intestinal absorption, exchanges with bone and intracellular compartments and renal excretion; normal concentrations of serum phosphate are in the range of 3.0-4.5 mg/dl (EFSA, 2013). While serum phosphate rises continuously as total phosphorus intake increases, with no apparent reduction in dose-related absorptive capacity (such as that evident in calcium absorption), serum phosphate concentration is also determined by the interaction of regulatory hormones, cellular flux and renal excretion. Tubular reabsorption of phosphorus is regulated by a number of factors; including FGF-23, which is produced by osteoblasts and inhibits phosphate reabsorption, thereby suppressing synthesis of $1,25(OH)_2D$.

Excess phosphorus intake may result in hyperphosphataemia, causing secondary hyperparathyroidism, which leads to increased production of $1,25(OH)_2D$ and consequent bone resorption to restore calcium homeostasis. Chronic secondary hyperparathyroidism will eventually reduce bone mineral density and can result in ectopic calcification. These effects are typically not witnessed in humans except in patients with end-stage renal disease. As long as renal capacity is adequate, excess phosphate is excreted. In some supplementation studies using high phosphorus dosages, osmotic diarrhoea and mild gastrointestinal symptoms have been reported.

b) Different forms of phosphorus and clarity on the forms of phosphorus that are relevant to the UL

Phosphorus is widely found in foods as phosphates; especially foods rich in protein, such as dairy products (100-900 mg/100 g), meats (200 mg/100 g), fish (200 mg/100 g) and grain products (100-300 mg/100 g). Estimates of habitual dietary intakes in European countries are on average around 1,000-1,500 mg/day, ranging up to about 2,600 mg/day. The contribution of food supplements to phosphorus intake is low (EFSA, 2005).

c) Usual intakes, RDAs, AIs

The IOM and EFSA have set an RDA and AI, respectively, for phosphorus (see Appendix IV). The average intakes of phosphorus in Ireland are outlined in Appendix V.

ULs established by other organisations

The IOM (1997) set ULs based upon the upper boundary of adult normal values of serum phosphate, which is reached at a daily phosphorus intake of 3.5 g (113 mmol), a level that is not associated with any adverse effect. On the basis that high serum phosphate levels in infants and children were well-tolerated, The IOM set no UL for phosphorus up to 12 months of age and proposed ULs of 3 g in children aged 1-8 y and older adults > 70 y; 3.5 g during pregnancy and 4 g during lactation and in all persons aged 9-70 y.

EFSA's (2005) panel acknowledged the reports of gastrointestinal symptoms, such as osmotic diarrhoea, nausea and vomiting in some healthy subjects taking phosphate supplements with doses >750 mg/day and considered that these were not a suitable basis to establish an upper level for phosphorus from all sources. While increased serum PTH has been reported in acute or short term loading studies, no significant changes in markers of bone metabolism could be demonstrated in studies of up to six weeks duration with doses up to 3,000 mg/day. Thus, EFSA (2005) concluded there were insufficient data to establish a UL for phosphorus.

Recent update on phosphate in food additives and risk factors for disease

Phosphoric acid and phosphate salts are added as food additives in processed foods and in soft drinks as acidity regulators and stabilisers (EFSA, 2013). In the US, the contribution from phosphorus-containing food additives was estimated at 320 mg/day, i.e. 20-30% of the adult phosphorus intake (Calvo and Park, 1996). In that report, Calvo and Park noted the increase in use of phosphate-containing food additives and called for clinical studies to investigate whether a high background phosphorus intake combined with a habitually low calcium intake might promote the secondary hyperparathyroidism and concomitant bone resorption in humans that had been observed in animal studies. In its 1997 report, the IOM made a recommendation that the practical effect of phosphate-containing food additives on trace mineral status (iron, copper, and zinc) should be evaluated.

Following a time-lapse of 15 years or so, the issue has arisen again with the publication of a review article by Ritz *et al*. (2012) that suggests an association between intake of phosphates as food additives and elevated serum phosphate concentrations in the general population, leading to an increased risk of cardiovascular disease and overall mortality. This was followed by a review from Calvo and Uribarri (2013) that explores the potential adverse impact of the increasing phosphorus content of the American diet on renal, cardiovascular, and bone health in the general population. The central issue appears to be that dietary phosphorus intakes are underestimated due to inaccurate food composition data, given the high proportion of unknown phosphate-containing ingredients in processed foods. A chronic high phosphorus-low calcium intake, typically apparent in persons with a high intake of processed foods (usually socially disadvantaged with unhealthy dietary practices), may induce chronic secondary hyperparathyroidism and its consequent adverse effects.

In response to a request from the European Commission, EFSA (2013) undertook an evaluation of the review by Ritz *et al*. (2012) and made some recommendations that may in time be relevant to the assessment of ULs for phosphorus. Currently, no specific data on the contribution of phosphorus-containing food additives to the total intake of phosphorus in the EU have been identified, but this is likely to be increasing due to the higher consumption of processed foods and carbonated soft drinks. Cola soft drinks contain between 120-200 mg/L phosphorus. Fruit flavoured soft drinks are mostly acidulated with citrate rather than phosphoric acid, and contain little or no phosphate (EFSA, 2013). While the EFSA panel concluded that the Ritz *et al*. (2012) review had limitations, mainly that the evidence was not based on a systematic review and that other reports had produced conflicting results, the panel recommended that phosphoric acid and phosphates (E 338 341; E 343) and polyphosphates (E 450 452) for use as food additives should be re-evaluated by EFSA with high priority by 31 December, 2018, as set out in Regulation (EC) No 257/2010. In the context of this re-evaluation, the relevant and most up-to-date literature will be reviewed systematically and a meta-analysis of the data will be performed (EFSA, 2013).

Special considerations

In individuals with end-stage renal disease, hyperphosphataemia may lead to secondary hyperparathyroidism, which leads to increased production of $1,25(OH)_2D$ and consequent bone resorption to restore calcium homeostasis. Chronic secondary hyperparathyroidism will eventually reduce bone mineral density and can result in ectopic calcification. For individuals with adequate renal capacity, excess phosphate is excreted in the urine.

In some supplementation studies using high phosphorus dosages, osmotic diarrhoea and mild gastrointestinal symptoms have been reported.

Conclusions

It is not recommended that Ireland adopt a UL for phosphorus. EFSA have acknowledged reports of gastrointestinal symptoms in individuals taking phosphate supplements and have concluded that these were not a suitable basis for establishing a UL for phosphorus from all sources. However, emerging evidence should be reviewed regularly to ensure consumers in Ireland are not at risk of over-exposure.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for phosphate.

References

- **Calvo MS and Park YK (1996)** Changing phosphorus content of the U.S. diet: potential for adverse effects on bone. *J Nutr*. 126: 1168S-1180S
- **Calvo MS and Uribarri J (2013)** Public health impact of dietary phosphorus excess on bone and cardiovascular health in the general population. *American Journal of Clinical Nutrition*, 2013 Jul; 98(1):6-15
- **European Food Safety Authority (EFSA) (2005)** Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on request from the Commission related to tolerable upper intake level of phosphorus
- **European Food Safety Authority (2013)** Assessment of one published review on health risks associated with phosphate additives in food. *EFSA Journal* 2013;11(11):3444, 27pp. doi:10.2903/j.efsa.2013.3444
- **Ritz E, Hahn K, Ketteler M, Kuhlmann MK and Mann J (2012)** Phosphate Additives in Food-a Health Risk. Deutsches *Arzteblatt International*, 109 (4), 49-55
- **Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (IOM) (1997)** Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride

Sodium & Chloride

Background

a) Description of sodium and chloride

Sodium and chloride are essential nutrients normally found in most foods together as sodium chloride (salt). Therefore, this report presents data on these micronutrients together. Sodium is the major extra cellular electrolyte and exists as the water-soluble cation. Chloride is also mainly found in the extracellular fluid and exists as the water-soluble anion. The sodium cation actively regulates osmotic and electrolyte balances. The chloride anion is a passive participant in this regulatory process. Sodium is also involved in nerve conduction, active cellular transport and the formation of mineral apatite of bone. The plasma membrane enzyme sodium-potassium ATPase plays a central role for sodium involved in water balance, nerve conduction and active transport. In addition, chloride in the form of hydrochloric acid is an important component of gastric juices aiding the digestion and absorption of many nutrients.

Low plasma or serum sodium is seldom a consequence of low dietary intake but rather a consequence of an increase in losses, e.g. excessive sweating, high gastrointestinal losses, increased renal excretion, use of diuretics. Chloride loss usually accompanies sodium loss. Excess chloride depletion causes hypochloraemic alkalosis, a syndrome seen in people with significant vomiting.

Sodium and chloride interact with the nutrient potassium. An increase in the intake of potassium results in an increase the urinary excretion of sodium and chloride thus blunting a rise in blood pressure resulting from excess sodium intake. In general, the ratio of sodium and potassium is more closely associated with blood pressure than intake of either substance alone in older adults.

Sodium and chloride are typically consumed as sodium chloride (salt) which is absorbed mainly in the small intestine. Absorbed sodium and chloride remain in the extracellular compartments. Most of this sodium chloride is excreted in the urine provided sweating is not excessive. A number of systems and hormones regulate the sodium and chloride balance.

b) Different forms of sodium and chloride and clarity on the forms of sodium and chloride that are relevant to the UL

Both sodium and chloride are permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

Sodium chloride (salt) is the major source of sodium in foods. 1 mmol of sodium chloride (approximates 58 mg) is equivalent to 35.5 mg chloride and 23 mg sodium.

The main source of chloride is also from salt or salt substitutes added to food during processing and manufacturing and/or during cooking. The main sources of chloride from foods in the diet are from cereals and cereal products, meat and meat products and vegetables.

c) Usual intakes, RDAs, AIs

The IOM has set an AI for sodium and chloride (see Appendix IV). The average intakes of sodium and chloride in Ireland are outlined in Appendix V. In Ireland, meat and fish (especially cured/processed meats) and bread account for more than half of salt in the adult's diet. Estimates of salt intakes using food intake data from the IUNA surveys compared to urinary excretion indicated that discretionary salt accounts for about 25-30% of total salt intake in adults (IUNA, 2011).

In developing its salt reduction programme, the FSAI determined that an achievable target for the adult Irish population is a mean intake of 6 g salt (2.4 g sodium) per day. Whilst the FSAI considers this to be an achievable target for the Irish population, it does not regard it as an optimal or ideal level of consumption (FSAI, 2005).

ULs established by other organisations

EFSA (2005) completed two separate reports on the ULs for sodium and chloride. However, it was noted that both of these EFSA opinions should be read in conjunction with each other. In addition, EFSA also advises referring to the opinion derived on the UL for potassium when considering both of these minerals. EFSA concluded that there were insufficient data to establish tolerable upper intake levels for either sodium or chloride. EFSA noted that there is strong evidence available indicating that current levels of chloride and sodium consumption as sodium chloride (salt) have been associated with a greater likelihood of increased blood pressure, a risk factor for cardiovascular disease and renal disease.

The IOM (2005) presents data on the effects of sodium and chloride together for the reason that the cation sodium and anion chloride are normally found in most foods together as sodium chloride (salt). The scientific rationale for setting the ULs is based on the impact of sodium on blood pressure. The IOM noted that the task of establishing a UL for sodium was difficult given that the relationship between sodium intake and blood pressure is progressive and continuous without an apparent threshold. Environmental and genetic factors also exert an effect on blood pressure and further complicate this relationship. The most relevant reports in determining a UL for sodium were three trials in which the lowest level of dietary sodium intake was close to the IOM established AI for sodium. Based on these three trials, a LOAEL for dietary sodium of 2.3 g/day (100 mmol)/day) was derived. An uncertainty factor (UF) of 1.0 was applied to derive a UL of 2.3 g (100 mmol)/day for total sodium intake. The UL for chloride was set at an equimolar basis with sodium. The UL established for chloride is 3.6 g (100 mmol)/day. The ULs for sodium and chloride for pregnant and lactating women are the same as for non-pregnant women. The extrapolation of a UL for children from the adult UL is deemed appropriate. The IOM ULs for sodium and chloride represent total intake from food, water and supplements.

Special considerations

For certain subgroups of the population, the UL for sodium chloride may not be applicable.

These subgroups include:

- Individuals whose blood pressure is most sensitive to increased sodium intake, e.g. older individuals, hypertensive individuals, diabetics or individuals with chronic kidney disease
- Individuals with an especially high incidence of heart disease related to high blood pressure
- Individuals with excessive sweat loss
- Those unaccustomed to physical activity in hot climates as vigorous activity in high temperatures can affect the sodium chloride balance

Conclusions

The IOM ULs for sodium and chloride are considered most appropriate for Ireland. The IOM has set ULs for sodium and chloride together as they are normally found together as sodium chloride in most foods. The UL for sodium was derived from reports assessing the impact of sodium on blood pressure. The UL for chloride was set at an equimolar basis with sodium. EFSA has not established a UL for either sodium or chloride due to a lack of sufficient data.

Recommendations for Ireland

It is recommended that Ireland adopts the IOM UL for sodium and chloride (IOM, 2005) as shown in Table 3.14.

Table 3.14. Tolerable Upper Intake Level of Sodium and Chloride (IOM, 2005)

Life Stage Group		Salt Equivalent (g/day)	Sodium (g(mmol)/day)	Chloride (g(mmol)/day)
Infants	0-6 mo	*ND*	*ND*	*ND*
	7-12 mo	*ND*	*ND*	*ND*
Children	1-3 y	3.75	1.5 (65)	2.3 (65)
	4-8 y	4.75	1.9 (83)	2.9 (83)
Males	9-13 y	5.5	2.2 (95)	3.4 (95)
	14-18 y	5.75	2.3 (100)	3.6 (100)
	19-70 y	5.75	2.3 (100)	3.6 (100)
	>70 y	5.75	2.3 (100)	3.6 (100)
Females	9-13 y	5.75	2.3 (100)	3.6 (100)
	14-18 y	5.75	2.3 (100)	3.6 (100)
	19-70 y	5.75	2.3 (100)	3.6 (100)
	>70 y	5.75	2.3 (100)	3.6 (100)
Pregnancy	14-18 y	5.75	2.3 (100)	3.6 (100)
	19-50 y	5.75	2.3 (100)	3.6 (100)
Lactation	14-18 y	5.75	2.3 (100)	3.6 (100)
	19-50 y	5.75	2.3 (100)	3.6 (100)

ND = non determinable

Please note: A narrow margin exists between the IOM established AI value and UL. The sodium chloride (salt) content of many processed foodstuffs on the market may exceed the UL established by the IOM.

References

- **European Food Safety Authority (EFSA) (2005)** Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the tolerable upper intake level of sodium
- **European Food Safety Authority (EFSA) (2005)** Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the tolerable upper intake level of chloride
- **Food Safety Authority of Ireland (FSAI) (2005)** Salt and Health: Review of the Scientific Evidence and Recommendations for Public Policy in Ireland
- **Institute of Medicine (IOM) (2005)** Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulphate
- **Irish Universities Nutrition Alliance (IUNA) (2011)** Executive Summary Report on Salt Intakes in Irish Adults

Potassium

Background

a) Description of potassium

Potassium is an essential nutrient and is the principal cation in the intra-cellular fluid with potassium concentrations approximately thirty times greater inside than outside the cell.

Potassium, in conjunction with sodium, functions to regulate the membrane potential of the cells and subsequently, nerve and muscle function and blood pressure. Potassium also plays a role in the acid-base balance and is a cofactor for a number of enzymes.

The blood concentration of potassium is tightly regulated and normally 3.6 to 5.2 mmol/L. Hypokalaemia (low serum potassium) can result from excessive uptake of potassium by the cells or potassium depletion from the body. Insulin excess, catecholamine increases, Cushing's disease (high levels of the hormone cortisol), potassium-wasting diuretics, e.g. thiazide diuretics, chronic kidney disease, diarrhoea, vomiting and laxative abuse can all result in hypokalaemia. It is unlikely that a low dietary intake of potassium will lead to clinical potassium depletion except during circumstances such as starvation and anorexia nervosa. Refeeding syndrome also results in depletion of potassium due to the anabolism induced by refeeding and also as a result of the insulin surge that occurs. The symptoms of hypokalaemia are related to alterations in membrane potential and cellular metabolism. They include fatigue, muscle weakness and cramps, and intestinal paralysis. Severe hypokalaemia may result in muscular paralysis or cardiac arrhythmias that can be fatal.

Hyperkalaemia (high serum potassium) can also occur with the most common cause related to kidney function. Hyperkalaemia is a serious and potentially life-threatening disorder. It can cause muscle fatigue, weakness, paralysis, cardiac arrhythmias and nausea.

Potassium interacts with sodium. An increase in the intake of potassium results in an increase in the urinary excretion of sodium and chloride thus blunting a rise in blood pressure resulting from excess sodium intake. Generally, the ratio of sodium to potassium is more closely associated with blood pressure than the intake of either substance alone in older adults. Potassium also interacts with calcium. Potassium regulates acid-base balance and appears to have a positive effect on calcium balance. Potassium can ameliorate effects of sodium on calcium depletion.

b) Different forms of potassium and clarity on the forms of potassium that are relevant to the UL

In healthy people, about 85-90% of dietary potassium is absorbed from the gut. The potassium balance is primarily regulated by renal excretion in urine. A small proportion can be lost in sweat and faeces.

Potassium is permitted to be added to foods and used in the manufacture of food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

Fruits and vegetables, particularly leafy greens, vine fruit (such as tomatoes), root vegetables, and nuts are all good sources of potassium in the diet. A number of food additives also contain potassium. Salt substitutes, in which part of the sodium chloride has been substituted with potassium salts, can also contribute to potassium intake.

c) Usual intakes, RDAs, AIs

The IOM and EFSA have set an AI for potassium (see Appendix IV). The average intakes of potassium in Ireland are outlined in Appendix V.

ULs established by other organisations

In the generally healthy population with normal kidney function, a potassium intake from foods above the AI poses no potential for increased risk because excess potassium is readily excreted in the urine. Hence, neither EFSA nor the IOM have established a UL for potassium.

EFSA (2005) did not find sufficient evidence to establish a UL for potassium. Potassium intakes from foods have not been associated with adverse effects in normal healthy children and adults. However, the EFSA opinion noted that doses of supplemental potassium as high as 5-7 g/day in addition to dietary intake, have been reported to cause conductive effects and compromise heart function in otherwise healthy adults. Additionally, gastrointestinal symptoms have been observed in individuals taking certain forms of potassium supplements, e.g. slow matrix release, wax-matrix formulations, with doses ranging from 0.9 to 4.7 g/day or more. However, these adverse effects were thought to be related to the formulation of the supplement as opposed to the dose.

The IOM (2004) did not establish a UL for potassium. Similar to EFSA, the IOM notes that in otherwise healthy individuals, there was no evidence that a high level of potassium intake from foods has adverse effects and hence, did not establish a UL. In contrast however, the IOM report recommended that potassium supplements should only be provided under medical supervision. The IOM report noted that supplemental potassium can lead to acute toxicity in healthy individuals as well as adverse effects due to chronic consumption.

Special considerations

Potentially vulnerable groups to the adverse effects of intake of potassium at the UL include:

- Individuals engaging in strenuous activities leading to dehydration
- Individuals with impaired kidney function, diabetes mellitus, severe heart failure, adrenal insufficiency
- Individuals on drug treatment that can substantially impair potassium excretion, e.g. angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blockers (ARB) and potassium-sparing diuretics
- Elderly persons who may have impaired kidney function due to advancing age and/or are taking medications that may interact with potassium balance
- Pregnant women with preeclampsia

In the above sub-groups, various adverse effects such as hyperkalaemia, conductive effects and compromised heart function have been reported after moderate to high acute or sub-chronic intakes of potassium in the form of supplements or potassium-containing salt substitutes.

Conclusions

Neither EFSA nor the IOM have established a UL for potassium as intakes from foods have not been associated with adverse effects. However, emerging evidence should be reviewed regularly to ensure that consumers in Ireland are not at risk of over-exposure.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for potassium.

References

- **European Food Safety Authority (EFSA) (2005)** Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a Request from the Commission related to the Tolerable Upper Intake Level of Potassium
- **Institute of Medicine (IOM) (2005)** Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulphate

Iron

Background

a) Description of iron

Iron is a metal whose roles in biological systems are due to its ability to interconvert between the ferrous (Fe^{2+}) and ferric (Fe^{3+}) oxidation states. It is a vital component of the oxygen-carrying proteins haemoglobin (in red blood cells, comprising almost two-thirds of total body iron) and myoglobin (in muscle). Iron is also a component of the cytochromes (in mitochondria), various other enzymes and several transport and storage proteins. The total adult body content of iron is 2.2 to 3.8 g under iron-adequate conditions.

Iron deficiency causes anaemia, adverse pregnancy outcomes, impaired psychomotor development and cognitive performance, and reduced immune function. It is reckoned to be the commonest nutritional deficiency worldwide; the highest prevalence being among women of childbearing age and in infants. Most vulnerable are infants over six months, toddlers, adolescents and pregnant women (due to high iron requirements), the elderly and those consuming foods containing iron-absorption inhibitors (due to poor iron absorption) and menstruating women or people with pathological blood loss (due to high iron losses).

