Nutritional risk analysis approaches for establishing maximum levels of vitamins and minerals in food (dietary) supplements

IADSA

International Alliance of Dietary/
Food Supplement Associations

The International Alliance of Dietary/Food Supplement Associations (IADSA) brings together over 50 associations of dietary supplement manufacturers and distributors from across the world. IADSA's central goal is to ensure a greater exchange of information about the science and regulation of dietary supplements and ingredients among industry, scientists, regulators and consumers.

Nutritional risk analysis approaches for establishing maximum levels of vitamins and minerals in food (dietary) supplements

Prepared on behalf of IADSA by

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Summary

Science-based approaches to nutritional risk analysis and the establishment of upper levels of intake for nutrients are based primarily on principles and guidelines from the Codex Alimentarius Commission, the Food and Agriculture Organisation (FAO) and the World Health Organisation (WHO). These international organisations rely in turn on a number of expert committees that develop Dietary Reference Intakes (DRIs) including the Recommended Daily Allowance (RDA) and the tolerable upper intake level (UL). These quantitative values are used by risk managers and policy makers when planning diets and developing nutrition and health policies to assess nutrient adequacy for groups and individuals, and when assessing potential risk of adverse effects from excessive nutrient intake, respectively. The Codex standards, codes and practical guidelines act as global reference points for national food control agencies, for consumers, food producers and processes, and for international trade. The Codex objectives are to help all nations join the international community in formulating and harmonising food and food supplement standards, and to provide benchmarks against which national food measures and regulations are evaluated within the legal parameters of the World Trade Organisation Agreements.

Risk analysis for nutrients differs from that for other substances in foods because vitamins and minerals are essential for life, and consequently adverse effects can result from suboptimal intakes and deficiencies as well as from excessive intakes. The key challenge for risk managers is to balance the risk of deficiency in some individuals with risk of overconsumption in others in the same population. Nutritionists focus on preventing dietary deficiencies and the development of the concept of recommended daily amounts. In contrast, the study of adverse effects at high intakes is within the province of toxicology, which has developed different tools and principles in order to avoid adverse effects. These differences in scientific concepts becomes important if and when countries around the world propose maximum amounts of nutrients in fortified foods and in food supplements, and particularly if the policy approaches are based on, or limited to, fractions or multiples of the RDA.

This report explains why RDA-based upper safe levels are not scientific or appropriate to establish maximum levels of vitamins and minerals in food supplements. It sets out the three distinct, but closely related, components of nutritional risk analysis as described by Codex and FAO/WHO, namely nutritional risk assessment, nutritional risk management and nutritional risk communication. The principles of scientific risk assessment include a problem formulation stage and four steps related to hazard identification, hazard characterisation, dietary intake assessment from all dietary sources including conventional foods, foods with added nutrients and food supplements, and a nutrient risk characterisation, where the safety and intake data are fully integrated and applied in the context of the diet as a whole. This report uses nutrient risk assessments and approaches for the establishment of ULs and Highest Observed Intakes (HOIs, where ULs cannot be established because of absence of adverse effects) from three national authoritative bodies, which were included in the FAO/WHO model for establishing upper levels of intake for nutrients. These organisations are the European Food Safety Authority (EFSA), the US Institute of Medicine

(IOM) and the United Kingdom Expert Group on Vitamins and Minerals (EVM). This UL risk assessment model now has widespread scientific and policy support around the world. The report also explains how scientific committees draw on a wide array of available consumption data and how to estimate the habitual nutrient intake distributions from all sources to reflect the reality of the diverse patterns of intake and dietary contexts that exist around the world. In cases where intake data are limited, mathematical modelling can be used to handle uncertainties in the intake estimates. In addition, national and international population-based nutrition surveys can be used for monitoring nutrient intakes and identifying potential shortfalls and excesses within the population. A pragmatic approach, if and when maximum amounts of vitamins and minerals in foodstuffs, including food supplements, are being established, is to use the best available data. For countries where robust, regional data are not readily available, the best solution is often to utilise methodologies and data from different parts of the world in order to provide the most appropriate and valid picture of intakes from foods, food supplements and, where applicable, water. Some nutritional risk assessments provide the entire distribution of intake, while others provide only the mean and the 95 or 97.5 percentile intakes.

The current report reviews and provides examples of the application of the principles of nutritional risk assessment and nutritional risk management in order to underpin the regulatory developments in establishing maximum levels of vitamins and minerals in food supplements in Europe and in the Association of Southeast Asian (ASEAN) countries. This report also uses both quantitative and qualitative risk management approaches, which include the use of the Population Safety Index (