Many factors affect the bioavailability of dietary iron; principally physiological status via homeostatic responses which can alter intestinal iron absorption in response to deficiency or excess; increased absorption occurring in anaemia, pregnancy, lactation and growth. Also important are dietary factors which influence the solubility of non-haem iron including acids such as ascorbic acid, (positive effect), and certain components of dietary fibre (phytates, phosphates and oxalates) and calcium (negative effect). High oral iron doses can overwhelm the mucosal barrier, as occurs in acute iron intoxication. This all complicates the assessment of dietary intakes of iron and hence the derivation of ULs.

b) Different forms of iron and clarity on the forms of iron that are relevant to the UL

The richest food sources of iron are red meats, especially offal. Cereals and pulses are moderately good sources, pale meats (pork and poultry), and green vegetables are intermediate sources, while milk and dairy products are poor sources. The amounts in food vary greatly, depending on soil, climate and processing. About half of the iron from meat/poultry/fish is haem iron (generally comprising less than 12% of total dietary iron, which is 15-35% available); non-haem iron (from eggs, dairy food and plant sources) is much less well absorbed. Foods, e.g. breads, breakfast cereals and bars, may be fortified with non-haem iron up to 24 mg Fe per serving (IOM).

Iron in biological systems exists mainly bound to high affinity iron-binding proteins, which reduce the levels of free non-bound iron in the tissues; free iron is thought to increase oxidative stress via the Fenton reaction and hence, lead to tissue damage (demonstrated in vitro).

Body iron is highly conserved; excretion via the kidneys is very low (0.1 mg/d), the main losses occurring only via sloughed-off body cells (gut, 0.6 mg Fe/day and skin, 0.2-0.3 mg Fe/d), or blood loss (menstrual losses are variable but have been estimated to be below 1.6 mg Fe/d in 95% of women, leading to an average total loss of approximately 2.5 mg Fe/d).

Iron is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

c) Usual intakes, RDAs, AIs

Dietary iron supplements are consumed by approximately a quarter of women (fewer men) according to NHANES III data, the median intake being approximately 21 mg Fe/day. Data from the EFSA for EU countries indicate that average intakes, including supplements, can be as high as 22 mg Fe/d (in Swedish men); the highest 97.5th percentile intake being 72 mg Fe/d (in Irish women). EFSA and the IOM have set an RDA for iron, with EFSA also setting an AR for iron (see Appendix IV). The average intakes of iron in Ireland are outlined in Appendix V.

ULs established by other organisations

Animal toxicity data are complicated by large species and strain differences in response to dietary iron overload. Different iron salts have different toxicities, e.g. ferrous sulphate > succinate > fumarate > gluconate in rats. Reported effects include decreased growth (rats), emetic (cats), gastric irritant (rabbits), free-radical production by colonic bacteria (rat, pig), tumour promoter (mouse colon, rat kidney).

Accidental poisoning with medicinal iron (young children are particularly at risk) causes acute damage of gastrointestinal, hepatic, pancreatic and cardiovascular structures. An acute oral dose of 60 mg/kg body weight can be lethal, whereas doses below 10-20 mg iron/kg body weight do not cause acute systemic toxicity. Supplemental iron intakes of 50-60 mg/d consumed in the short-term have been reported to cause gastrointestinal effects including nausea, discomfort and constipation, particularly if taken without food.

Long-term iron overload has been reported to occur in people (mainly adults) receiving high-dose medical treatment of 160-1,200 mg iron/d, causing clinical symptoms including liver cirrhosis. Dietary overload (Bantu siderosis) has been reported among consumers of Bantu beer brewed in iron containers (providing 50-100 mg iron/d).

Consumption of iron from supplements may increase the proportion of people with biochemical indicators of high iron stores (serum ferritin above 200 µg/L for women, and 300 µg for men), although the threshold above which adverse effects occur is not known. The risk of adverse effects from iron overload from food (including fortified food but excluding supplements) in the general population, including people heterozygous for hereditary haemochromatosis (see below), is considered by EFSA to be low.

EFSA proposes that because of the poor correlation between iron intake and biochemical indicators of iron status, between biochemical indicators and body stores, and between body stores and actual clinical effects, the dose-response relationship between iron intake and adverse effects of iron accumulation has not been adequately defined. It does not consider that the adverse effects following short-term oral doses of 50-60 mg/d supplemental non-haem iron are a suitable basis to establish ULs for iron from all sources. Nor does it regard the evidence of any causal relationship between iron intake or stores and chronic disease to be convincing. Thus, it considers that there are insufficient data to establish ULs for iron.

In contrast, the IOM has set ULs ranging from 40 mg Fe/d (young children) to 45 mg Fe/d (adults, including pregnant and lactating women). It acknowledges that the risk of adverse effects from dietary sources appears to be low and that between 50 and 75% of pregnant and lactating women consume higher amounts than the UL from food and supplements, though generally under medical supervision. The IOM also argues that people susceptible to adverse effects from iron, including those with hereditary haemochromatosis (most of whom remain undiagnosed until adverse effects are apparent), may not be protected by the UL for iron, but that ULs for such subpopulations cannot be determined until clear dose-response relationships between iron intake and the risk of adverse effects becomes available.

Special considerations

People who are homozygous for hereditary haemochromatosis (reported to occur in 0.3 to 0.5% of Caucasian populations) develop iron overload (due to increased absorption) with clinical symptoms (including hepatomegaly, liver fibrosis, diabetes mellitus, joint inflammation, cardiomyopathy and hepatoma) even at normal dietary intakes. The occurrence of the mutations in the HFE gene varies among different populations; the frequency of the C282Y allele is 5.1 to 9.7% in northern Europe, while the H63D allele is found at frequencies of more than 5% in Mediterranean counties, the Middle East and the Indian subcontinent. The main treatment for haemochromatosis is venesection/phlebotomy, i.e. removal of blood, which causes the mobilisation of some of the excess stored iron to replace the blood cells; this has a greater impact on iron stores than diet, although patients are recommended not to consume iron-containing supplements or fortified foods, together with only modest alcohol consumption. Early diagnosis is acknowledged to be the best way to avoid adverse effects, but screening is not routine in Ireland.

Other conditions which confer risk from dietary iron are chronic alcoholism, alcoholic cirrhosis, other liver diseases, iron-loading abnormalities especially thalassaemias, congenital atransferrinaemia and acaeruloplasminaemia.

There is some conflicting epidemiological evidence linking high iron intakes with increased risk of certain chronic diseases (cardio vascular disease, Type 2 Diabetes and cancer of the gastrointestinal tract). This has led the IOM to recommend that men and postmenopausal women avoid iron supplements and highly fortified foods.

High intakes of supplemental dietary iron may inhibit zinc absorption if taken without food, but not if both are taken with food.

High intakes of dietary calcium inhibit the absorption of both haem and non-haem iron, though little effect on serum ferritin concentrations (a measure of iron stores) has been observed in supplementation trials using calcium at levels of 1,000 to 1,500 mg/d.

Conclusions

The IOM ULs for iron are considered to be most appropriate for Ireland due to the high incidence of hereditary haemochromatosis. The IOM has set ULs ranging from 40 mg Fe/d (young children) to 45 mg Fe/d (adults, including pregnant and lactating women). EFSA has not established a UL for iron due to insufficient evidence of a causal relationship between iron intake or stores and chronic disease.

Recommendations for Ireland

It is recommended that Ireland adopts the IOM UL for iron (IOM, 2011) as shown in Table 3.15.

Table 3.15. Tolerable Upper Intake Level of Iron (IOM, 2011)

Life Stage Group		Iron (mg/d)
Infants	0-6 mo	40
	7-12 mo	40
Children	1-3 y	40
	4-8 y	40
Males	9-13 y	40
	14-18 y	45
	19-70 y	45
	>70 y	45
Females	9-13 y	40
	14-18 y	45
	19-70 y	45
	>70 y	45
Pregnancy	14-18 y	45
	19-50 y	45
Lactation	14-18 y	45
	19-50 y	45

References

- **European Food Safety Authority (EFSA) (2004)** Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the commission related to the tolerable upper intake level of iron
- **Institute of Medicine (IOM) (2001)** Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc

Zinc

Background

a) Description of zinc

Zinc is a classified as a group IIB post-transition metal and exists as Zn^{2+} in all body tissues and fluids. Zinc has structural, regulatory or catalytic roles in over 300 enzymes involved in the metabolism of proteins, fats and carbohydrates. It maintains the configuration of other proteins such as pre-secretory granules of insulin and some mammalian gene transcription proteins. It is therefore essential for growth and development. Total body zinc is between 2 and 4 g.

Zinc deficiency is rare; it leads to growth and developmental retardation and delayed puberty in children, and diverse effects in adults due to its many roles.

Interactions with a number of dietary factors influence zinc uptake: phytate (a component of dietary fibre) reduces absorption; iron and copper compete with zinc for absorption whereas the amino acids histidine, methionine and cysteine are thought to facilitate absorption by releasing zinc from zinc-calcium-phytate complexes. Low zinc intakes may decrease folate absorption.

Absorption of dietary zinc ranges from 15-60%, most of which is excreted in the bile, there being no apparent specific storage in the body. When intakes are raised, fractional absorption decreases and intestinal excretion increases while urinary losses remain constant. At very high intakes, the excess zinc is lost via the hair.

b) Different forms of zinc and clarity on the forms of zinc that are relevant to the UL

Zinc is associated with proteins in foods; thus high-protein foods are good sources (especially dark-coloured meats), as are certain shellfish (due to concentration from seawater). Wholegrains are high in zinc but bioavailability is low due to phytate content. Other sources of zinc include water and food stored in galvanised containers.

c) Usual intakes, RDAs, AIs

Bioavailability is greatest in refined diets containing red meat and lowest in high-fibre vegetarian diets. It is estimated that 70% of dietary zinc in western diets is provided by animal products. Mean dietary intakes in the EU are reported as 13 mg/d for adult males and 9 mg/d for adult females. Intakes are considered adequate when compared with estimated average requirements (EARs); however, the dietary requirement may be as much as 50% greater than intake for vegetarians. Both the IOM and EFSA have set an RDA for zinc (see Appendix IV). The average intakes of zinc in Ireland are outlined in Appendix V.

Factors such as stress, infection and trauma, can cause plasma zinc levels to drop.

Zinc is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

ULs established by other organisations

In experimental animals, high zinc intakes have a negative effect on copper absorption. Negative effects of high levels of zinc supplementation on iron metabolism have also been demonstrated: affecting iron storage, encouraging depletion, interfering with uptake in the liver and causing anaemia due to increased turnover.

In humans, cases have been documented of both acute and chronic zinc toxicity; the acute form (symptoms of which are gastrointestinal disturbances) caused by consumption of food or drink stored in galvanised containers, and the chronic and sub-chronic caused by prolonged intakes ranging from 50 to 300 mg Zn/d from zinc supplements. Many of the chronic effects are similar to those seen in copper deficiency; thus the IOM chose the adverse effects on copper metabolism as the basis for setting ULs for total daily intake of zinc from food, water and supplements. The IOM ULs range from 4 mg Zn/d in infants up to 40 mg Zn/d in adults; the latter are similar to the 95th percentile of intakes from food and supplements in the NHANES 1988-1994 data.

EFSA takes into consideration, recent data on copper balance suggesting that a moderately deficient intake of zinc (3 mg/d) is more detrimental to copper metabolism and function than moderately high intakes (53 mg/d), provided copper intakes are adequate to high (3 mg/d). Further, the higher dietary zinc intake did not worsen the negative copper balance when dietary copper was low (1 mg/d). Other recent evidence also shows no adverse effects of zinc intakes of 40 mg/d on lipoprotein metabolism, blood profile and circulating levels of peripheral blood leucocyte and lymphocyte subsets. Thus, EFSA considers that no adverse effects are observed at a zinc intake of 50 mg/day. The UL is set at 25 mg/d for adults, including pregnant and lactating women. The ULs for children and adolescents are calculated on the basis of reference body weight$^{0.75}$. The 97.5th percentile of total zinc intakes recorded in EU countries for all age groups is similar to the UL, which is not considered to be of concern.

Special considerations

People with Menke's disease (a rare genetic defect in the uptake of copper from gut cells into the blood) are susceptible to excess zinc intake which may further limit copper absorption.

Conclusions

The EFSA ULs for zinc are considered most appropriate for Ireland. EFSA examined data on copper balance when deriving the ULs for zinc. EFSA considered that no adverse effects are observed at a zinc intake of 50 mg/day and has therefore, set a UL for adults of 25 mg/day.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for zinc (EFSA, 2002) as shown in Table 3.16.

Table 3.16. Tolerable Upper Intake Level of zinc (EFSA, 2002)

Age	Zinc (mg/d)
0-12 mo	*ND*
1-3 yrs	7
4-6 yrs	10
7-10 yrs	13
11-14 yrs	18
15-17 yrs	22
> 17 yrs	25
Pregnancy	25
Lactation	25

ND = non determinable

References

- **European Food Safety Authority (EFSA) (2002)** Opinion of the scientific committee on food on the tolerable upper intake level of zinc
- **Institute of Medicine (IOM) (2001)** Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc

Copper

Background

a) Description of copper

Copper is a transition metal, which exists in biological systems primarily as cupric (Cu^{2+}), and minimally, cuprous (Cu^{+}) in solution. Copper functions as a component of many enzymes and proteins. Many copper metalloenzymes act as oxidases which reduce molecular oxygen. Copper is required for infant growth, immune function, bone strength, red and white cell maturation, and iron, cholesterol and glucose metabolism. The human body contains between 50-150 mg, mostly bound to proteins.

Copper deficiency is rare; symptoms include anaemia, neutropenia and bone abnormalities.

High levels of dietary zinc are known to adversely affect copper absorption and bioavailability. Copper absorption may be inhibited by sucrose, fructose, animal proteins, S-amino acids, histidine and ferrous iron. High dietary amounts of ascorbic acid supplements, molybdenum, calcium and/or phosphorus and cadmium have been shown to adversely affect copper absorption and bioavailability.

Absorption of copper depends on dietary intake, shown to range from 56% at low intakes (0.78 mg/d) to 12% at high intakes (7.53 mg/d). A theoretical maximum absorptive capacity of 63-67% has been estimated; on typical EU diets, average absorption is 30-40%. Copper balance can be achieved over a broad range of intakes, mainly by regulating excretion in bile, though the achievement of balance may take approximately three weeks.

b) Different forms of copper and clarity on the forms of copper that are relevant to the UL

The richest dietary sources of copper are organ meats, seafood, nuts and seeds. Good sources are wheat bran cereals and wholegrain products. Water distributed via copper piping can add 1.0 mg/d to intakes in acid and soft water areas (0.1 mg/d in hard water areas). The maximum concentration permitted in drinking water in the EU is 2.0 mg/L (EU Directive 98/83).

c) Usual intakes, RDAs, AIs

Mean dietary intakes of copper in the EU have been estimated to range from 1.0-2.3 mg/d in adult males and 0.9-1.8 mg/d in adult females; it is not used much in food fortification and very few people consume dietary supplements containing copper (median intakes 0.1-0.5 mg/d). The IOM and EFSA have set an RDA and AI, respectively, for copper (see Appendix IV). The average intakes of copper in Ireland are outlined in Appendix V.

Copper is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

ULs established by other organisations

Sensitivity to high intakes of copper in animals varies according to species and to the chemical form consumed. It causes liver, kidney and brain damage, probably due to oxidation.

In humans, acute copper toxicity causes gastrointestinal effects, and is usually caused by consumption of foods and beverages stored in copper-containing vessels. Chronic copper toxicity has its most pronounced effects on liver function; hepatic mitochondria are likely to be an important target. Thus, IOM set ULs on the basis of liver damage as the critical endpoint; its values range from 1.0 mg/d (for one to three year-olds) to 10.0 mg/day (adults) total copper from food, water and supplements. The 99th percentile of intakes recorded in the 1988-1994 NHANES data was 4.7 mg/d.

EFSA uses Cu-induced nausea to define the acute level, 4 mg/L of bottled water, at which no adverse effect was observed. Based on data on copper poisoning, the WHO has concluded that the fatal oral dose of copper salts is approximately 200 mg/kg body weight.

Chronic toxicity has been less studied; it has arisen due to a high copper content of drinking water. Interpretation of elevated serum copper and caeruloplasmin levels is complicated by the fact that these occur as part of the acute-phase response in inflammatory conditions, such as chronic heart disease.

Childhood idiopathic copper toxicosis has been associated with high copper content of drinking water or diet.

EFSA proposes that, although gastrointestinal effects of copper toxicity are better documented in humans than liver damage, it is the latter that should be used as the critical endpoint from which to derive ULs, since the aim of the UL is to identify safety of maximal copper intakes over a long period. Based on this type of evidence, it considers that no adverse effects are observed at total copper intakes of 10 mg/d in adults. Also, homeostatic data indicate that (in healthy people) body copper status is resistant to change except under extreme dietary conditions. In the light of this evidence, EFSA set a UL of 5 mg/day for adults; the values for children (1-4 mg/d) are based on relative body weight (using reference weights). The 97.5th percentile of total copper intake for all age groups in EU countries is close to the UL, which is not considered to be of concern. However, it is noted that the additional intakes from drinking water, which can be appreciable, may need to be taken into account.

Special considerations

People with Wilson's disease (an autosomal recessive disease of copper storage, incidence 1 in 30,000 worldwide) are a sensitive population; if untreated, copper accumulates in the liver, the cornea and the central nervous system, leading ultimately to hepatic failure and death.

There may also be a genetic component in many cases of Indian childhood cirrhosis, arising from consumption of milk that has been boiled and stored in copper and brass containers.

Conclusions

The EFSA ULs for copper are considered most appropriate for Ireland. Both EFSA and the IOM have set ULs for copper derived using liver damage as the critical endpoint since the aim of the UL is to identify safety of maximal copper intakes over a long period. However, it should be noted that additional intakes of copper from drinking water may need to be taken into account.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for copper (EFSA, 2003) as shown in Table 3.17.

Table 3.17. Tolerable Upper Intake Level of copper (EFSA, 2003)

Age	Copper (mg/d)
0-12 mo	*ND*
1-3 yrs	1
4-6 yrs	2
7-10 yrs	3
11-14 yrs	4
15-17 yrs	4
> 17 yrs	5
Pregnancy	*ND*
Lactation	*ND*

ND = non determinable

References

- **European Food Safety Authority (EFSA) (2003)** Opinion of the scientific committee on food on the tolerable upper intake level of copper
- **Institute of Medicine (IOM) (2001)** Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc

Selenium

Background

a) Description of selenium

Selenium (Se) is an essential dietary element involved in the formation of a number of proteins involved in thyroid, neural, immune and gastrointestinal function. Selenium nutritional status is strongly related to the Se content of soil with areas of the world such as Denmark, Finland, New Zealand, and parts of China and Russia having areas of low Se while plains of the USA, Canada and parts of Colombia have high Se soil.

Se exists in inorganic form as selenate, selenite and selenide. It exists in organic forms as seleno-cysteine (SeCys), seleno-methionine (SeMet) and is an essential component of the selenoproteins. There are about 30 mammalian selenoproteins identified but the major selenoproteins of relevance to human nutrition include glutathione peroxidase (GPx), iodothyronine deiodinase and selenoprotein P. Most selenoproteins are involved in oxidation/ reduction reactions, thus making selenium an important antioxidant nutrient. A significant body of epidemiological data implicates a higher selenium status with a reduced incidence of various chronic diseases, such as cancer (particularly prostate cancer) and cardiovascular disease.

Se deficiency occurs in areas of China and Russia with low soil Se. Severe clinical deficiency results in Keshan disease, an often fatal condition causing insufficiency of cardiac function, cardiac enlargement, and abnormal rhythm. Selenium deficiency has also been implicated in the aetiology of Kashin-Beck disease which is a chronic bone disease causing osteochondropathy, enlarged joints, shortened fingers/toes and dwarfism. Selenium deficiency may induce goitre (iodine deficiency) due to its role in deiodinases. Chronic low selenium intake reduces innate immunity via the selenoproteins. An apparent hierarchical response to Se deficiency exists with the brain, endocrine and reproductive organs preferentially provided with and retaining more Se compared to other tissues.

The interaction between selenium and vitamin E is well established. Low levels of Se can be compensated for, to some extent, by vitamin E. Selenium also interacts with iodine.

Absorption of selenium is efficient and is not regulated. More than 90% of selenomethionine, the major dietary form of the element, is absorbed by the same mechanism as methionine itself. Although little is known about selenocysteine absorption, it appears to be absorbed very well. SeCys is incorporated into very specific selenoproteins whereas SeMet replaces Met. Bioavailability of SeCys and SeMet from plants is good but not as good from animal sources. SeMet enters the amino acid pool and is well retained but makes a low contribution to selenoproteins due to processing. SeCys is less well retained than SeMet but retained in selenoproteins via selenide. The liver is the major organ regulating the handling of selenium, including its excretion. Methylation of selenium occurs in the liver prior to excretion by the kidneys with evidence suggesting that selenosugars are the major forms excreted.

Selenium can be exhaled as dimethyl selenide in cases of excess selenium intakes and can also be shed in skin.

b) Different forms of selenium and clarity on the forms of selenium that are relevant to the UL

Selenium is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

The selenium content of food varies depending on the selenium content of the soil where the animal was raised or the plant was grown. In addition, the addition of selenium to animal feed can potentially result in improved selenium content of animal derived products, e.g. eggs. A WHO report on the selenium content of foods shows the following composition: meats and seafood 0.4 to 1.5 µg/g; muscle meats, 0.1 to 0.4 µg/g; cereals and grains, less than 0.1 to greater than 0.8 µg/g; dairy products, less than 0.1 to 0.3 µg/g; and fruits and vegetables, less than 0.1 µg/g. Brazil nuts are a particularly rich source of selenium, containing 18-12 µg/g. Thus, the same foodstuffs may have more than a ten-fold difference in selenium content. The amount of selenium available in the soil for plant growth and corresponding variations in the intake of selenium by humans, varies considerably among regions and countries.

c) Usual intakes, RDAs, AIs

Mean daily Se intakes from all sources and from food sources alone, for Irish adults aged 18-64 y were 52 and 50 µg/day respectively in the NSIFC survey in 2001. As yet, there are no published data on selenium intakes from the more recent Irish food surveys.

The IOM has set an RDA and EFSA has set an AI for selenium (see Appendix IV). It is acknowledged by both that requirements increase during pregnancy and lactation. It is noteworthy that selenium requirements are based on maintaining optimum plasma glutathione peroxidase (GPx) activity. However, the selenium requirement to optimise the activity of other selenoproteins remains unresolved.

ULs established by other organisations

It is well known that Se can induce toxicity. However, it is likely that several mechanisms of toxicity may operate and vary among different selenium compounds. Clinical symptoms associated with selenium toxicity are usually referred to as selenosis and include symptoms such as hair or nail loss, nail abnormalities, mottled teeth, skin lesions, foul body and breath odour and changes in peripheral nerves. EFSA and the IOM derived a UL for Se from a NOAEL of 850 µg/day based on symptoms of clinical selenosis in a Chinese study. The NOAEL was derived from a study on a large number of subjects and is expected to include sensitive individuals.

The EFSA committee decided to use a UF of three to derive a UL of 300 µg Se/day for adults. Given the lack of data available to derive a UL for children, the committee extrapolated the UL from adults to children on a body weight basis. The UL values cover selenium intake from all sources of food, including supplements.

The IOM committee chose a UF of two to protect sensitive individuals to derive a UL of 400 µg Se/day for adults. The committee concluded that the toxic effect is not severe but may not be readily reversible, so a UF greater than one, is needed.

Special considerations

The knowledge that there are areas in the world where there is a human intake of selenium with no or only very small safety margins to levels where toxicity may occur, puts certain people at risk of exceeding the UL. However, in most European countries, including Ireland, the mean intake levels are much lower and in fact, may be insufficient for much of the population.

Conclusions

The EFSA ULs for selenium are considered most appropriate for Ireland. Both EFSA and the IOM selected a NOAEL based on the symptoms of clinical selenosis in a Chinese study in order to derive the UL. EFSA has not established a UL for infants <1 year of age due to a lack of data. Therefore, the IOM UL for infants <1 year of age is considered appropriate for Ireland.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for selenium (EFSA, 2006) and adopts the IOM UL for infants <1 year (IOM, 2000) as shown in Table 3.18

Table 3.18. Tolerable Upper Intake Level for selenium (µg/day) (EFSA, 2006)

Age (years)	Selenium (µg/day)
<1 year	45*
1-3 y	60
4-8 y	90-130
9-13 y	130-200
14-18 y	250
Adults+	300

* The IOM UL value for infants < 1 year is: 45 µg/day for 0-6 months and 60 µg/day for 7-12 months

References

- **European Food Safety Authority (EFSA) (2006)** Tolerable Upper Intake levels Vitamins and Minerals. Scientific Panel on Dietetic Products, Nutrition and Allergies
- **Institute of Medicine (IOM) (2000)** Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids
- **Murphy J, Hannon EM, Kiely M, Flynn A, Cashman KD (2002)** Selenium intakes in 18-64-y-old Irish adults. *Eur J Clin Nutr.*256(5):402-8
- **World Health Organization (WHO) (1987)** Selenium, Environmental Health Criteria 58, Geneva: World Health Organization

Iodine

Background

a) Description of iodine

Iodine is an essential dietary element for synthesis of the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). The thyroid hormones are involved in the maintenance of metabolic rate, cellular metabolism and integrity of connective tissue.

Low levels of iodine intake are compensated for by a variety of mechanisms such as the enlargement of the thyroid gland (goitre). It is only when such mechanisms fail that symptoms of hypothyroidism (elevated levels of thyroid stimulating hormone (TSH)) present. These include lethargy, weakness, weight gain, poor concentration, oedema, myalgia, dry skin, delayed tendon reflexes and slow heart rate. Iodine deficiency during pregnancy is associated with an increased risk of miscarriage, stillbirth and congenital abnormality. Iodine deficiency in the developing foetus can result in cretinism.

Iodine interacts with selenium and possibly with vanadium. Natural goitrogens (which impair thyroid hormone synthesis) may be present in foodstuffs such as soybeans, walnuts and brassicas or formed from foods such as corn and maize.

Ingested iodine and iodate are reduced to iodide in the gut and almost completely absorbed by the small intestine. Iodine can also be absorbed through the skin. Once in the circulation, iodine is principally removed by the thyroid gland. The thyroid selectively concentrates iodide in amounts required for adequate thyroid hormone synthesis. The concentrations of iodine in the thyroid gland affect the uptake of iodine, the ratio of T3 to T4 and the rate of release of these hormones into circulation. This process is also under hormonal control by the hypothalamus. Excess iodine is excreted in urine.

b) Different forms of iodine and clarity on the forms of iodine that are relevant to the UL

Iodine is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

High levels of iodine are present in marine fish, shellfish, marine algae, seaweed and sea salt. Milk and dairy products also constitute a major source of iodine. There has been a general increase in the iodine content of milk in recent years through the use of iodine supplemented feeds in dairy herds. Milk is also contaminated with iodine through the use of iodophor disinfectants used in sanitisation and teat dipping. The iodine content of milk shows seasonal variation with concentrations of iodine in winter milk considerably higher than in summer milk as dairy herds are more dependent on the iodine-rich artificial feeds during these months (Nawoor *et al.*, 2006; Philips, 1997). Additionally, organic milk has been found to be lower in iodine content than conventional milk and is thought to be a result of general mineral restrictions in organic farming (Bath *et al.*, 2012; Rey-Crespo *et al.*, 2013). The iodine content of cereals and grains is variable as the level is dependent on the iodine content of the soil. In most European countries, iodine intake is maintained by the use of iodised table salt (15-25 mg I/kg). However, the availability and use of iodised salt are not widespread in Ireland.

c) Usual intakes, RDAs, AIs

The IOM has set an RDA and EFSA has set an AI for iodine (see Appendix IV). Iodised salt is mandatory in Canada and discretionary in the United States. The average intakes of iodine for some population groups in Ireland are outlined in Appendix V.

ULs established by other organisations

In response to iodine excess, thyroid stimulating hormone (TSH) concentrations can become elevated. An elevated TSH concentration is not necessarily clinically adverse but could be an indicator for increased risk of developing hypothyroidism. Both the EFSA (2002) and the IOM (2001) UL are based on the two same short-term dose response studies that demonstrated marginal TSH changes at intake levels of 1,700 – 1,800 µg/day. No other adverse effects were observed at these levels of iodine intake. EFSA considered the application of an UF of three to be adequate and this resulted in a UL of 600 µg/day. In comparison, the IOM applied a lower UF of 1.5 and this resulted in a UL of 1,100 µg/day. In relation to elevated TSH, EFSA stated that it 'could be considered as indicating a risk of induced hypothyroidism' whereas the IOM referred to its 'mild, reversible nature'. Both EFSA and the IOM extrapolated the ULs from adults to give ULs for children and adolescents (based on body surface area and body weight respectively) and both also set the UL for pregnancy and lactation as the same as the adult UL.

Special considerations

For certain subgroups of the population, the UL for Iodine may not be applicable. These subgroups include:

- Individuals with iodine deficiency disorders. Such individuals are more sensitive to iodine exposures
- Individuals who are being treated with iodine under medical supervision

Conclusions

The EFSA UL for iodine is considered most appropriate for Ireland. Both EFSA and the IOM have established ULs for iodine based on the same two short-term dose response studies which observed changes in TSH levels in response to iodine intake levels of 1,700-1,800 µg/day, but applied different uncertainty factors. Both institutes used the adult ULs to derive ULs for children and set the same ULs for pregnancy and lactation as the adult UL.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for iodine (EFSA, 2002) as shown in Table 3.19.

Table 3.19. Tolerable Upper Intake Level of Iodine (EFSA, 2002)

Age	Iodine (µg/d)
0-12 mo	*ND*
1-3 yrs	200
4-6 yrs	250
7-10 yrs	300
11-14 yrs	450
15-17 yrs	500
≥18 yrs	600
Pregnancy	600
Lactation	600

ND = non determinable

References

- **Bath S.C., Button S., Rayman M.P. (2012)** Iodine concentration of organic and conventional milk: implications for iodine intake. *British Journal of Nutrition* **107**: 935-940
- **European Food Safety Authority (EFSA) (2002)** Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Iodine
- **Institute of Medicine (IOM) (2001)** Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc
- **Nawoor Z., Burns R., Smith D. F., Sheehan S., O'Herlihy C., Smyth P. P. A. (2006)** Iodine intake in pregnancy in Ireland — A cause for concern? *Irish Journal of Medical Science* **175**: 21-24
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- **Rey-Crespo C., Miranda M., Lopez Alonso M. (2013)** Essential trace and toxic element concentrations in organic and conventional milk in NW Spain. *Food and Chemical Toxicology* **55**: 513-518

Manganese

Background

a) Description of manganese

Manganese is an abundant transition element that can exist in a number of oxidation states. Mn (II) is the main form in biological systems. Manganese is a catalytic cofactor for a number of enzymes and activates a range of others. Manganese deficiency has only been observed under experimental conditions.

Manganese-iron interactions have been demonstrated. The possible mechanism for this interaction is competition for similar binding and absorption sites. Phytate, calcium and phosphorus may also interfere with manganese absorption. There is a suggestion that ethanol may enhance manganese toxicity.

Absorption of manganese takes place throughout the length of the intestine. Manganese absorption is relatively inefficient with about 3-8% of orally ingested manganese absorbed. Manganese is taken up from the blood by the liver and transported to extrahepatic tissues by transferrin and possibly albumin and α2macroglobulin. Manganese accumulates in mitochondria-rich tissues such as the pancreas and the liver. It also accumulates in the brain. Manganese is excreted largely in the faeces, mainly as a result of biliary excretions.

b) Different forms of manganese and clarity on the forms of manganese that are relevant to the UL

Manganese is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I. Manganese is present in foods, particularly green vegetables, nuts, bread and other cereals. Tea is also a rich source of manganese.

c) Usual intakes, RDAs, AIs

There is no information from the national surveys on manganese intakes in Ireland. Both the IOM and EFSA have set an AI for manganese (see Appendix IV).

ULs established by other organisations

EFSA (2000) did not set a UL due to the limitations of the human data and the non-availability of a NOAEL from the animal studies. EFSA noted that the occupational exposure to manganese by inhalation is neurotoxic and oral intake of manganese, despite its poor absorption in the gastrointestinal tract, has also been shown to cause neurotoxic effects.

Elevated blood manganese concentrations and neurotoxicity were selected as the critical adverse effects on which the IOM (2001) UL for manganese is based. A NAOEL of 11 mg/day of manganese from food was identified based on the available data and an uncertainty factor of one was selected. A UL of 11mg/day was derived. For children and adolescents, the adult UL was adjusted on the basis of relative weight. The ULs for pregnant and lactating women are the same as those for the non-pregnant women. The UL represents total intake from food, water and supplements.

Special considerations

For certain subgroups of the population, the UL for manganese may not be applicable.

These subgroups include:

- Anaemic individuals. This group may be vulnerable due to the increased manganese absorption that occurs in states of iron deficiency
- Individuals with impaired biliary clearance, e.g. liver disease, older individuals. They may be susceptible to manganese accumulation and toxicity

Conclusions

The IOM ULs for manganese are considered most appropriate for Ireland. The IOM has set a UL based on the critical adverse effects; elevated blood manganese and neurotoxicity. EFSA has not established a UL for manganese due to insufficient data from human and animal studies but have noted that occupational exposure by inhalation and oral intake of manganese can result in neurotoxic effects.

Recommendations for Ireland

It is recommended that Ireland adopts the IOM UL for manganese (IOM, 2001) as shown in Table 3.20.

Table 3.20. Tolerable Upper Intake Level of Manganese (IOM, 2001)

Life Stage Group		Manganese (mg/d)
Infants	0-6 mo	*ND*
	7-12 mo	*ND*
Children	1-3 y	2
	4-8 y	3
Males	9-13 y	6
	14-18 y	9
	19-70 y	11
	>70 y	11
Females	9-13 y	6
	14-18 y	9
	19-70 y	11
	>70 y	11
Pregnancy	14-18 y	9
	19-50 y	11
Lactation	14-18 y	9
	19-50 y	11

References

- **European Food Safety Authority (EFSA) (2000)** Opinion of the Scientific Committee on Food and the Tolerable Upper Intake Level of Manganese
- **Institute of Medicine (IOM) (2001)** Dietary Reference intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc

Molybdenum

Background

a) Description of molybdenum

Molybdenum is a transition element that exists in five oxidation states, of which +4 and +6 are the predominant species.

Molybdenum functions as a co-factor for a number of enzymes. All of the molybdoenzymes are oxidoreductases. In humans, xanthine oxidase, sulphite oxidase and aldehyde oxidase are important molybdoenzymes.

Molybdenum is considered an essential dietary element for mammals though the clinical signs of dietary molybdenum deficiency in otherwise healthy individuals have not been described. A single case suggestive of molybdenum deficiency was identified in a patient receiving total parenteral nutrition lacking molybdenum for 12 months.

Molybdenum is readily absorbed from food. It is widely distributed in the cells and in the extracellular fluid. The greatest amount can be found in the kidneys, liver and bones. Molybdenum is primarily excreted in the urine, with significant amounts also excreted in bile.

Molybdenum interacts with copper and sulphates in living organisms. Molybdenum supplementation can deplete levels of the essential trace element copper and has been used as a chelating agent for conditions such as Wilson's disease (an inherited disorder of copper accumulation).

b) Different forms of molybdenum and clarity on the forms of molybdenum that are relevant to the UL

Molybdenum is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I. In general, foods from above ground plant material, such as legumes, leafy vegetables and cauliflower contain relatively high concentrations of molybdenum compared with food from tubers or animals.

c) Usual intakes, RDAs, AIs

There is a lack of information on molybdenum in food composition databases and hence, dietary intake data are limited. There is no information from the national surveys on molybdenum intakes in Ireland. The IOM has set an RDA and EFSA has set an AI for molybdenum (see Appendix IV).

ULs established by other organisations

An EFSA UL (2000) was established using a nine week study in the rat (Fungewe *et al.*, 1990). The UL is based on a NOAEL of 0.9 mg/kg body weight/day for reproductive toxicity. A UF of 100 was used (comprised of ten for protecting sensitive human sub-populations with inadequate copper intake/deficient copper metabolism, another ten to cover the lack of knowledge about the reproductive effect of molybdenum in humans and incomplete data on the toxicokinetics in man).

This provides a UL of approx. 0.01 mg/kg body weight/day, equivalent to 0.6 mg/person/day for adults, which also covers pregnant and lactating women. The UL for children is extrapolated from the adult UL on a body weight basis. The EFSA UL for molybdenum represents intake from all sources.

Similar to EFSA, the IOM (2001) UL is based on adverse reproductive effects in rats fed a high level of molybdenum. A NOAEL OF 0.9 mg/kg/day was established and an UF of 30 was used (the usual value of ten for extrapolating from experimental animals to humans and an UF of three for intra-species variation). The resulting UL for adults is rounded to 2 mg/day. The UL for adults is adjusted for children and adolescents on the basis of relative body weight. The UL for pregnant and lactating women is the same as that for non-pregnant women and non-lactating women because the UL is based on adverse reproductive effects in animals and there are no reports of molybdenum toxicity in lactating women. The IOM UL represents total intake from food, water and supplements.

The EFSA and the IOM ULs are based on reproduction and foetal development in rats and mice. In deriving the UL, both institutions considered the same study and selected the same NOAEL; however, different UFs were applied. The UF EFSA applied was approximately three times greater compared to the IOM UF.

However, in this EFSA opinion on molybdenum, a default body weight of 60kg was used to convert the 'safe' level of 0.01 mg/kg bw/day to an UL of 0.6 mg per day. This reference body weight is not gender specific and is low compared with current average weights for adult men and women in Ireland (86kg and 70kg respectively). Therefore, the FSAI and EFSA have agreed that when deriving a UL for molybdenum for the adult population of Ireland, it would be more appropriate to use a reference body weight of 70kg for both sexes resulting in a UL of 0.7 mg/day. Table 3.21 below outlines the EFSA UL using 60kg and the re-calculated EFSA UL using 70kg.

Table 3.21. EFSA Tolerable Upper Intake Level for Molybdenum established for Adults using a Reference Body Weight of 60kg and using a Reference Body Weight of 70kg

Micronutrient (year UL was established)	Upper level of intake per kg body weight per day	EFSA established UL for adults using various reference body weights		EFSA UL for adults recalculated using a reference body weight of 70kg	
		Reference body weight (kg)	UL	Reference body weight (kg)	UL
Molybdenum (2000)	0.01 mg/kg body weight /day	60	0.6 mg/day	70	0.7 mg/day

Special considerations

For certain subgroups of the population, the UL for molybdenum may not be applicable.

These subgroups include:

- Individuals who are deficient in dietary copper or who have a dysfunction of copper metabolism that may render them copper deficient

Conclusions

The EFSA UL for molybdenum is considered most appropriate for Ireland. Both EFSA and the IOM based the UL on reproduction and foetal development in rats and mice. Both institutions chose the same NOAEL when deriving the UL but EFSA chose an uncertainty factor three times greater than that selected by the IOM. EFSA has used a reference body weight of 60kg to derive its UL for molybdenum. However, when this was looked at in an Irish context, it was agreed by both the FSAI and EFSA that a body weight of 70kg, which is more representative of the adult population of Ireland, should be used to derive the UL recommended for adults in Ireland.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for molybdenum (EFSA, 2000) as shown in Table 3.22.

Table 3.22. Tolerable Upper Intake Level of Molybdenum (EFSA, 2000)

Age	Molybdenum (mg/d)
0-12 mo	*ND*
1-3 yrs	0.1
4-6 yrs	0.2
7-10 yrs	0.25
11-14 yrs	0.4
15-17 yrs	0.5
>17 yrs	0.7*
Pregnancy	0.7*
Lactation	0.7*

ND = non determinable

*Re-calculated EFSA UL for adults using a reference body weight of 70kg

References

- **European Food Safety Authority (EFSA) (2000)** Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Molybdenum
- **Institute of Medicine (IOM) (2001)** Dietary Reference intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc

Fluoride

Background

a) Description of fluoride

Fluorine is gaseous halogen. It is the most electronegative and reactive of all elements, therefore it occurs naturally only in ionic forms (fluorides) after reaction with metallic elements or hydrogen. Fluoride is ubiquitous in nature and, in the body, is mainly associated with calcified tissue (bone and teeth) due to its high affinity for calcium.

Fluoride has no known essential function for human growth and development. Though fluoride is not essential for tooth development, exposure to fluoride leads to incorporation into the hydroxyapatite of developing tooth enamel and dentin. The resulting fluoroapatite is more resistant to acids than hydroxyapatite. In addition, dietary fluoride also exerts an effect on erupted teeth and inhibits sugar metabolism by oral bacteria.

No signs of fluoride deficiency have been identified. There is some evidence that fluoride may interact with certain nutrients and dietary substances. The presence of calcium, magnesium, phosphorus and aluminium decreases the absorption of fluoride. In the case of calcium, the inhibitory effect depends on the presence of food. The rate and extent of fluoride absorption from the gastrointestinal tract are reduced by ingestion with foods and liquids that are rich in calcium, such as milk.

Fluoride absorption occurs by passive diffusion in both the stomach and small intestine. On average, 80-90% of fluoride ingested is absorbed. Due to fluoride's high affinity for calcium, the vast majority of body fluoride is found in calcified tissues. Elimination of absorbed fluoride occurs through the kidneys.

b) Different forms of fluoride and clarity on the forms of fluoride that are relevant to the UL

Fluoride is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

Major fluoride food sources are water and water-based beverages or foods reconstituted with fluoridated water, e.g. soup, marine fish, fluoridated salt, and tea. Oral exposure to fluoride occurs through water, food (including fluoridated table salt), fluoride supplements, toothpaste and other cosmetic dental products.

c) Usual intakes, RDAs, AIs

In Ireland, all public drinking water is fluoridated, a programme which began in 1964 (Forum on Fluoridation, 2002). Originally, public drinking water was required to be fluoridated to a level between 0.8 to 1.0 ppm. This level of fluoridation has since been reduced and now public water supplies are fluoridated to a level to between 0.6 and 0.8 ppm (S.I. No. 42 of 2007). Not all individuals in Ireland access water from the public supplies and therefore, will not consume fluoridated water.

Both EFSA and the IOM have derived an AI for fluoride (see Appendix IV). The EFSA AI for adult males is 3.4 mg/day and 2.9 mg/day for females.

ULs established by other organisations

For EFSA (2005), the critical endpoint for the derivation of the UL of oral fluoride intake differs based on age group. For children from the age of one to eight years, it is based on moderate dental fluorosis and for all ages above eight years, it is based on bone fracture. Different ULs are set for these groups.

The occurrence of moderate dental fluorosis is <5% in populations at fluoride intakes of 0.1 mg/kg body weight per day and this value is used to calculate the UL for children up to the age of eight years on a body weight basis. No UF is deemed necessary to derive a UL from this intake, because it is derived from population studies.

Therapeutic doses of fluoride in postmenopausal osteoporosis suggest an increasing risk for skeletal fractures at or above fluoride intakes of 0.6 mg/kg body weight. An uncertainty factor of five is applied (due to short duration of studies and taking into consideration the studies were not designed to systemically define a LOAEL) to derive a UL for children older than eight years and adults. An intake of 0.12 mg/kg body weight/day converts on a body weight basis (60kg) into a UL of 7 mg/day for adults. This UL applies to pregnant and lactating women.

The UL for fluoride applies to intake from water, beverages and food stuffs, including fluoridated salt, dental health products and fluoride tablets for caries prevention. EFSA notes that there is narrow margin between recommended intakes and the prevention of dental caries and the ULs.

EFSA did not establish a UL for infants. Breast-fed infants have very low fluoride intakes from human milk (2-40 µg/day). EU legislation governing infant formulae and follow-on formulae specifies a maximum fluoride content of 100 µg/100kcal (Directive 2006/141/EC). Probabilistic modelling has been completed to estimate fluoride intake by infants up to age of four months from infant formula reconstituted with fluoridated tap water in Ireland (Anderson *et al.*, 2004). The estimates were based on calculated infant formula consumption and accepted body weight standards, together with reported concentrations of fluoride in infant formula powder and measured values for the fluoride content of water in Ireland. The average daily intake of fluoride from infant formula reconstituted with fluoridated tap water over the first four months of life was estimated to be in the range of 0.106 and 0.170 mg/kg body weight /day (Anderson *et al.*, 2004). At these predicted chronic intakes of fluoride, dental fluorosis may be considered to be the only risk at these low doses (Anderson *et al.*, 2004).

Similar to EFSA, the IOM (1997) critical endpoint for establishing a UL for fluoride differed by age group. However, endpoints chosen by the IOM were different from EFSA. The UL for infants and young children (eight years and younger) is based on the critical adverse effect of developing fluorosis of the anterior teeth. The UL for individuals aged nine years and older is based on adverse effect of developing early signs of skeletal fluorosis, which is associated with an intake of fluoride greater than 10 mg/day for a period of ten years. The UL for individuals aged nine years and older is 10 mg/day. The IOM UL values for fluoride represent total intake from food, water and supplements.

However, in this EFSA opinion on fluoride, a default body weight of 58kg was used to convert the 'safe' level of 0.12 mg/kg bw/day to an UL of 7 mg per day. This reference body weight is not gender specific and is low compared with current average weights for adult men and women in Ireland (86kg and 70kg respectively). Therefore, the FSAI and EFSA have agreed that when recommending a UL for fluoride for the adult population of Ireland, it would be more appropriate to use a reference body weight of 70kg for both sexes resulting in a UL of 8mg/day. Table 3.23 outlines the EFSA UL using 58kg and the re-calculated EFSA UL using 70kg.

Table 3.23. EFSA Tolerable Upper Intake Level for Fluoride established for Adults using a Reference Body Weight of 58kg and using a Reference Body Weight of 70kg

Micronutrient (year UL was established)	Upper level of intake per kg body weight per day	EFSA established UL for adults using various reference body weights		EFSA UL for adults recalculated using a reference body weight of 70kg	
		Reference body weight (kg)	UL	Reference body weight (kg)	UL
Fluoride (2005)	0.12 mg/kg body weight/day	58	7 mg/day	70	8 mg/day

Conclusions

The EFSA UL for fluoride is considered most appropriate for Ireland. The critical end points, moderate dental fluorosis (one to eight years) and bone fracture (>8 years), were chosen by EFSA in order to derive the UL. EFSA has used a reference body weight of 58kg to derive its UL for fluoride. However, when this was looked at in an Irish context, the FSAI and EFSA agreed that a body weight of 70kg, which is more representative of the adult population of Ireland, should be used to derive the UL recommended for adults in Ireland.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for fluoride (EFSA, 2005) as shown in Table 3.24.

Table 3.24. Tolerable Upper Intake Level of Fluoride (EFSA, 2005)

Age	Fluoride (mg/d)
0-12 mo	*ND*
1-3 yrs	1.5
4-8 yrs	2.5
9-14 yrs	5
>15 yrs	8*
Pregnancy	8*
Lactation	8*

ND = non determinable

*Re-calculated EFSA UL for adults using a reference body weight of 70kg

References

- **Anderson WA, Pratt I, Ryan MA, Flynn A (2004)** A probabilistic estimation of fluoride intake by infants up to the age of four months from infant formula reconstituted with tap water in the fluoridated regions of Ireland. *Caries Research* 38:421-429
- **European Food Safety Authority (EFSA) (2005)** Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on request from the Commission related to tolerable upper intake level of Fluoride
- **European Food Safety Authority (EFSA) (2013)** Scientific Opinion on Dietary Reference Values for fluoride *EFSA Journal 2013*: 11(8):3332
- **Forum on Fluoridation (2002)** Forum on Fluoridation Report. The Stationary Office: Dublin: The Government of Ireland
- **Institute of Medicine (IOM) (1997)** Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride
- **Irish Universities Nutrition Alliance (2011)** The National Adult Nutrition Survey (NANS) http://www.iuna.net/?p=106
- S.I. No. 42/2007 – Fluoridation of Water Supplies Regulations, 2007

Chromium

Background

a) Description of chromium

Elemental chromium does not occur naturally, but its compounds are ubiquitous in water, soil and biological systems, the most stable forms being the 0 (metals and alloys), +3 (trivalent, occurring in food and supplements) and +6 (hexavalent) valence states. Chromium compounds with oxidation states below +3 are reducing, and above +3 are oxidising. Hexavalent chromium is almost all man-made, and is strongly oxidising in biological systems (and carcinogenic); because it doesn't occur in food, it has not been evaluated by EFSA.

Chromium is considered to be an essential nutrient. It potentiates the action of insulin and may improve glucose tolerance; it may also possibly have beneficial effects on lipid metabolism.

Deficiency in humans is rare; the clinical signs and symptoms include impaired plasma glucose utilisation and increased insulin requirements, weight loss, neuropathy, elevated plasma fatty acids and abnormalities in nitrogen metabolism.

b) Different forms of chromium and clarity on the forms of chromium that are relevant to the UL

Absorption of dietary trivalent chromium depends on its chemical properties, the amount present, and interactions with other dietary components (which can chelate chromium, e.g. phytate). Absorption of chromium salts in humans is generally low; it has been reported to range from 0.13% (chromium chloride) up to 2.8% (chromium picolinate), and from food the range reported is 0.4 to 2.5%.

Absorption may be enhanced by dietary vitamin C, whereas antacids reduce absorption and retention of chromium. Aspirin has been shown to cause tissue and urine levels of chromium to increase in experimental animals. Diets high in simple sugars (35% of energy) have been shown to increase urinary excretion of chromium.

Rich sources of dietary chromium include meats, oils and fats, bread, nuts and cereals, some beers and wines. Wholegrains are good sources whereas refined cereals are poorer sources. Acidic foods may acquire chromium during processing from stainless steel vessels or utensils.

Dietary intakes of chromium in the EU and USA can range from <10 µg Cr/d up to 580 µg Cr/day. Supplements contain up to 100 µg Cr per daily serving.

c) Usual intakes, RDAs, AIs

There are currently no EU or UK recommended intakes for chromium. COMA (UK) has concluded that a safe and adequate intake lies above 25 µg/d for adults and between 0.1 and 1.0 µg/kg body weight per day for children. The IOM set only AIs for chromium, ranging from 0.2 µg/d for infants to 45 µg/d for lactating women (see Appendix IV).

Chromium is permitted to be added to foods and food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I.

The EFSA committee does not consider that organic complexes of chromium, e.g. chromium picolinate, can be evaluated as a nutrient source in PARNUTs unless data on bioavailability in humans are provided.

ULs established by other organisations

Acute toxicity has been investigated in rats and mice and varies with the compound and sex of the animal. The LD50 levels established range from 140 g/kg (water soluble trivalent chromium) up to 3,250 mg/kg body weight (chromium nitrate nonahydrate). Chronic toxicity studies with rats and mice have been shown to affect fertility; sub-chronic doses do not appear to have much effect.

In humans, hexavalent chromium is considered to be responsible for the excess cancer risk observed in chromium workers, though this is based partly on animal carcinogenicity and genotoxicity results. Trivalent and metallic chromium have not been classified by the IARC with respect to carcinogenicity in humans due to a lack of adequate data. The results of chronic studies in humans have been limited; some adverse effects have been reported due to intakes of up to 1 mg/d chromium as picolinate for up to 64 weeks.

Only one case of lethal poisoning has been reported in a woman who consumed 48 g of chromium sulphate (from leather tanning solution) which caused acute renal shock, pancreatitis, haemorrhage, gut mucosal necrosis and cardiogenic shock (the cause of death).

EFSA (2003) concludes that there are insufficient data on trivalent chromium salts to establish a dose-response relationship therefore, ULs cannot be derived. However, the EGVM (UK, 2003), consider (based on rat studies) that a total daily intake of approximately 0.15 mg trivalent chromium per kg body weight per day (or 10 mg/person) would be expected not to cause adverse health effects in humans. This guidance level excludes chromium picolinate which has been shown in vitro to induce DNA damage (via mechanism(s) that are not clear).

The 1996 WHO report on Trace Elements in Human Nutrition and Health states that 'the relatively non-toxic nature of chromium as found in food indicates that the tolerable limit for chromium is quite high. Findings that supplements of 125-200 µg of chromium/day, in addition to the usual dietary intake, can in some cases, reverse hypoglycaemia and impaired glucose tolerance, and improve both circulating insulin levels and the lipid profile, suggest that the upper limit of the safe range of population mean intakes could be above 250 µg/d. However, until more is known about chromium, it seems appropriate that supplementation of this element should not exceed this amount' (WHO, 1996).

Similarly, the IOM does not consider that sufficient data exist to set ULs, stating only that, although no adverse effects have been convincingly associated with excess intake from food or supplements, mainly because it is very poorly absorbed, caution may yet be warranted.

Special considerations

It is possible that poor chromium status may contribute to the incidence of impaired glucose tolerance and Type 2 Diabetes. However, this is difficult to prove in the absence of good information on chromium intakes, or a widely acceptable method for measuring chromium status.

Conversely, there are data suggesting that people with pre-existing renal or liver disease may be particularly susceptible to adverse effects from excess chromium. Thus, these individuals should avoid supplemental chromium intake.

Conclusions

The WHO guidance level of 250 µg/d is considered most appropriate for Ireland. Neither EFSA nor the IOM have established a UL for chromium due to a lack of sufficient data.

Recommendations for Ireland

It is recommended that Ireland adopts the WHO guidance that daily amount of chromium provided in supplements should not exceed 250 µg/d.

References

- **European Food Safety Authority (EFSA) (2003)** Opinion of the scientific committee on food on the tolerable upper intake level of chromium
- **Institute of Medicine (IOM) (2001)** Dietary Reference intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc
- **World Health Organization (WHO) (1996)** Trace Elements in Human Nutrition and Health: A Report of a Re-evaluation of the Role of Trace Elements in Human Health and Nutrition. Geneva http://whqlibdoc.who.int/publications/1996/9241561734_eng.pdf?ua=1

Boron

Background

a) Description of boron

Boron occurs in foods as borate and boric acid. It is not considered to be an essential nutrient for humans, no specific biochemical function for has been identified and there are therefore, no recommended intakes. The WHO established an acceptable safe range of population mean intakes for boron of 1-13 mg/d. There is some evidence that it may influence mineral metabolism, particularly calcium, and have a beneficial effect on bone calcification and maintenance, possibly via vitamin D and oestrogen.

The soluble salt, borate, is absorbed with at least 90% efficiency, distributes evenly throughout the body tissues (including across the placenta) and is readily excreted in the urine.

b) Different forms of boron and clarity on the forms of boron that are relevant to the UL

Fruit-based beverages and products (including wine, cider and beer), tubers and legumes, have been found to have the highest concentrations of boron. Chocolate powder and pecan nuts are among the foods highest in boron. The main contributors in the US diet (accounting for 27% of dietary boron) are reported to be coffee, milk, apples, dried beans and potatoes.

Boron compounds (as boric acid, borax and other borates) can be found in a wide range of consumer products, including detergents, preservatives, adhesives, cosmetics, fertilisers, insecticides and herbicides.

c) Usual intakes, RDAs, AIs

Boron intake data in the EU are limited. In the UK, the mean intake from food (mainly plant foods, also wine, cider and beer) is estimated at 1.5 mg/d in adults, with the 97.5th percentile at 2.6 mg/d. Mean intake from water, which can be an important source of boron, especially mineral water, is estimated to be between 0.2 and 0.6 mg/d. Supplements may contain 1.5 to 10.0 mg boron/dose.

In NHANES III, the median intake of US adults taking boron supplements was reported to be approximately 0.14 mg/d. However, the highest intakes were up to 20 mg/d.

ULs established by other organisations

In animals, doses of more than 13 mg/kg body weight/d cause adverse effects, the most critical being those on reproduction and development, e.g. testicular atrophy, infertility and reduced foetal body weight in rats and mice.

In humans, numerous reports of boron intoxication describe a variety of symptoms, most commonly gastrointestinal (vomiting, diarrhoea and abdominal pain) following ingestion of 0.14-0.43 g boric acid/kg body weight (equivalent to approximately 25-76 mg boron/kg body weight) over days or weeks. These effects were not considered adequate for establishing ULs for boron by either the IOM or EFSA. Thus, reproductive and developmental effects in animals were chosen as the critical endpoint by the IOM, whose ULs range from 3.0 mg/d for one to three year-olds up to 20 mg/d for adults.

EFSA calculated the UL from the level at which no adverse effect (on foetal body weight, the most sensitive indicator) was observed in rats (9.6 mg/kg body weight/d). This was extrapolated to humans by dividing by an uncertainty factor of 60 (to allow for differences between rats and humans, and variability among humans), ultimately deriving a UL of 0.16 mg/kg body weight per day, equivalent to 10 mg/d for adults (including pregnant women). The ULs for children were extrapolated from the adult values, based on body surface area, and range from 3 mg/d for one to three year-olds up to 9 mg/d for 15-17 year olds. The UL applies only to boron in the form of boric acid and borates.

However, in this EFSA opinion on boron, a default body weight of 62.5kg was used to convert the 'safe' level of 0.16 mg/kg bw/day to an UL of 10 mg per day. This reference body weight is not gender specific and is low compared with current average weights for adult men and women in Ireland (86kg and 70kg respectively). Therefore, the FSAI and EFSA have agreed that when recommending a UL for boron for the adult population of Ireland, it would be more appropriate to use a reference body weight of 70kg for both sexes resulting in a UL of 11 mg/day. Table 3.25 outlines the EFSA UL using 62.5kg and the re-calculated EFSA UL using 70kg.

Table 3.25. EFSA Tolerable Upper Intake Level for Boron established for Adults using a Reference Body Weight of 62.5kg and using a Reference Body Weight of 70kg

Micronutrient (year UL was established)	Upper level of intake per kg body weight per day	EFSA established UL for adults using various reference body weights		EFSA UL for adults recalculated using a reference body weight of 70kg	
		Reference body weight (kg)	**UL**	**Reference body weight (kg)**	**UL**
Boron (2004)	0.16 mg/kg body weight/day	62.5	10 mg/day	70	11 mg/day

Conclusions

The EFSA ULs for boron are considered most appropriate for Ireland. The EFSA UL for boron refers only to boron in the form of boric acid and borates. EFSA has used a reference body weight of 62.5kg to derive its UL for boron. However, when this was looked at in an Irish context, the FSAI and EFSA agreed that a body weight of 70kg, which is more representative of the adult population of Ireland, would be used to derive the UL recommended for adults in Ireland.

Recommendations for Ireland

It is recommended that Ireland adopts the EFSA UL for boron (EFSA, 2004) as shown in Table 3.26.

Table 3.26. Tolerable Upper Intake Level of Boron (EFSA, 2004)

Life Stage Group	Boron (mg/d)
1-3 y	3
4-6 y	4
7-10 y	5
11-14 y	7
15-17 y	9
≥18 y	11*

*Re-calculated EFSA UL for adults using a reference body weight of 70kg

References

- **European Food Safety Authority (EFSA) (2004)** Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the commission related to the tolerable upper intake level of boron (sodium borate and boric acid)
- **Institute of Medicine (IOM) (2001)** Dietary Reference intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc

Silicon

Background

a) Description of silicon

Silicon is a non-metallic element that has not been demonstrated to be a dietary essential for humans.

The functional role of silicon in humans has not yet been identified. In animals, silicon appears to play a role in bone formation and metabolism.

Silicon deficiency has not been observed in humans.

Silicon is thought to act as an antidote to aluminium toxicity by reducing the bioavailability of aluminium. Modest amounts of silicon in water can protect fish against aluminium toxicity.

A significant proportion (~50%) of dietary silicon is excreted in the urine suggesting that silicon in the diet is fairly well absorbed. Silicon in the blood is not bound to protein and exists as silicic acid. Silicon is mainly found in connective tissues including the aorta, trachea, tendon, bone and skin. Higher serum concentrations of silicon have been measured in chronic kidney failure patients compared to healthy controls demonstrating the significance of renal elimination of silicon.

b) Different forms of silicon and clarity on the forms of silicon that are relevant to the UL

Silicon is not permitted to be added to foods for the purposes of fortification but can be used in the manufacture of food supplements under EU legislation (Directive 2002/46/EC; Regulation 1925/2006), see Appendix I. In addition, silicon is added to foods as an anti-caking and anti-foaming agent. However, the bioavailability of the additive form of silicon is low.

Concentrations of silicon are higher in plant based foods than in animal based foods, particularly unrefined grains that are high in fibre as refining reduces the silicon content of foods. Beer, coffee and water also contribute to the dietary intake of silicon.

c) Usual intakes, RDAs, AIs

EFSA has to date, not reviewed silicon in terms of establishing a recommended intake. A recommended intake for silicon has not been established by the IOM due to insufficient data and a lack of functional criteria.

ULs established by other organisations

Both EFSA (2004) and the IOM (2001) concluded that there were insufficient data on the dose-response relationship for establishing a UL for silicon. EFSA noted that the estimated typical dietary intakes of silicon (20-50 mg/day) corresponding to 0.3-0.8 mg/kg body weight/day in a 60kg person are unlikely to cause adverse effects. Similarly, the IOM noted that the limited toxicity data on silicon suggest that typical levels of intake have no risk of inducing adverse effects. The IOM also stated that there was no evidence that silicon naturally occurring in food and water produces adverse effects. The IOM referred to the limited reports indicating that intake of magnesium trisilicate (6.5 mg elemental silicon per tablet) as an antacid over a long period of time may result in urolithiasis (renal silicate stone formation). The IOM notes that there is no justification for the addition of silicon to food supplements.

Conclusions

Neither EFSA nor the IOM established a UL for silicon due to a lack of sufficient evidence. Scientific evidence should be reviewed regularly to ensure that individuals are not at risk of over-exposure.

Recommendations for Ireland

It is not recommended that Ireland adopts a UL for silicon.

References

- **European Food Safety Authority (EFSA) (2004)** Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on Request from the Commission Related to the Tolerable Upper Intake Level of Silicon
- **Institute of Medicine (IOM) (2001)** Dietary Reference intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc

APPENDIX I. FORMS OF VITAMINS AND MINERALS PERMITTED

Table 1a. Vitamin formulations which may be used in the manufacture of food supplements and which may be added to foods according to EU legislation

Vitamin A	Vitamin D	Vitamin E	Vitamin K	Thiamin	Riboflavin	Niacin
Retinol Retinyl acetate Retinyl palmitate Beta-carotene	Cholecalciferol Ergocalciferol	D-alpha-tocopherol DL-alpha-tocopherol D-alpha-tocopheryl acetate DL-alpha-tocopheryl acetate D-alpha-tocopheryl acid succinate Mixed tocopherols** Tocotrienol tocopherol**	Phylloquinone (phytomenadione) Menaquinone**	Thiamin hydrochloride Thiamin mononitrate Thiamine monophosphate chloride** Thiamine pyrophosphate chloride**	Riboflavin Riboflavin 5'-phosphate, sodium	Nicotinic acid Nicotinamide Inositol hexanicotinate (inositol hexaniacinate)**

Pantothenic Acid	Vitamin B_6	Folic Acid	Vitamin B_{12}	Biotin	Vitamin C
D-pantothenate, calcium D-pantothenate, sodium Dexpanthenol Pantethine**	Pyridoxine hydrochloride Pyridoxine 5' -phosphate Pyridoxine dipalmitate* Pyroxidal 5'-phosphate**	Pteroylmonoglutamic acid Calcium-L-methylfolate** (6S)-5-methyltetrahydrofolic acid, glucosamine salt**	Cyanocobalamin Hydroxocobalamin 5'-deoxyadenosylcobalamin** Methylcobalamin**	D-biotin	L-ascorbic acid Sodium-L-ascorbate Calcium-L-ascorbate Potassium-L-ascorbate L-ascorbyl 6-palmitate Magnesium L-ascorbate** Zinc L-ascorbate**

* Only permitted to be added to foods, not permitted in the manufacture of food supplements

** Only permitted to be used in the manufacture of food supplements, not permitted to be added to foods

Sources: Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements; Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods.

Table 1b. Mineral Substances which may be used in the Manufacture of Food Supplements and which may be added to Foods according to EU Legislation

Calcium	Magnesium	Iron	Copper	Iodine	Zinc	Manganese	Sodium	
Calcium carbonate	Magnesium acetate	Ferrous carbonate	Cupric carbonate	Sodium iodide	Zinc acetate	Manganese carbonate	Sodium bicarbonate	
Calcium chloride	Magnesium carbonate	Ferrous citrate	Cupric citrate	Sodium iodate	Zinc chloride	Manganese chloride	Sodium carbonate	
Calcium salts of citric acid	Magnesium chloride	Ferric ammonium citrate	Cupric gluconate	Potassium iodide	Zinc citrate	Manganese citrate	Sodium chloride**	
Calcium citrate malate	Magnesium salts of citric acid	Ferrous gluconate	Cupric sulphate	Potassium iodate	Zinc gluconate	Manganese gluconate	Sodium gluconate	
Calcium gluconate	Magnesium gluconate	Ferrous fumarate	Copper lysine complex		Zinc lactate	Manganese glycerophosphate	Sodium lactate	
Calcium glycerophosphate	Magnesium glycerophosphate	Ferric sodium diphosphate	Copper L-aspartate**		Zinc oxide	Manganese sulphate	Sodium hydroxide	
Calcium lactate	Magnesium salts of orthophosphoric acid	Ferrous lactate	Copper bisglycinate**		Zinc carbonate	Manganese ascorbate**	Sodium salts of orthophosphoric acid	
Calcium salts of orthophosphoric acid	Magnesium lactate	Ferrous sulphate	Copper (II) oxide**		Zinc sulphate	Manganese L-aspartate**	Sodium citrate	
Calcium malate**	Magnesium hydroxide	Ferric diphosphate (ferric pyrophosphate)			Zinc bisglycinate**	Manganese bisglycinate**	Sodium sulphate**	
Calcium hydroxide	Magnesium oxide	Ferric saccharate			Zinc L-ascorbate**	Manganese pidolate**		
Calcium oxide	Magnesium sulphate	Elemental iron (carbonyl+electrolytic +hydrogen reduced)			Zinc L-asparate**			
Calcium sulphate	Magnesium potassium citrate**	Ferrous bisglycinate**			Zinc L-lysinate**			
Calcium acetate**	Magnesium bisglycinate**	Ferrous ammonium phosphate**			Zinc mlate**			
Calcium L-ascorbate**	Magnesium L-lysinate**	Ferric sodium EDTA**			Zinc mono-L-methionine sulphate**			
Calcium bisglycinate**	Magnesium malate**	Ferrous L-pidolate**			Zinc L-pidonate**			
Calcium pyruvate**	Magnesium L-pidolate**	Ferrous phosphate**			Zinc picolinate**			
Calcium succinate**	Magnesium L-ascorbate**	Iron (II) taurate**						
Calcium L-lysinate**	Magnesium pyruvate**							
Calcium L-pidolate**	Magnesium succinate**							
Calcium L-threonate**	Magnesium taurate**							
Calcium phosphoryl oligosaccharides	Magnesium acetyl taurate**							

* Only permitted to be added to foods, not permitted in the manufacture of food supplements

** Only permitted to be used in the manufacture of food supplements, not permitted to be added to foods

Sources: Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements; Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods.

	Potassium	Selenium	Chromium	Molybdenum	Fluoride	Phosphorus	Boron	Silicon
	Potassium bicarbonate	Sodium selenate	Chromium (III) chloride (and its hexahydrate)	Ammonium molybdate (molybdenum (VI))	Potassium fluoride	Sodium monoflurophosphate**	Boric Acid**	Choline-stabilished orthosilicic acid**
	Potassium carbonate	Sodium hydrogen selenite	Chromium (III) sulphate (and its hexahydrate)	Sodium molybdate (molybdenum (VI))	Sodium fluoride		Sodium borate**	Silicon dioxide**
	Potassium chloride	Sodium selenite	Chromium (III) lactate trihydrate**	Potassium molybdate (molybdenum (VI))**	Calcium fluoride**			Silicic acid**
	Potassium citrate	selenium enriched yeast**	Chromium picolinate**					Organic silicon (monomethyl-silanetriol)
	Potassium gluconate	L-selenomethionine**	Chromium nitrate**					
	Potassium glycerophosphate	selenious acid**	Chromium enriched yeast**					
	Potassium lactate							
	Potassium hydroxide							
	Potassium salts of orthophosphoric acid							
	Potassium L-pidolate**							
	Potassium malate**							
	Potassium sulphate**							

APPENDIX II. TOLERABLE UPPER INTAKE LEVELS FOR IRELAND

Table 2. Tolerable Upper Intake Levels for Vitamins and Minerals Recommended for Ireland Derived from EFSA

Life Stage Group	Vit A (µg RE/d)[a]	Vit D (µg/day)	Vit E (mg/d)	Niacin (mg/d)		Vit B_6 (mg/d)	Folic Acid (µg/d)	Calcium (mg/d)	Magnesium (mg/d)[b]	Zinc (mg/d)	Copper (mg/d)	Selenium (µg/d)	Iodine (µg/d)	Molybdenum[c] (mg/d)	Fluoride[c] (mg/d)	Boron[c] (mg/d)
				Nicotinamide	Nicotinic Acid											
Infants																
0-6 mo	600[d]	25	*ND*	*ND*	*ND*	*ND*	*ND*	*See IOM*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
7-12 mo	600[d]	25	*ND*	*ND*	*ND*	*ND*	*ND*	*See IOM*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Children																
1-3 y	800	50	100	150	2	5	200	*See IOM*	*ND*	7	1	60	200	0.1	1.5	3
4-6 y	1,100	50	120	220	3	7	300	*See IOM*	250	10	2	90	250	0.2	2.5	4
Males																
7-10 y	1,500	50	160	350	4	10	400	*See IOM*	250	13	3	130	300	0.25	2.5/5[g]	5
11-14 y	2,000	100	220	500	6	15	600	*See IOM*	250	18	4	200	450	0.4	5	7
15-17 y	2,600	100	260	700	8	20	800	2,500	250	22	4	250	500	0.5	8[f]	9
≥ 18 y	3,000	100	300	900	10	25	1,000	2,500	250	25	5	300	600	0.7[f]	8[f]	11[f]
Females																
7-10 y	1,500	50	160	350	4	10	400	*ND*	250	13	3	130	300	0.25	2.5/5[g]	5
11-14 y	2,000	100	220	500	6	15	600	*ND*	250	18	4	200	450	0.4	5	7
15-17 y	2,600	100	260	700	8	20	800	2,500	250	22	4	250	500	0.5	8[f]	9
≥ 18 y	3,000 (1,500[e])	100	300	900	10	25	1,000	2,500	250	25	5	300	600	0.7[f]	8[f]	11[f]
Pregnancy	3,000	100	300	*ND*	*ND*	25	1,000	2,500	250	25	*ND*	300	600	0.7[f]	8[f]	11[f]
Lactation	3,000	100	300	*ND*	*ND*	25	1,000	2,500	250	25	*ND*	300	600	0.7[f]	8[f]	11[f]

UL is the highest average daily nutrient intake level likely to pose no risk of adverse health effects for nearly all people in a particular group. Unless otherwise specified, the UL represents total intake from food, water, and supplements. ULs could not be established for all vitamins. In the absence of a UL, extra caution may be warranted in consuming levels above the recommended intake, therefore sources of intake should only be from food to prevent high levels of intake.

ND = Not Determinable. This value is not determined due to the lack of data of adverse effects in this age group and concern regarding the lack of ability to handle excess amounts.

Vitamins and minerals where no UL has been recommended for Ireland: beta carotene, vitamin K, thiamin, riboflavin, vitamin B_{12}, biotin, pantothenic acid, phosphorus, potassium, chromium, silicon.

[a] As preformed vitamin A only.

[b] The EFSA UL for magnesium represents intake from supplements, water or added to food and beverages. The UL does not include Mg normally present in food and beverages.

[c] Calculation of UL requires a body reference weight and the reference weight used by EFSA was 60kg which is low in an Irish context. Re-calculations were made using a reference body weight of 70kg

[d] The IOM for infants <1 year is recommended

[e] Because the UL may not adequately address the possible risk of bone fracture in particularly vulnerable groups, it would be advisable for postmenopausal women, who are at greater risk of osteoporosis and fracture, to restrict their intake to 1,500 µg RE/day.

[f] Re-calculated EFSA UL for adults using a reference body weight of 70kg

[g] Children aged 4-8years/adolescents aged 9-14 years

Sources: EFSA (2006) *Tolerable Upper Intake Levels for Vitamins and Minerals, Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies*; EFSA (2012) *Scientific Opinion on the Tolerable Upper Intake Level of vitamin D, Scientific Panel on Dietetic Products, Nutrition and Allergies*

Table 3. Tolerable Upper Intake Levels for Vitamins and Minerals Recommended for Ireland Derived from the IOM

Life Stage Group	Vitamin C (mg/d)	Sodium (g/d)	Chloride (g/d)	Iron (mg/d)	Manganese (mg/d)	Calcium (mg/d)
Infants						
0-6 mo	*ND*	*ND*	*ND*	40	*ND*	1,000
7-12 mo	*ND*	*ND*	*ND*	40	*ND*	1,500
Children						
1-3 y	400	1.5	2.3	40	2	2,500
4-8 y	650	1.9	2.9	40	3	2,500
Males						
9-13 y	1,200	2.2	3.4	40	6	3,000
14-18 y	1,800	2.3	3.6	45	9	3,000
19-30 y	2,000	2.3	3.6	45	11	*See EFSA*
31-50 y	2,000	2.3	3.6	45	11	*See EFSA*
51-70 y	2,000	2.3	3.6	45	11	*See EFSA*
>70 y	2,000	2.3	3.6	45	11	*See EFSA*
Females						
9-13 y	1,200	2.2	3.4	40	6	3,000
14-18 y	1,800	2.3	3.6	45	9	3,000
19-30 y	2,000	2.3	3.6	45	11	*See EFSA*
31-50 y	2,000	2.3	3.6	45	11	*See EFSA*
51-70 y	2,000	2.3	3.6	45	11	*See EFSA*
>70 y	2,000	2.3	3.6	45	11	*See EFSA*
Pregnancy						
14-18 y	1,800	2.3	3.6	45	9	3,000
19-50 y	2,000	2.3	3.6	45	11	*See EFSA*
Lactation						
14-18 y	1,800	2.3	3.6	45	9	3,000
19-50 y	2,000	2.3	3.6	45	11	*See EFSA*

UL is the highest average daily nutrient intake level likely to pose no risk of adverse health effects for nearly all people in a particular group. Unless otherwise specified, the UL represents total intake from food, water, and supplements. ULs could not be established for all vitamins. In the absence of a UL, extra caution may be warranted in consuming levels above the recommended intake, therefore sources of intake should only be from food to prevent high levels of intake.

Vitamins and minerals where no UL has been recommended for Ireland: beta carotene, vitamin K, thiamin, riboflavin, vitamin B_{12}, biotin, pantothenic acid, phosphorus, potassium, chromium, silicon

ND = Not Determinable. This value is not determined due to the lack of data of adverse effects in this age group and concern regarding the lack of ability to handle excess amounts

Sources: IOM (2006) *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*; IOM (2011) *Dietary Reference Intakes for Calcium and Vitamin D. Washington: National Academies Press*

APPENDIX III. FULL LIST OF TOLERABLE UPPER INTAKE LEVELS AVAILABLE FROM EFSA AND THE IOM

Table 4a. Tolerable Upper Intake Levels, Vitamins, EFSA

Age	Vitamin A (µg RE/d)[a]	Vitamin C	Vitamin D (µg/d)	Vitamin E (mg/d)	Vitamin K	Thiamin	Riboflavin
0-1 y	*ND*	*ND*	25	*ND*	*ND*	*ND*	*ND*
1-3 y	800	*ND*	50	100	*ND*	*ND*	*ND*
4-6 y	1,100	*ND*	50	120	*ND*	*ND*	*ND*
7-10 y	1,500	*ND*	50	160	*ND*	*ND*	*ND*
11-14 y	2,000	*ND*	100	220	*ND*	*ND*	*ND*
15-17 y	2,600	*ND*	100	260	*ND*	*ND*	*ND*
≥ 17 y	3,000	*ND*	100	300	*ND*	*ND*	*ND*
Pregnancy	3,000	*ND*	100	300	*ND*	*ND*	*ND*
Lactation	3,000	*ND*	100	300	*ND*	*ND*	*ND*

Age	Niacin		Vitamin B_6 (mg/d)	Folate (µg/d)	Vitamin B_{12}	Panto-thenic Acid	Biotin	Beta-carotene
	Nicotinic acid (mg/d)	Nicotinamide (mg/d)						
0-1 y	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
1-3 y	2	150	5	200	*ND*	*ND*	*ND*	*ND*
4-6 y	3	220	7	300	*ND*	*ND*	*ND*	*ND*
7-10 y	4	350	10	400	*ND*	*ND*	*ND*	*ND*
11-14 y	6	500	15	600	*ND*	*ND*	*ND*	*ND*
15-17 y	8	700	20	800	*ND*	*ND*	*ND*	*ND*
≥ 17 y	10	900	25	1,000	*ND*	*ND*	*ND*	*ND*
Pregnancy	ND	ND	25	1,000	*ND*	*ND*	*ND*	*ND*
Lactation	ND	ND	25	1,000	*ND*	*ND*	*ND*	*ND*

NOTE: UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to a lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, and carotenoids. In the absence of a UL, extra caution may be warranted in consuming levels above recommended intakes. Members of the general population should be advised not to routinely exceed the UL. The UL is not meant to apply to individuals who are treated with the nutrient under medical supervision or to individuals with predisposing conditions that modify their sensitivity to the nutrient.

ND = non-determinable

[a] As preformed vitamin A only

Sources: EFSA (2006) *Tolerable Upper Intake Levels for Vitamins and Minerals, Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies*; EFSA (2012) *Scientific Opinion on the Tolerable Upper Intake Level of Vitamin D, Scientific Panel on Dietetic Products, Nutrition and Allergies*

Table 4b. Tolerable Upper Intake Levels, Minerals, EFSA

Age	Boron (mg/d)	Calcium (mg/d)	Chromium	Copper (mg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron	Magnesium (mg/d)	Manganese	Molybdenum (mg/d)
1-3 y	3	*ND*	*ND*	1	1.5	200	*ND*	*ND*	*ND*	0.1
4-6 y	4	*ND*	*ND*	2	2.5	250	*ND*	250	*ND*	0.2
7-10 y	5	*ND*	*ND*	3	2.5/5[b]	300	*ND*	250	*ND*	0.25
11-14 y	7	*ND*	*ND*	4	5[b]	450	*ND*	250	*ND*	0.4
15-17 y	9	*ND*	*ND*	4	7	500	*ND*	250	*ND*	0.5
>17 y	10	2500[a]	*ND*	5	7	600	*ND*	250	*ND*	0.6
Pregnancy	10	2500	*ND*	*ND*	7	600	*ND*	250	*ND*	0.6
Lactation	10	2500	*ND*	*ND*	7	600	*ND*	250	*ND*	0.6

Age	Nickel	Phosphorus	Selenium (µg/d)	Silicon	Vanadium	Zinc (mg/d)	Sodium	Tin	Chloride	Potassium
1-3 y	*ND*	*ND*	60	*ND*	*ND*	7	*ND*	*ND*	*ND*	*ND*
4-6 y	*ND*	*ND*	90	*ND*	*ND*	10	*ND*	*ND*	*ND*	*ND*
7-10 y	*ND*	*ND*	130	*ND*	*ND*	13	*ND*	*ND*	*ND*	*ND*
11-14 y	*ND*	*ND*	200	*ND*	*ND*	18	*ND*	*ND*	*ND*	*ND*
15-17 y	*ND*	*ND*	250	*ND*	*ND*	22	*ND*	*ND*	*ND*	*ND*
>17 y	*ND*	*ND*	300	*ND*	*ND*	25	*ND*	*ND*	*ND*	*ND*
Pregnancy	*ND*	*ND*	300	*ND*	*ND*	25	*ND*	*ND*	*ND*	*ND*
Lactation	*ND*	*ND*	300	*ND*	*ND*	25	*ND*	*ND*	*ND*	*ND*

NOTE: A UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to a lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, and carotenoids. In the absence of a UL, extra caution may be warranted in consuming levels above recommended intakes. Members of the general population should be advised not to routinely exceed the UL. The UL is not meant to apply to individuals who are treated with the nutrient under medical supervision or to individuals with predisposing conditions that modify their sensitivity to the nutrient.

ND = non-determinable

[a] Adults ≥ 19 years

[b] UL for children aged 4-8 years of 2.5 mg/d; UL for adolescents aged 9-14 years of 5 mg/d

Sources: EFSA (2006) *Tolerable Upper Intake Levels for Vitamins and Minerals, Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies*

Table 5a. Tolerable Upper Intake Levels, Vitamins, IOM

Life Stage Group	Vit A (µg/d)[a]	Vit C (mg/d)	Vit D (µg /d)	Vit E (mg /d)[b,c]	Vit K	Thia-min	Ribo-flavin	Niacin (mg /d)[c]	Vit B_6 (mg /d)	Folate (µg /d)[c]	Vit B_{12}	Panto-thenic Acid	Biotin	Choline (g/d)	Carot-enoids[d]
Infants															
0-6 mo	600	*ND*[e]	25	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
6-12 mo	600	*ND*	38	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Children															
1-3 y	600	400	63	200	*ND*	*ND*	*ND*	10	30	300	*ND*	*ND*	*ND*	1.0	*ND*
4-8 y	900	650	75	300	*ND*	*ND*	*ND*	15	40	400	*ND*	*ND*	*ND*	1.0	*ND*
Males															
9-13 y	1,700	1,200	100	600	*ND*	*ND*	*ND*	20	60	600	*ND*	*ND*	*ND*	2.0	*ND*
14-18 y	2,800	1,800	100	800	*ND*	*ND*	*ND*	30	80	800	*ND*	*ND*	*ND*	3.0	*ND*
19-30 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
31-50 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
51-70 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
> 70 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
Females															
9-13 y	1,700	1,200	100	600	*ND*	*ND*	*ND*	20	60	600	*ND*	*ND*	*ND*	2.0	*ND*
14-18 y	2,800	1,800	100	800	*ND*	*ND*	*ND*	30	80	800	*ND*	*ND*	*ND*	3.0	*ND*
19-30 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
31-50 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
51-70 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
> 70 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
Pregnancy															
14-18 y	2,800	1,800	100	800	*ND*	*ND*	*ND*	30	80	600	*ND*	*ND*	*ND*	3.0	*ND*
19-30 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	800	*ND*	*ND*	*ND*	3.5	*ND*
31-50 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*
Lactation															
14-18 y	2,800	1,800	100	800	*ND*	*ND*	*ND*	30	80	600	*ND*	*ND*	*ND*	3.0	*ND*
19-30 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	800	*ND*	*ND*	*ND*	3.5	*ND*
31-50 y	3,000	2,000	100	1,000	*ND*	*ND*	*ND*	35	100	1,000	*ND*	*ND*	*ND*	3.5	*ND*

NOTE: A UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to a lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, and carotenoids. In the absence of a UL, extra caution may be warranted in consuming levels above recommended intakes. Members of the general population should be advised not to routinely exceed the UL. The UL is not meant to apply to individuals who are treated with the nutrient under medical supervision or to individuals with predisposing conditions that modify their sensitivity to the nutrient.

[a] As preformed vitamin A only.

[b] As a-tocopherol; applies to any form of supplemental a-tocopherol.

[c] The ULs for vitamin E, niacin, and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of the two.

[d] β-Carotene supplements are advised only to serve as a provitamin A source for individuals at risk of vitamin A deficiency.

[e] *ND* = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

Sources: Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper

Table 5b. Tolerable Upper Intake Levels, Minerals, IOM

Life Stage Group	Arsenic[a]	Boron (mg/d)	Calcium (mg/d)	Chromium	Copper (µg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)[b]	Manganese (mg/d)	Molybdenum (µg/d)	Nickel (mg/d)	Phosphorus (g/d)	Selenium (µg/d)	Silicon[c]	Vanadium (mg/d)[d]	Zinc (mg/d)	Sodium (g/d)	Chloride (g/d)
Infants																			
0-6 mo	*ND*[e]	*ND*	1,000	*ND*	*ND*	0.7	*ND*	40	*ND*	*ND*	*ND*	*ND*	*ND*	45	*ND*	*ND*	4	*ND*	*ND*
6-12 mo	*ND*	*ND*	1,500	*ND*	*ND*	0.9	*ND*	40	*ND*	*ND*	*ND*	*ND*	*ND*	60	*ND*	*ND*	5	*ND*	*ND*
Children																			
1-3 y	*ND*	3	2,500	*ND*	1,000	1.3	200	40	65	2	300	0.2	3	90	*ND*	*ND*	7	1.5	2.3
4-8 y	*ND*	6	2,500	*ND*	3,000	2.2	300	40	110	3	600	0.3	3	150	*ND*	*ND*	12	1.9	2.9
Males																			
9-13 y	*ND*	*11*	3,000	*ND*	5,000	10	600	40	350	6	1,100	0.6	4	280	*ND*	*ND*	23	2.2	3.4
14-18 y	*ND*	*17*	3,000	*ND*	8,000	10	900	45	350	9	1,700	1.0	4	400	*ND*	*ND*	34	2.3	3.6
19-30 y	*ND*	*20*	2,500	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	4	400	*ND*	1.8	40	2.3	3.6
31-50 y	*ND*	*20*	2,500	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	4	400	*ND*	1.8	40	2.3	3.6
51-70 y	*ND*	*20*	2,000	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	4	400	*ND*	1.8	40	2.3	3.6
> 70 y	*ND*	*20*	2,000	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	3	400	*ND*	1.8	40	2.3	3.6
Females																			
9-13 y	*ND*	11	3,000	*ND*	5,000	10	600	40	350	6	1,100	0.6	4	280	*ND*	ND	23	2.2	3.4
14-18 y	*ND*	17	3,000	*ND*	8,000	10	900	45	350	9	1,700	1.0	4	400	*ND*	ND	34	2.3	3.6
19-30 y	*ND*	20	2,500	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	4	400	*ND*	1.8	40	2.3	3.6
31-50 y	*ND*	20	2,500	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	4	400	*ND*	1.8	40	2.3	3.6
51-70 y	*ND*	20	2,000	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	4	400	*ND*	1.8	40	2.3	3.6
> 70 y	*ND*	20	2,000	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	3	400	*ND*	1.8	40	2.3	3.6
Pregnancy																			
14-18 y	*ND*	17	3,000	*ND*	8,000	10	900	45	350	9	1,700	1.0	*3.5*	400	*ND*	*ND*	34	2.3	3.6
19-30 y	*ND*	20	2,500	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	*3.5*	400	*ND*	*ND*	40	2.3	3.6
31-50 y	*ND*	20	2,500	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	*3.5*	400	*ND*	*ND*	40	2.3	3.6
Lactation																			
14-18 y	*ND*	17	3,000	*ND*	8,000	10	900	45	350	9	1,700	1.0	4	400	*ND*	*ND*	34	2.3	3.6
19-30 y	*ND*	20	2,500	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	4	400	*ND*	*ND*	40	2.3	3.6
31-50 y	*ND*	20	2,500	*ND*	10,000	10	1,100	45	350	11	2,000	1.0	4	400	*ND*	*ND*	40	2.3	3.6

NOTE: A UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to a lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, and carotenoids. In the absence of a UL, extra caution may be warranted in consuming levels above recommended intakes. Members of the general population should be advised not to routinely exceed the UL. The UL is not meant to apply to individuals who are treated with the nutrient under medical supervision or to individuals with predisposing conditions that modify their sensitivity to the nutrient.

[a] Although the UL was not determined for arsenic, there is no justification for adding arsenic to food or supplements.

[b] The ULs for magnesium represent intake from a pharmacological agent only and do not include intake from food and water.

[c] Although silicon has not been shown to cause adverse effects in humans, there is no justification for adding silicon to supplements.

[d] Although vanadium in food has not been shown to cause adverse effects in humans, there is no justification for adding vanadium to food and vanadium supplements should be used with caution. The UL is based on adverse effects in laboratory animals and these data could be used to set a UL for adults but not children and adolescents.

[e] *ND* = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

Sources: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001); *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005); and *Dietary Reference Intakes for Calcium and Vitamin D* (2011). These reports may be accessed via www.nap.edu.

APPENDIX IV. DIETARY REFERENCE VALUES OTHER THAN ULS AVAILABLE FROM EFSA AND THE IOM

Table 6a. EFSA Dietary Reference Values; Recommended Dietary Allowance and Adequate Intake for Vitamins

Life Stage Group	Vit C (mg/d)	Panto-thenic acid (mg/ day)	Biotin (µg/ day)	Niacin (mg NE/ MJ)[a]	Folate (µg DFE/ day)[b]	Vit A (µg RE/ day)	Vit E (mg/d)	Vit B_{12} (µg/d)	Vit B_6 (mg/d)	Cho-line (mg/d)	Vit D (µg/d)	Thia-mine (mg/ MJ)	Ribo-flavin (mg/d)	Vit K (µg/d)
Infants														
0-6 mo	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
7-11mo	20	3*	6*	1.6	80*	250	5*	1.5*	0.3*	160*	10*	0.1	0.4*	10*
Children														
1-3 y	20	4*	20*	1.6	120	250	6*	1.5*	0.6	140*	15*c	0.1	0.6	12*
4-6 y	30	4*	25*	1.6	140	300	9*	1.5*	0.7	170*	15*c	0.1	0.7	20*
Males														
7-10 y	45	4*	25*	1.6	200	400	9*	2.5*	1.0	250*	15*c	0.1	1	30*
11-14 y	70	5*	35*	1.6	270	600	13*	3.5*	1.4	340*	15*c	0.1	1.4	45*
15-17 y	100	5*	35*	1.6	330	750	13*	4*	1.7	400*	15*c	0.1	1.6	65*
≥ 18 y	110	5*	40*	1.6	330	750	13*	4*	1.7	400*	15*c	0.1	1.6	70*
Females														
7-10 y	45	4*	25*	1.6	200	400	9*	2.5*	1.0	250*	15*c	0.1	1	30*
11-14 y	70	5*	35*	1.6	270	600	11*	3.5*	1.4	340*	15*c	0.1	1.4	45*
15-17 y	90	5*	35*	1.6	330	650	11*	4*	1.6	400*	15*c	0.1	1.6	65*
≥ 18 y	95	5*	40*	1.6	330	650	11*	4*	1.6	400*	15*c	0.1	1.6	70*
Pregnancy	105	5*	40*	1.6	600	700	11*	4.5*	1.8	480*	15*c	0.1	1.9	70*
Lactation	155	7*	45*	1.6	500	1,300	11*	5*	1.7	520*	15*c	0.1	2	70*

NOTE: This table presents Recommended Dietary Allowance (RDA) AND Adequate Intakes (AI) in ordinary type followed by an asterisk (*). RDA is the level of (nutrient) intake that is more than enough for virtually all healthy people in a group. AI is the value estimated when requirements cannot be determined. RDA is the term used by the IOM and in Ireland; PRI is the equivalent term used by EFSA.

If an RDA is set for a vitamin or mineral there, will also be a corresponding AR set for the vitamin or mineral.

ND = Not Determinable.

[a] NE: niacin equivalent (1 mg niacin = 1 niacin equivalent = 60 mg dietary tryptophan)

[b] DFE: Dietary folate equivalent (DFE = µg natural food folate + 1.7 times µg folic acid from fortified foods)

[c] Under conditions of assumed minimal cutaneous vitamin D synthesis. In the presence of endogenous cutaneous vitamin D synthesis, the requirement for dietary vitamin D is lower or may be even zero

Sources: EFSA (2013) *Scientific Opinion on Dietary Reference Values for vitamin C EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)*; EFSA (2014) *Scientific Opinion on Dietary Reference Values for pantothenic acid EFSA Panel on NDA*; EFSA (2014) *Scientific Opinion on Dietary Reference Values for biotin EFSA Panel on NDA*; EFSA (2014) *Scientific Opinion on Dietary Reference Values for niacin EFSA Panel on NDA*; EFSA (2014) *Scientific Opinion on Dietary Reference Values for folate EFSA Panel on NDA*; EFSA (2015) *Scientific Opinion on Dietary Reference Values for vitamin A EFSA Panel on NDA*; EFSA (2015) *Scientific Opinion on Dietary Reference Values for vitamin E EFSA Panel on NDA*; EFSA (2015) *Scientific Opinion on Dietary Reference Values for vitamin B_{12} EFSA Panel on NDA*; EFSA (2016) *Scientific Opinion on Dietary Reference Values for vitamin B_6 EFSA Panel on NDA*; EFSA (2016) *Scientific Opinion on Dietary Reference Values for choline EFSA Panel on NDA*; EFSA (2016) *Scientific Opinion on Dietary Reference Values for vitamin D EFSA Panel on NDA*; EFSA (2016) *Scientific Opinion on Dietary Reference Values for thiamine EFSA Panel on NDA; EFSA (2017) Scientific Opinion on Dietary Reference Values for riboflavin EFSA Panel on NDA; EFSA (2017) Scientific Opinion on Dietary Reference Values for vitamin K EFSA Panel on NDA*

Table 6b. EFSA Dietary Reference Values; Recommended Dietary Allowance and Adequate Intake for Minerals

Life Stage Group	Molyb-denum (µg/d)	Mang-anese (mg/d)	Iodine (µg/d)	Fluoride (mg/d)	Iron (mg/d)	Zinc (mg/d)	Sele-nium (µg/d)	Calcium (mg/d)	Magn-esium (mg/d)	Phos-phorus (mg/d)	Copper (mg/d)	Potassium (mg/d)
Infants												
0-6 mo	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	ND	ND	ND
7-11 mo	10*	0.02*-0.5*	70*	0.4*	11	2.9	15*	280*	*80**	160*	0.4*	750*
Children												
1-3 y	15*	0.5*	90*	0.6*	7	4.3	15*	450	170*	250*	0.7*	800*
4-6 y	20*	1.0*	90*	1.0/0.9*[a]	7	5.5	20*	800	230*	440*	1.0*	1,100*
Males												
7-10 y	30*	1.5*	90*	1.5*	11	7.4	35*	800	230*	440*	1.0*	1,800*
11-14 y	45*	2.0*	120*	2.2*	11	10.7	55*	1,150	300*	640*	1.3*	2,700*
15-17 y	65*	3.0*	130*	3.2*	11	14.2	70*	1,150	300*	640*	1.3*	3,500*
≥ 18 y	65*	3.0*	150*	3.4*	11	9.4-16.3[c]	70*	1,000/950[e]	350*	550*	1.6*	3,500*
Females												
7-10 y	30*	1.5*	90*	1.4*	11	7.4	35*	800	230*	440*	1.0*	1,800*
11-14 y	45*	2.0*	120*	2.3*	11	10.7	55*	1,150	250*	640*	1.1*	2,700*
15-17 y	65*	3.0*	130*	2.8*	13	11.9	70*	1,150	250*	640*	1.1*	3,500*
≥ 18 y	65*	3.0*	150*	2.9*	16/11[b]	7.5-12.7[c]	70*	1,000/950[e]	300*	550*	1.3*	3,500*
Pregnancy	65*	3.0*	200*	2.9*	16	+1.6[d]	70*	1,000/950[e]	300*	550*	1.5*	3,500*
Lactation	65*	3.0*	200*	2.9*	16	+2.9[d]	85*	1,000/950[e]	300*	550*	1.5*	4,000*

NOTE: This table presents recommended dietary allowance (RDA) and adequate intakes (AI) in ordinary type followed by an asterisk (*). RDA is the level of (nutrient) intake that is more than enough for virtually all healthy people in a group. AI is the value estimated when requirements cannot be determined. RDA is the term used by the IOM and in Ireland; PRI is the equivalent term used by EFSA.

If an RDA is set for a vitamin or mineral there will also be a corresponding AR set for the vitamin or mineral.

ND = Not Determinable.

[a] AI for males 4-6years of 1.0mg/d; AI for females 4-6 years of 0.9mg/d

[b] RDA for premenopausal women of 16 mg/d (the RDA covers the requirement of approximately 95 % of premenopausal women); RDA for postmenopausal women of 11 mg/d

[c] Determined by the level of phytate intake (ranging from 300-1,200mg/day)

[d] The RDA covers the requirement of approximately 95% of premenopausal women

[e] RDA for Adults 18-24years of 1,000mg/d; RDA for adults >25years of 950mg/d

Sources: EFSA (2013) *Scientific Opinion on Dietary Reference Values for molybdenum EFSA Panel on NDA*; EFSA (2013) *Scientific Opinion on Dietary Reference Values for manganese EFSA Panel on NDA*; EFSA (2014) *Scientific Opinion on Dietary Reference Values for iodine EFSA Panel on NDA*; EFSA (2013) *Scientific Opinion on Dietary Reference Values for fluoride EFSA Panel on NDA*; EFSA (2015) *Scientific Opinion on Dietary Reference Values for iron EFSA Panel on NDA*; EFSA (2014) *Scientific Opinion on Dietary Reference Values for zinc EFSA Panel on NDA*; EFSA (2014) *Scientific Opinion on Dietary Reference Values for selenium EFSA Panel on NDA*; EFSA (2015) *Scientific Opinion on Dietary Reference Values for calcium EFSA Panel on NDA*; EFSA (2015) *Scientific Opinion on Dietary Reference Values for magnesium EFSA Panel on NDA*; EFSA (2015) *Scientific Opinion on Dietary Reference Values for phosphorus EFSA Panel on NDA*; EFSA (2015) *Scientific Opinion on Dietary Reference Values for copper EFSA Panel on NDA*; EFSA (2016) *Scientific Opinion on Dietary Reference Values for potassium EFSA Panel on NDA*

Table 6c. EFSA Dietary Reference Values; Average Requirement for Vitamins and Minerals

Life Stage Group	Vitamin C (mg/d)	Niacin (mg NE/MJ)[a]	Zinc (mg/d)	Folate (µg DFE/d)[b]	Calcium (mg/d)	Iron (mg/d)	Vitamin A (µg RE/d)
Infants							
0-6 mo	*ND*	1.3	*ND*	*ND*	*ND*	*ND*	*ND*
7-11 mo	*ND*	1.3	2.4	*ND*	*ND*	8	190
Children							
1-3 y	15	1.3	3.6	90	390	5	205
4-6 y	25	1.3	4.6	110	680	5	245
Males							
7-10 y	40	1.3	6.2	160	680	8	320
11-14 y	60	1.3	8.9	210	960	8	480
15-17 y	85	1.3	11.8	250	960	8	580
≥ 18 y	90	1.3	7.5-12.7[c]	250	860/750	6	570
Females							
7-10 y	40	1.3	6.2	160	680	7	320
11-14 y	60	1.3	8.9	210	960	7	480
15-17 y	75	1.3	9.9	250	960	7	490
≥ 18 y	80	1.3	6.2-10.2[d]	250	860/750	7/6[e]	490
Pregnancy	?	1.3	(+1.3)		860/750	7	540
Lactation	(+50)	1.3	(+2.4)	380	860/750	7	1,020

AR is the level of (nutrient) intake that is enough for half of the people in a healthy group, given a normal distribution of requirement

ND = Not Determinable.

[a] NE: niacin equivalent (1 mg niacin = 1 niacin equivalent = 60 mg dietary tryptophan)

[b] DFE: Dietary folate equivalent (DFE = µg natural food folate + 1.7 times µg folic acid from fortified foods)

[c] Calculated using a reference weight of 68.1kg

[d] Calculated using a reference weight of 58.5kg

[e] AR for premenopausal women of 7 mg/d; AR for postmenopausal women of 6 mg/d

Table 7a. The IOM Dietary Reference Values; Recommended Dietary Allowances and Adequate Intakes for Vitamins

Life Stage Group	Vit A (µg/d)[a]	Vit C (mg/d)	Vit D (µg/d)[b,c]	Vit E (mg/d)[d]	Vit K (µg/d)	Panto-thenic Acid (mg/d)	Thiamin (µg/d)	Vit B_6 (mg/d)	Vit B_{12} (µg/d)	Biotin (µg/d)	Folate (µg/d)[e,f]	Niacin (mg)[g]	Ribo-flavin (mg/d)	Choline (mg/d)[h]
Infants														
0-6 mo	400*	40*	10*	4*	2.0*	1.7*	200*	0.1*	0.4*	5*	65*	2*	0.3*	125*
6-12 mo	500*	50*	10*	5*	2.5*	1.8*	300*	0.3*	0.5*	6*	80*	4*	0.4*	150*
Children														
1-3 y	300	15	15	6	30*	2*	500	0.5	0.9	8*	150	6	0.5	200*
4-8 y	400	25	15	7	55*	3*	600	0.6	1.2	12*	200	8	0.6	250*
Males														
9-13 y	600	45	15	11	60*	4*	900	1	1.8	20*	300	12	0.9	375*
14-18 y	900	75	15	15	75*	5*	1,200	1.3	2.4	25*	400	16	1.3	550*
19-30 y	900	90	15	15	120*	5*	1,200	1.3	2.4	30*	400	16	1.3	550*
31-50 y	900	90	15	15	120*	5*	1,200	1.3	2.4	30*	400	16	1.3	550*
51-70 y	900	90	15	15	120*	5*	1,200	1.7	2.4	30*	400	16	1.3	550*
> 70 y	900	90	20	15	120*	5*	1,200	1.7	2.4	30*	400	16	1.3	550*
Females														
9-13 y	600	45	15	11	60*	4*	900	1	1.8	20*	300	12	0.9	375*
14-18 y	700	65	15	15	75*	5*	1,000	1.2	2.4	25*	400	14	1	400*
19-30 y	700	75	15	15	90*	5*	1,100	1.3	2.4	30*	400	14	1.1	425*
31-50 y	700	75	15	15	90*	5*	1,100	1.3	2.4	30*	400	14	1.1	425*
51-70 y	700	75	15	15	90*	5*	1,100	1.5	2.4	30*	400	14	1.1	425*
> 70 y	700	75	20	15	90*	5*	1,100	1.5	2.4	30*	400	14	1.1	425*
Pregnancy														
14-18 y	750	80	15	15	75*	6*	1,400	1.9	2.6	30*	600	18	1.4	450*
19-50 y	770	85	15	15	90*	6*	1,400	1.9	2.6	30*	600	18	1.4	450*
Lactation														
14-18 y	1,200	115	15	19	75*	7*	1,400	2	2.8	35*	500	17	1.6	550*
19-50 y	1,300	120	15	19	90*	7*	1,400	2	2.8	35*	500	17	1.6	550*

NOTE: This table presents recommended dietary allowances (RDA) in bold type or adequate intakes (AI) in ordinary type followed by an asterisk (*).

An RDA is the average daily dietary intake level sufficient to meet the nutrient requirements of nearly all healthy individuals in a group (97-98%). It is calculated from an Estimated Average Requirement (EAR). If sufficient scientific evidence is not available to establish an EAR, and thus calculate an RDA, an AI is usually developed. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the group, but lack of or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a] As retinol activity equivalents (RAEs). 1 RAE = 1µg retinol, 12µg β-Carotene, 24µg α-carotene, or 24µg β-cryptoxanthin. The RAE for dietary provitamin A cartonoids is twofold greater than retinol equivalents (RE), whereas RAE for preformed vitamin A is the same as RE.

[b,c] As cholecalciferol. 1µg cholecalciferol = 40 IU vitamin D; Under the assumption of minimal sunlight

[e] In view of evidence linking folate with neural tube defects in the foetus there are special recommendations for all women capable of becoming pregnant to take 400µg daily

[d] As α-tocopherol. α-tocopherol includes RRR-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the 2R-stereoisomeric forms of α-tocopherol (RRR-, RRS-, and RRS-α-tocopherol) that occur in fortified foods and supplements. It does not include the 2S stereoisomeric forms of α x-tocopherol (SSR-, SRS-, and SSS-α-tocophero), also found in fortified foods and supplements.

[f] As dietary folate equivilants (DFE). DFE = µg natural food folate + 1.7 times µg folic acid form fortified foods

[g] As niacin equivelants(NE). 1mg of niacin = 60mg of trytophan; 0-6months = preformed niacin (not NE)

[h] Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages

Sources: OM (2006) *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*; IOM (2011) *Dietary Reference Intakes for Calcium and Vitamin D. Washington*: National Academies Press

Table 7b. The IOM Dietary Reference Values; Recommended Dietary Allowances and Adequate Intakes for Minerals

Life Stage Group	Calcium (mg/d)	Chromium (µg/d)	Copper (µg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)	Manganese (mg/d)	Molybdenum (µg/d)	Phosphorus (mg/day)	Potassium (g/day)	Selenium (µg/d)	Sodium (g/d)	Chloride (g/d)	Zinc (mg/d)
Infants															
0-6 mo	200*	0.2*	200*	0.01*	110*	0.27*	30*	0.0003*	2*	100*	0.4*	15*	0.12*	0.18*	2*
7-12 mo	260*	5.5*	220*	0.5*	130*	11	75*	0.6*	3*	275*	0.7*	20*	0.37*	0.57*	3
Children															
1-3 y	700	11*	340	0.7*	90	7	80	1.2*	17	460	3*	20	1*	1.5*	3
4-8 y	1,000	15*	440	1*	90	10	130	1.5*	22	500	3.8*	30	1.2*	1.9*	5
Males															
9-13 y	1,300	25*	700	2*	120	8	240	1.9*	34	1,250	4.5*	40	1.5*	2.3*	8
14-18 y	1,300	35*	890	3*	150	11	410	2.2*	43	1,250	4.7*	55	1.5*	2.3*	11
19- 30 y	1,000	35*	900	4*	150	8	400	2.3*	45	700	4.7*	55	1.5*	2.3*	11
31-50 y	1,000	35*	900	4*	150	8	420	2.3*	45	700	4.7*	55	1.5*	2.3*	11
51-70 y	1,000	30*	900	4*	150	8	420	2.3*	45	700	4.7*	55	1.3*	2*	11
>70 y	1,200	30*	900	4*	150	8	420	2.3*	45	700	4.7*	55	1.2*	1.8*	11
Females															
9-13 y	1,300	21*	700	2*	120	8	240	1.6*	34	1,250	4.5*	40	1.5*	2.3*	8
14-18 y	1,300	24*	890	3*	150	15	360	1.6*	43	1,250	4.7*	55	1.5*	2.3*	9
19-30 y	1,000	25*	900	3*	150	18	310	1.8*	45	700	4.7*	55	1.5*	2.3*	8
31-50 y	1,000	25*	900	3*	150	18	320	1.8*	45	700	4.7*	55	1.5*	2.3*	8
51-70 y	1,200	20*	900	3*	150	8	320	1.8*	45	700	4.7*	55	1.3*	2*	8
>70 y	1,200	20*	900	3*	150	8	320	1.8*	45	700	4.7*	55	1.2*	1.8*	8
Pregnancy															
14-18 y	1,300	29*	1,000	3*	220	27	400	2*	50	1,250	4.7*	60	1.5*	2.3*	12
19-50 y	1,000	30*	1,000	3*	220	27	350	2*	50	700	4.7*	60	1.5*	2.3*	11
	1,000	30*	1,000	3*	220	27	360	2*	50	700	4.7*	60	1.5*	2.3*	11
Lactation															
14-18 y	1,300	44*	1,300	3*	290	10	360	2.6*	50	1,250	5.1*	70	1.5*	2.3*	13
19-50 y	1,000	45*	1,300	3*	290	9	320	2.6*	50	700	5.1*	70	1.5*	2.3*	12

NOTE: This table presents Recommended Dietary Allowances (RDA) in bold type or Adequate Intakes (AI) in ordinary type followed by an asterisk (*).

An **RDA** is the average daily dietary intake level sufficient to meet the nutrient requirements of nearly all healthy individuals in a group (97-98%). It is calculated from an Estimated Average Requirement (EAR). If sufficient scientific evidence is not available to establish an EAR, and thus calculate and RDA, an AI is usually developed. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

Sources: IOM (2006) *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*; IOM (2011) *Dietary Reference Intakes for Calcium and Vitamin D. Washington*: National Academies Press.

Table 8a. The IOM Dietary Reference Values; Average Requirements for Vitamins

Life Stage Group	Vitamin A (µg/d)[a]	Vitamin C (mg/d)	Vitamin D (µg/d)	Vitamin E (mg/d)[b]	Thiamin (mg/d)	Vitamin B_6 (mg/d)	Vitamin B_{12} (µg/d)	Folate (µg/d)[c]	Niacin (mg/d)[d]	Riboflavin (mg/d)
Infants										
0-6 mo										
7-12 mo										
Children										
1-3 y	210	13	10	5	0.4	0.4	0.7	120	5	0.4
4-8 y	275	22	10	6	0.5	0.5	1	160	6	0.5
Males										
9-13 y	445	39	10	9	0.7	0.8	1.5	250	9	0.8
14-18 y	630	63	10	12	1	1.1	2	330	12	1.1
19-30 y	625	75	10	12	1	1.1	2	320	12	1.1
31-50 y	625	75	10	12	1	1.1	2	320	12	1.1
51-70 y	625	75	10	12	1	1.4	2	320	12	1.1
>70 y	625	75	10	12	1	1.4	2	320	12	1.1
Females										
9-13 y	420	39	10	9	0.7	0.8	1.5	250	9	0.8
14-18 y	485	56	10	12	0.9	1	2	330	11	0.9
19-30 y	500	60	10	12	0.9	1.1	2	320	11	0.9
31-50 y	500	60	10	12	0.9	1.1	2	320	11	0.9
51-70 y	500	60	10	12	0.9	1.3	2	320	11	0.9
>70 y	500	60	10	12	0.9	1.3	2	320	11	0.9
Pregnancy										
14-18 y	530	66	10	12	1.2	1.6	2.2	520	14	1.2
19-50 y	550	70	10	12	1.2	1.6	2.2	520	14	1.2
Lactation										
14-18 y	885	96	10	16	1.2	1.7	2.4	450	13	1.3
19-50 y	900	100	10	16	1.2	1.7	2.4	450	13	1.3

Average Requirement (AR) is the average daily nutrient intake level that is estimated to meet the needs of half of the healthy individuals in a life stage or gender group.

[a] As retinol activity equivalents (RAEs). 1 RAE = 1µg retinol, 12µg β-Carotene, 24µg x-carotene, or 24µg β-cryptoxanthin.

[b] As α-tocopherol. α-tocopherol includes RRR-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the 2R-stereoisomeric forms of α-tocopherol (RRR-, RRS-, and RRS-α-tocopherol) that occur in fortified foods and supplements. It does not include the 2S stereoisomeric forms of α x-tocopherol (SSR-, SRS-, and SSS-α-tocophero), also found in fortified foods and supplements.

[c] As dietary folate equivalents (DFE). (DFE = µg natural food folate + 1.7 times µg folic acid from fortified food)

[d] As Niacin equivalents (NE). 1mg of Niacin = 60µg of tryptophan.

Sources: IOM (2006) *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*; IOM (2011) *Dietary Reference Intakes for Calcium and Vitamin D*. Washington: National Academies Press

Table 8b. The IOM Dietary Reference Values; Average Requirements (AR) for Minerals

Life Stage Group	Calcium (mg/d)	Copper (µg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)	Molybdenum (µg/d)	Phosphorus (mg/day)	Selenium (µg/d)	Zinc (mg/d)
Infants									
0-6 mo									
7-12 mo				6.9					2.5
Children									
1-3 y	500	260	65	3	65	13	380	17	2.5
4-8 y	800	340	65	4.1	110	17	405	23	4
Males									
9-13 y	1,100	540	73	5.9	200	26	1,055	35	7
14-18 y	1,100	685	95	7.7	340	33	1,055	45	8.5
19-30 y	800	700	95	6	330	34	580	45	9.4
31-50 y	800	700	95	6	350	34	580	45	9.4
51-70 y	800	700	95	6	350	34	580	45	9.4
>70 y	1,000	700	95	6	350	34	580	45	9.4
Females									
9-13 y	1,100	540	73	5.7	200	26	1,055	35	7
14-18 y	1,100	685	95	7.9	300	33	1,055	45	7.3
19-30 y	800	700	95	8.1	255	34	580	45	6.8
31-50 y	800	700	95	8.1	265	34	580	45	6.8
51-70 y	1,000	700	95	5	265	34	580	45	6.8
>70 y	1,000	700	95	5	265	34	580	45	6.8
Pregnancy									
14-18 y	1,100	785	160	23	335	40	1,055	49	10.5
19-50 y	800	800	160	22	290	40	580	49	9.5
	800	800	160	22	300	40	580	49	9.5
Lactation									
14-18 y	1,100	985	209	7	300	35	1,055	59	10.9
19-50 y	800	1,000	209	6.5	255	36	580	59	10.4
	800	1,000	209	6.5	265	36	580	59	10.4

Average requirement (AR) is the average daily nutrient intake level that is estimated to meet the needs of half of the healthy individuals in a life stage or gender group. Although the term average is used, it is actually an estimated median requirement.

Sources: IOM (2006) *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington: National Academies Press; IOM (2011) *Dietary Reference Intakes for Calcium and Vitamin D*. Washington: National Academies Press

APPENDIX V. NATIONAL DIETARY MICRONUTRIENT INTAKE DATA

Table 9a. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from Food Sources only in Irish Pre-school Children for the Total Population (*n*500)

	Mean	SD	5th	95th	97.5th
Vitamins					
Total Vitamin A (µg)	631	462	192	1,337	1,610
Retinol (µg)	295	305	96	620	706
Carotene (µg)	2,015	1,927	153	5,634	7,185
Vitamin D (µg)	2.5	2.7	0.4	9.1	11.2
Vitamin C (mg)	78	48	22	161	184
Thiamin (mg)	1	0.3	0.6	1.6	1.8
Riboflavin (mg)	1.5	0.5	0.7	2.4	2.6
Pre-formed Niacin (mg)	11.1	3.9	5.6	18.3	20.1
Total Niacin Equivalents (mg)	19.5	5.6	11.6	30	31.9
Vitamin B_6 (mg)	1.3	0.4	0.7	2.2	2.4
Total folate* (µg)	169	71	88	297	333
Folic acid** (µg)	51.9	59.8	0.0	153	220
Vitamin B_{12} (µg)	3.8	1.9	1.3	7.2	8.1
Biotin (µg)	20.9	12.5	9.8	35.7	43.8
Pantothentate (mg)	4.1	1.3	2.2	6.6	7.4
Minerals					
Potassium (mg)	1,750	431	1,077	2,475	2,701
Calcium (mg)	769	271	402	1,296	1,452
Phosphorus (mg)	833	231	506	1,268	1,410
Magnesium (mg)	154	40	94	227	240
Iron (mg)	7.1	2.5	3.7	12	13.2
Zinc (mg)	5.2	1.6	3.1	8.1	9.2
Copper (mg)	0.5	0.2	0.3	0.9	1
Iodine (µg)	155	81	49	316	349

*Contains natural food folates and folic acid from fortified foods
** Risk assessment is based on folic acid rather than folate. Consideration should be given to whether the risk assessment should be based on folic acid intakes in the total population or in consumers only

Source: Irish Universities Nutrition Alliance (2012) The National Pre-School Nutrition Survey (2011) http://www.iuna.net/?p=169 Accessed July 2014

Table 9b. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from All Sources (including food supplements*) in Irish Pre-school Children for the Total Population (*n*500)

	Mean	SD	5th	95th	97.5th
Vitamins					
Total Vitamin A (µg)	688	497	205	1,465	1,701
Retinol (µg)	350	371	101	840	1,156
Carotene (µg)	2,033	1,953	153	5,667	7,418
Vitamin D (µg)	3.3	3.8	0.4	11.4	13.6
Vitamin C (mg)	85	52	23	175	203
Thiamin (mg)	1.1	0.4	0.6	1.8	2.1
Riboflavin (mg)	1.6	0.6	0.8	2.6	3
Pre-formed Niacin (mg)	11.9	4.9	5.6	21	23.8
Total Niacin Equivalents (mg)	20.2	6.2	11.6	31.5	34
Vitamin B_6 (mg)	1.4	0.6	0.7	2.5	3
Total folate** (µg)	179	80	90	327	395
Vitamin B_{12} (µg)	4	2	1.4	7.5	8.4
Biotin (µg)	22.9	16.3	9.9	53.4	65.5
Pantothentate (mg)	4.5	1.8	2.4	8	9.8
Minerals					
Potassium (mg)	1,750	431	1,077	2,475	2,701
Calcium (mg)	773	273	402	1,319	1,452
Phosphorus (mg)	834	232	506	1,268	1,410
Magnesium (mg)	155	41	94	227	242
Iron (mg)	7.4	3.2	3.7	12.6	15
Zinc (mg)	5.3	1.8	3.1	8.7	10.1
Copper (mg)	0.6	0.2	0.3	0.9	1.1
Sodium (mg)	1,193	415	591	2,010	
Salt equivalent (g)	3	1	1.5	5	
Iodine (µg)	157	81	50	316	349

* Tables provide information on everyone in the population (those consuming and not consuming food supplements). Sometimes risk assessments of food supplement products require consideration of supplement consumer's only (omitting non-users). These data are not available for tabulation.

** Contains natural food folates, folic acid from fortified foods and folic acid from supplements

Source: Irish Universities Nutrition Alliance (2012) The National Pre-School Nutrition Survey (2011) http://www.iuna.net/?p=169 Accessed July 2014

Table 10a. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from Food Sources Only in Irish Children (5-12 yrs) for the Total Population by Gender

	BOYS (*n*293)					GIRLS (*n*301)				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Total Vitamin A (µg)	665	453	142	1,559	1,838	580	457	163	1,290	1,463
Retinol (µg)	273	260	81	539	652	266	327	76	558	692
Carotene (µg)	2,352	2,140	196	6,818	8,424	1,886	1,720	251	5,020	6,479
Vitamin D (µg)	1.4	1.1	0.3	3.7	4.4	1.6	1.2	0.4	3.4	5.2
Vitamin E (mg)	5.7	2.9	2.1	11.9	12.9	5.3	2.5	2.3	9.8	11.7
Vitamin C (mg)	72	42	21	163	187	77	49	23	173	225
Thiamin (mg)	1.5	0.5	0.9	2.4	2.6	1.3	0.4	0.7	2.1	2.3
Riboflavin (mg)	1.9	0.7	0.8	3.2	3.6	1.6	0.6	0.7	2.8	3
Pre-formed Niacin (mg)	17.8	6.1	9.3	28.5	31.1	15.2	5.2	8.5	23.9	28.7
Total Niacin Equivalents (mg)	29.6	8.7	17.3	44.7	49.2	26	7.3	16.3	38.8	45.4
Vitamin B_6 (mg)	2	0.7	1	3.4	3.7	1.7	0.6	1	2.9	3.2
Total folate* (µg)	231	85	110	381	448	198	75	107	356	423
Folic acid** (µg)	72.2	59.6	6.3	187	231	53.7	55.3	0.0	167	210
Vitamin B_{12} (µg)	4.5	2.2	1.8	8.6	9.7	4	2.2	1.5	7.8	9.4
Biotin (µg)	24.5	17.8	9.3	49.2	61.3	21.5	16.5	9.2	40	51.9
Pantothentate (mg)	5.4	2	2.6	9.4	10.4	4.6	1.7	2.4	7.8	8.9
Minerals										
Calcium (mg)	907	309	461	1,488	1,578	804	271	426	1,274	1,434
Phosphorus (mg)	1,085	306	641	1,605	1,832	961	253	593	1,445	1,500
Magnesium (mg)	205	57	122	308	346	182	43	121	260	280
Iron (mg)	9.9	3.3	5.5	16.2	17.6	8.3	2.5	4.8	12.8	13.7
Zinc (mg)	6.9	2.2	3.8	10.8	12.4	6.1	1.6	3.9	9	10.1
Copper (mg)	0.83	0.34	0.39	1.46	1.74	0.76	0.36	0.39	1.25	1.37

* Contains natural food folates and folic acid from fortified foods

** Risk assessment is based on folic acid rather than folate. Consideration should be given to whether the risk assessment should be based on folic acid intakes in the total population or in consumers only

Source: Irish Universities Nutrition Alliance (2005) The National Children's Food Survey http://www.iuna.net/?p=27 Accessed July 2014

Table 10b. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from All Sources (including food supplements*) in Irish Children (5-12 yrs) for the Total Population by Gender

	BOYS (*n*293)					GIRLS (*n*301)				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Total Vitamin A (µg)	762	537	155	1,790	1,964	661	523	164	1,468	1,776
Retinol (µg)	370	281	84	1,060	1,257	346	420	80	1,000	1,426
Carotene (µg)	2,357	2,138	196	6,818	8,424	1,892	1,719	251	5,020	6,479
Vitamin D (µg)	2.2	2.2	0.4	6.4	8.7	2.3	2.3	0.4	6.4	9.3
Vitamin E (mg)	6.7	4.5	2.1	15.4	17.8	6	3.7	2.3	12.6	18.5
Vitamin C (mg)	86	73	21	178	256	88	63	25	203	238
Thiamin (mg)	1.6	0.6	0.9	2.6	2.9	1.5	2.2	0.8	2.3	3
Riboflavin (mg)	2	0.8	0.8	3.4	3.8	1.8	2.2	0.7	2.9	3.5
Pre-formed Niacin (mg)	18.4	6.7	9.3	30.2	35.5	15.9	6.3	8.5	27.3	33.9
Total Niacin Equivalents (mg)	30.2	9.1	17.3	46.7	51.9	26.6	8.1	16.3	42.6	48.8
Vitamin B_6 (mg)	2.1	0.8	1	3.5	4.3	1.9	2.2	1	3.2	3.9
Total folate**(µg)	243	103	113	451	499	207	90	111	417	486
Vitamin B_{12} (µg)	4.7	2.3	1.8	8.8	9.8	4.2	2.6	1.5	8	9.7
Biotin (µg)	26.9	22.9	9.3	60.9	80.7	23.9	25.4	9.5	54	73.8
Pantothentate (mg)	5.7	2.2	2.6	10.4	11	4.9	2.9	2.4	8.5	10.3
Minerals										
Calcium (mg)	918	318	461	1,490	1,595	808	270	438	1,297	1,434
Phosphorus (mg)	1,089	306	651	1,624	1,832	961	253	594	1,445	1,500
Magnesium (mg)	206	58	125	311	348	182	44	121	266	285
Iron (mg)	10.3	3.8	5.5	17.1	20.3	8.5	2.8	4.9	13.7	15.6
Zinc (mg)	7	2.7	3.8	11.7	13.3	6.2	1.7	3.9	9.8	10.6
Copper (mg)	0.84	0.38	0.39	1.51	1.84	0.77	0.36	0.39	1.28	1.45

* Tables provide information on everyone in the population (those consuming and not consuming food supplements). Sometimes risk assessments of food supplement products require consideration of supplement consumer's only (omitting non-users). These data are not available for tabulation.

** Contains natural food folates, folic acid from fortified foods and folic acid from supplements

Source: Irish Universities Nutrition Alliance (2005) The National Children's Food Survey http://www.iuna.net/?p=27 Accessed July, 2014

Table 11a. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from Food Sources only in Irish Teens (13-17 yrs) for the Total Population by Gender

	MALES (*n*224)					FEMALES (*n*217)				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Total Vitamin A (µg)	808	526	186	1,944	2,241	606	369	130	1,401	1,524
Retinol (µg)	336	210	108	772	865	234	149	58	506	700
Carotene (µg)	2,832	2,687	272	8,410	12,032	2,233	1,893	243	6,063	7,180
Vitamin D (µg)	2.4	1.9	0.6	6	7.5	1.8	1.6	0.4	4.5	6
Vitamin E (mg)	7.9	4.7	2.8	16.2	23.9	6.6	3.2	2.7	12.5	14.4
Vitamin C (mg)	83	55	19	188	221	72	48	21	179	207
Thiamin (mg)	1.9	0.7	1	3.4	4	1.4	1.4	0.6	2.2	2.5
Riboflavin (mg)	2.3	1	0.9	4	4.6	1.5	0.8	0.5	2.9	3.4
Pre-formed Niacin (mg)	24.8	9.1	12.1	42	48.3	17.2	6.4	8.1	29.2	30.7
Total Niacin Equivalents (mg)	41.7	13.2	23	67.1	75.6	29.1	9.4	15	44.9	48.1
Vitamin B_6 (mg)	2.7	1	1.3	4.5	5	1.9	0.7	0.9	3.2	4
Total folate* (µg)	302	143	148	653	726	209	101	96	378	475
Folic acid** (µg)	89.3	98.9	0.0	338	412	53.1	74.2	0.0	178	249
Vitamin B_{12} (µg)	5.7	2.7	2.4	11.3	13.1	3.7	2.1	1.1	7.5	8.7
Biotin (µg)	30.8	23.4	13.8	60.1	75.2	19.7	10.5	7.2	35.5	41.8
Pantothentate (mg)	6.6	2.8	3	11.7	13.8	4.4	1.9	1.9	7.9	8.4
Minerals										
Calcium (mg)	1,063	408	522	1,905	2,047	734	326	294	1,376	1,554
Phosphorus (mg)	1,412	430	820	2,224	2,464	999	330	523	1,646	1,768
Magnesium (mg)	268	91	163	435	506	194	61	105	291	345
Iron (mg)	12.6	4.8	6.8	22.3	25.6	8.5	3.1	4.2	14.7	16.4
Zinc (mg)	9.8	3.2	5.5	15.5	18.8	6.7	2.3	3.3	10.7	11.9
Copper (mg)	1.11	0.55	0.59	1.99	2.58	0.82	0.32	0.42	1.5	1.78

* Contains natural food folates and folic acid from fortified foods

** Risk assessment is based on folic acid rather than folate. Consideration should be given to whether the risk assessment should be based on folic acid intakes in the total population or in consumers only

Source: Irish Universities Nutrition Alliance (2008) The National Teen's Food Survey http://www.iuna.net/?p=29 Accessed July, 2014

Table 11b. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from All Sources (including food supplements*) in Irish Teens (13-17 yrs) for the Total Population by Gender

	MALES (*n*224)					FEMALES (*n*217)				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Total Vitamin A (µg)	901	601	196	2,202	2,542	686	441	133	1,567	1,782
Retinol (µg)	416	315	109	1,186	1,326	308	262	61	927	1,097
Carotene (µg)	2,909	2,751	272	8,577	12,186	2,267	1,909	244	6,063	7,180
Vitamin D (µg)	3	2.6	0.7	8.9	10.2	2.3	2.2	0.4	7.2	9.2
Vitamin E (mg)	9.3	6.4	3	24.3	28.4	8	9.7	2.7	15.6	22.8
Vitamin C (mg)	98	87	22	237	311	92	100	21	209	315
Thiamin (mg)	2.2	2.4	1	3.7	4.8	1.9	3.2	0.7	3.7	9.9
Riboflavin (mg)	2.6	2.5	0.9	4.6	5.6	2	3.1	0.5	4.2	8.6
Pre-formed Niacin (mg)	26.5	11	12.7	48.6	56.1	18.7	8.3	8.1	34.9	39.8
Total Niacin Equivalents (mg)	43.3	14.6	23.2	71.3	79.6	30.5	10.8	15	50.2	52.9
Vitamin B_6 (mg)	3.1	2.5	1.4	5.4	7.7	2.5	3.1	0.9	5.1	9.5
Total folate** (µg)	320	157	149	687	763	230	129	97	501	581
Vitamin B_{12} (µg)	6	3.2	2.4	12.1	15.3	4.2	3.1	1.1	8.5	15
Biotin (µg)	37.9	38.6	14	123.4	180.5	25.9	36.2	7.2	68.5	107.5
Pantothentate (mg)	7.3	4.1	3.1	13.9	18.2	5.2	4	1.9	10.9	16.2
Minerals										
Calcium (mg)	1,070	409	522	1,905	2,047	738	328	311	1,383	1571
Phosphorus (mg)	1,413.4	430.1	820.7	2,223.9	2,464	1,000	331	523	1,646	1,768
Magnesium (mg)	270.7	92.2	163.1	434.8	512	196	62	105	319	345
Iron (mg)	14.1	11.5	6.8	25.7	28.7	10.7	11.6	4.2	20.8	33.1
Zinc (mg)	10.2	3.7	5.8	18.1	20.5	7.2	3.1	3.3	12.8	15.4
Copper (mg)	1.16	0.59	0.59	2.38	2.74	0.85	0.37	0.4	1.56	1.83

* Tables provide information on everyone in the population (those consuming and not consuming food supplements). Sometimes risk assessments of food supplement products require consideration of supplement consumer's only (omitting non-users). These data are not available for tabulation.

** Contains natural food folates, folic acid from fortified foods and folic acid from supplements

Source: Irish Universities Nutrition Alliance (2008) The National Teen's Food Survey http://www.iuna.net/?p=29 Accessed July, 2014

Table 12a. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from Food Sources Only in Irish Adults for the Total Population by Age

	18-64 yrs (*n*1,274)					>65 yrs (*n*226)				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Total Vitamin A (µg)	983	831	219	2159	2490	1186	791	284	2578	3087
Retinol (µg)	387	620	79	768	972	494	632	66	1275	1979
Carotene (µg)	3579	3204	293	9623	11625	4151	2990	399	10414	12067
Vitamin D (µg)	3.1	2.5	0.6	7.9	9.6	3.8	3.2	0.6	9.4	12
Vitamin E (mg)	8.5	4.7	2.7	17.2	19.3	8.6	5.4	2.2	19.1	23.8
Vitamin C (mg)	80	53	19	191	217	77	49	17	175	205
Thiamin (mg)	1.8	2.4	0.8	2.9	3.3	1.6	0.6	0.7	2.7	3.3
Riboflavin (mg)	1.9	0.9	0.8	3.5	4	1.7	0.7	0.7	3.1	3.4
Pre-formed Niacin (mg)	25	10.9	11.1	44.6	51.3	19.7	7.9	9.4	37.7	41.7
Total Niacin Equivalents (mg)	42.2	16	39.5	70.3	78.8	35.1	11.7	18.4	57.7	65.5
Vitamin B_6 (mg)	2.7	1.4	1.2	4.9	6.1	2.5	1.2	1.1	4.7	5.5
Total folate* (µg)	320	146	134	596	690	323	181	123	642	798
Vitamin B_{12} (µg)	5.4	3.8	1.6	11.3	13.1	5.7	3.9	1.7	10.7	17.3
Biotin (µg)	37	19	16	67	77	39	24	18	65	77
Pantothentate (mg)	5.9	2.4	2.8	10.6	11.9	5.7	2	3	9	10.6
Minerals										
Calcium (mg)	908	375	421	1,620	1,817	840	344	374	1,518	1,654
Phosphorus (mg)	1,394	464	746	2,228	2,434	1,288	435	662	2,169	2,364
Magnesium (mg)	286	103	148	467	525	261	92	125	430	479
Iron (mg)	12.3	5.2	5.2	5.9	21.8	10.8	4.3	4.3	5.1	18.7
Zinc (mg)	9.3	8.8	4.6	15.9	17.4	8.7	2.9	4.5	13.9	15.3
Copper (mg)	1.2	0.6	0.5	2.3	2.9	1.1	0.6	0.5	2	2.6
Sodium (mg)	2,944	953	1,564	4,654		2,499	926	1,222	4,246	
Salt equivalent (g)	7.36	2.38	3.91	11.63		6.25	2.31	3.06	10.62	
Iodine (µg)	151	100	48	316	377	148	73	41	292	316

* Contains natural food folates and folic acid from fortified foods

Source: Irish Universities Nutrition Alliance (2011) The National Adult Nutrition Survey http://www.iuna.net/?p=106 Accessed July, 2014

Table 12b. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from All Sources (including food supplements*) in Irish Adults for the Total Population by Age

	18-64 yrs (*n*1274)					>65 yrs (*n*226)				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Total Vitamin A (µg)	1,084	948	226	2,396	3,036	1,354	1,048	338	3,025	3576
Retinol (µg)	476	737	85	1190	1,659	638	377	66	1,937	2,904
Carotene (µg)	3,645	3,256	301	9,901	11,848	4,297	3,150	399	11,168	12,615
Vitamin D (µg)	4.3	6.2	0.7	12.5	15.9	6.9	10.5	0.7	24.2	29.3
Vitamin E (mg)	12.1	27.4	2.9	24.5	36.9	14.6	38.5	2.2	29.3	51.5
Vitamin C (mg)	128	241	20	379	632	118	262	17	347	495
Thiamin (mg)	3.1	8.7	0.8	5.8	16.3	2.8	9	0.7	3.7	12.4
Riboflavin (mg)	3.2	7.8	0.8	5.9	15.5	2.9	8.4	0.7	4.2	9.9
Pre-formed Niacin (mg)	28.8	20	11.2	57.4	72.3	26.6	42.7	9.8	49.3	67.7
Total Niacin Equivalents (mg)	46	23.3	21.2	82.6	94.8	42	43.4	19.4	69.9	88.6
Vitamin B_6 (mg)	4.1	8.6	1.2	8.7	14.7	4.3	15.2	1.1	6.8	12.6
Total folate** (µg)	373	314	136	730	848	390	415	124	869	1124
Vitamin B_{12} (µg)	7.7	32.5	1.7	14.1	23.7	6.5	5.9	1.8	16.3	28
Biotin (µg)	54	255	16	138	184	101	799	18	138	202
Pantothentate (mg)	8	12.3	2.8	16.9	28.6	7.2	7.1	3	14.2	27.1
Minerals										
Calcium (mg)	941	400	433	1,690	1,872	954	494	377	2,106	2,337
Phosphorus (mg)	1,397	465	753	2,242	2,434	1,292	432	711	2,169	2,364
Magnesium (mg)	295	110	152	484	544	273	120	128	480	529
Iron (mg)	14.4	14.5	6	25.8	33.1	15.8	25.8	5.3	27.8	114
Zinc (mg)	10.4	5.9	4.7	19.4	23.1	10.4	13.2	4.7	17.9	26
Copper (mg)	1.3	1.5	0.5	2.9	3.8	1.1	0.7	0.5	2.4	3.2
Iodine (µg)	157	103	48	334	388	155	85	41	311	368

* Tables provide information on everyone in the population (those consuming and not consuming food supplements). Sometimes risk assessments of food supplement products require consideration of supplement consumer's only (omitting non-users). These data are not available for tabulation.

** Contains natural food folates, folic acid from fortified foods and folic acid from supplements

Source: Irish Universities Nutrition Alliance (2011) The National Adult Nutrition Survey http://www.iuna.net/?p=106 Accessed July, 2014

Table 13a. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from Food Sources Only in Irish Adults for the Total Population by Gender and Age

	18-64 yrs					>65 yrs				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Males	(*n*634)					(*n*106)				
Total Vitamin A (µg)	1,031	866	253	2,147	2,432	1,221	774	247	2,793	3,255
Retinol (µg)	428	661	89	828	995	543	575	60	1,794	2,387
Carotene (µg)	3,622	3,168	302	9,416	10,927	4,071	3,040	375	9,537	11,999
Vitamin D (µg)	3.4	2.8	0.7	8.5	10.2	4.3	3.7	0.8	11.1	14.2
Vitamin E (mg)	9.3	5.2	2.8	18.4	20.9	9.0	5.6	1.8	19.1	24.2
Vitamin C (mg)	81	55	19	192	224	72	52	14	174	208
Thiamin (mg)	1.9	0.7	0.9	3.1	3.5	1.8	0.6	0.8	3.0	3.3
Riboflavin (mg)	2.2	0.9	0.9	4.0	4.3	1.8	0.7	0.7	3.1	3.4
Pre-formed Niacin (mg)	30.1	11.3	14.6	50.5	55.6	21.7	8.3	9.3	41.6	45.6
Total Niacin Equivalents (mg)	50.5	16.1	27.6	78.5	87.3	38.9	12.3	19.1	64.7	70.4
Vitamin B_6 (mg)	3.2	1.5	1.5	5.7	6.6	2.8	1.4	1.2	5.6	7.2
Total folate* (µg)	374	153	161	666	748	352	205	126	723	1,035
Folic acid** (µg)	67.9	88.6	0.0	263	310	54.6	77.3	0.0	234	271
Vitamin B_{12} (µg)	6.4	4.2	2.2	12.8	15.0	6.3	4.5	1.9	14.4	22.3
Biotin (µg)	42	18	19	72	89	40	19	17	68	91
Pantothentate (mg)	6.8	2.5	3.5	11.8	12.8	6.0	1.9	3.1	9.0	10.0
Females	(*n*640)					(*n*120)				
Total Vitamin A (µg)	935	793	203	2188	2,553	1,154	807	274	2,459	2,931
Retinol (µg)	346	574	70	654	835	451	678	70	1,038	1,901
Carotene (µg)	3,537	3,241	287	10,005	12,305	4,221	2,956	451	10,614	12,159
Vitamin D (µg)	2.8	2.1	0.5	7.1	8.5	3.4	2.6	0.6	8.6	10.0
Vitamin E (mg)	7.8	3.9	2.7	15.2	17.5	8.3	5.2	2.6	19.2	23.7
Vitamin C (mg)	79	51	18	184	214	81	46	23	189	210
Thiamin (mg)	1.7	3.3	0.7	2.4	2.9	1.5	0.6	0.7	2.5	3.0
Riboflavin (mg)	1.6	0.6	0.7	2.8	3.1	1.7	0.7	0.7	3.1	3.3
Pre-formed Niacin (mg)	19.9	7.7	9.2	34.9	38.1	18.0	7.1	9.4	31.0	39.3
Total Niacin Equivalents (mg)	33.9	10.7	17.6	53.8	56.7	31.7	10.1	17.5	50.2	57.9
Vitamin B_6 (mg)	2.2	1.1	1.1	3.8	4.3	2.3	0.9	1.1	4.2	4.6
Total folate* (µg)	266	116	120	489	534	298	154	122	652	701
Folic acid** (µg)	49.1	67.1	0.0	191	252	76.0	107.0	0.0	307	340
Vitamin B_{12} (µg)	4.5	3.0	1.4	8.5	10.4	5.1	3.2	1.6	9.9	15.3
Folic acid (µg)**	49.1	67.1	0.0	191	252	76.0	107.0	0.0	307	340

Continued on next page

	18-64 yrs					>65 yrs				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Females	(*n*640)					(*n*120)				
Biotin (µg)	32	17	13	58	65	37	28	18	61	81
Pantothentate (mg)	5.0	1.9	2.4	8.2	9.0	5.3	1.9	2.8	9.8	11.1
Minerals										
Males	(*n*634)					(*n*106)				
Calcium (mg)	1,043	403	493	1,767	2,017	886	359	349	1,585	1,867
Phosphorus (mg)	1,619	467	934	2,435	2,677	1,424	472	762	2,345	2,489
Magnesium (mg)	330	108	179	514	567	281	99	132	465	492
Iron (mg)	14.1	5.7	7.2	24.6	27.0	11.7	4.6	5.2	19.5	23.6
Zinc (mg)	10.9	3.6	5.9	17.3	18.7	9.4	3.1	4.8	15.3	16.6
Copper (mg)	1.3	0.7	0.6	2.4	3.0	1.1	0.5	0.5	2.1	2.6
Iodine (µg)	175	120	54	352	417	152	72	47	298	316
Females	(*n*640)					(*n*120)				
Calcium (mg)	776	289	366	1,293	1,442	800	327	375	1,414	1,609
Phosphorus (mg)	1,171	336	657	1,750	1,936	1,168	362	632	1,822	1,971
Magnesium (mg)	243	76	129	377	412	242	82	119	388	436
Iron (mg)	10.5	4.0	5.2	17.9	21.2	10.0	3.7	5.0	17.0	21.2
Zinc (mg)	7.7	2.6	4.2	12.0	13.4	8.0	2.6	4.4	12.7	13.7
Copper (mg)	1.0	0.6	0.5	2.0	2.4	1.0	0.7	0.5	1.7	2.6
Iodine (µg)	128	67	42	247	280	144	74	36	278	328

* Contains natural food folates and folic acid from fortified foods

** Risk assessment is based on folic acid rather than folate. Consideration should be given to whether the risk assessment should be based on folic acid intakes in the total population or in consumers only

Source: Irish Universities Nutrition Alliance (2011) The National Adult Nutrition Survey http://www.iuna.net Accessed August, 2015

Table 13b. Mean, SD and Percentile Values of Vitamin and Mineral Intakes from All Sources (including food supplements*) in Irish Adults for the Total Population by Gender and Age

	18-64 yrs					>65 yrs				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Vitamins										
Males	(*n*634)					(*n*106)				
Total Vitamin A (µg)	1,140	995	258	2,383	3,105	1,335	827	317	3,002	3,518
Retinol (µg)	530	801	100	1,236	1,845	639	632	60	2,045	2,543
Carotene (µg)	3660	3,197	308	9521	11,020	4,178	3,150	375	10,697	12,817
Vitamin D (µg)	4.6	7.1	0.7	12.8	16.1	5.2	4.5	0.8	12.7	18.5
Vitamin E (mg)	11.6	23.5	2.8	23.4	32.3	9.8	6.7	1.8	24.5	25.9
Vitamin C (mg)	114	152	19	310	582	102	146	14	347	623
Thiamin (mg)	2.9	5.8	0.9	5.3	13.2	2.1	2.5	0.8	3.4	3.8
Riboflavin (mg)	3.2	6.0	0.9	5.6	12.5	2.0	1.4	0.7	3.7	4.2
Pre-formed Niacin (mg)	32.9	15.7	15.3	61.5	77.2	23.7	12.9	9.7	45.6	57.6
Total Niacin Equivalents (mg)	53.3	19.7	28.3	91.1	98.2	41.0	16.0	21.3	69.5	79.1
Vitamin B_6 (mg)	4.1	5.4	1.5	7.6	12.4	3.1	1.9	1.2	6.2	7.9
Total folate**(µg)	407	209	168	768	840	427	533	126	945	1432
Vitamin B_{12} (µg)	7.3	6.9	2.2	15.5	22.7	6.4	4.5	1.9	14.4	22.3
Biotin (µg)	51	37	19	128	181	47	34	17	125	191
Pantothentate (mg)	8.6	11.9	3.5	17.2	25.0	6.4	2.6	3.1	12.3	13.4
Females	(*n*640)					(*n*120)				
Total Vitamin A (µg)	1,028	896	208	2,440	3,024	1,371	1,213	354	3,065	4,593
Retinol (µg)	423	663	75	1,151	1,566	638	1,020	70	1,833	3,499
Carotene (µg)	3,629	3,317	294	10,629	12,534	4,402	3,160	451	11,973	12,544
Vitamin D (µg)	3.9	5.2	0.6	12.1	15.5	8.5	13.6	0.6	28.8	33.8
Vitamin E (mg)	12.5	30.8	2.9	25.6	45.1	18.9	52.2	2.7	50.3	211.2
Vitamin C (mg)	141	304	20	474	797	132	333	23	358	439
Thiamin (mg)	3.4	10.8	0.7	9.5	19.1	3.5	12.1	0.7	6.5	26.5
Riboflavin (mg)	3.3	9.2	0.7	6.0	16.6	3.7	11.4	0.7	6.6	27.1
Pre-formed Niacin (mg)	24.7	22.8	9.7	48.9	70.5	29.2	57.3	10.2	64.1	138.5
Total Niacin Equivalents (mg)	38.8	24.2	18.9	67.1	86.3	42.8	57.7	18.5	77.4	159.2
Vitamin B_6 (mg)	4.2	10.9	1.1	11.8	26.4	5.4	20.7	1.1	10.1	51.2
Total folate* (µg)	339	388	123	672	882	357	271	122	881	923
Vitamin B_{12} (µg)	8.0	45.3	1.4	13.1	27.3	6.5	6.9	1.6	18.3	31.0
Biotin (µg)	57	358	14	149	184	149	1,096	18	195	229
Pantothentate (mg)	7.4	12.7	2.5	16.7	30.0	7.9	9.4	2.8	26.2	54.3

Continued on next page

	18-64 yrs					>65 yrs				
	Mean	SD	5th	95th	97.5th	Mean	SD	5th	95th	97.5th
Minerals										
Males	(*n*634)					(*n*106)				
Calcium (mg)	1,060	407	496	1,818	2,037	908	384	349	1,793	1,936
Phosphorus (mg)	1,623	467	934	2,435	2,677	1,427	470	762	2,345	2,489
Magnesium (mg)	336	112	183	527	589	285	103	132	485	504
Iron (mg)	15.0	9.0	7.4	26.3	32.8	18.1	27.6	5.3	79.7	115.7
Zinc (mg)	11.8	5.6	6.1	20.6	24.2	10.2	4.2	5.0	17.6	21.5
Copper (mg)	1.4	1.0	0.6	2.9	3.7	1.2	0.6	0.5	2.4	3.1
Iodine (µg)	179	122	54	365	428	153	73	47	305	329
Females	(*n*640)					(*n*120)				
Calcium (mg)	824	356	378	1,415	1,700	995	573	381	2,333	2,494
Phosphorus (mg)	1,174	337	658	1,760	1,936	1,173	364	641	1,858	2,008
Magnesium (mg)	255	93	135	411	469	262	132	125	477	635
Iron (mg)	13.7	18.4	5.5	24.1	37.6	13.8	24.1	5.1	23.6	109.0
Zinc (mg)	9.0	5.9	4.2	18.4	22.6	10.7	17.8	4.5	20.2	35.9
Copper (mg)	1.3	1.9	0.5	2.7	4.0	1.1	0.8	0.5	2.5	3.5
Iodine (µg)	134	74	42	262	310	157	95	36	363	425

* Tables provide information on everyone in the population (those consuming and not consuming food supplements).

Sometimes risk assessments of food supplement products require consideration of supplement consumer's only (omitting non-users).

These data are not available for tabulation.

** Contains natural food folates and folic acid from fortified foods

Source: Irish Universities Nutrition Alliance (2011) The National Adult Nutrition Survey http://www.iuna.net Accessed August, 2015

TERMS OF REFERENCE

Membership of the Safe Micronutrient Levels Expert Working Group

Membership of the working group comprises individuals with the technical ability and experience to develop scientific recommendations to guide:

1. Enforcement action by the FSAI on food supplements and food containing added micronutrients (vitamins and minerals) exceeding levels that can be safely tolerated by the general healthy population (considering age, gender and pregnancy)
2. Use of food supplements for key nutrients during pregnancy, e.g. folic acid, iron, vitamin D

Remit

The remit of the working group is to report back to the Public Health Nutrition Sub-committee with recommendations for:

1. National tolerable upper intake levels for micronutrients taking into consideration those established by EFSA and the IOM
2. Use of food supplements for key nutrients during pregnancy, e.g. folic acid, iron, vitamin D

Meetings

Where possible, this work will be carried out electronically. However, it is expected that meetings will be required to finalise the recommendations and report.

Confidentiality

The FSAI will endeavour to maintain the confidentiality of any correspondence marked confidential within its obligations under the Freedom of Information Act.

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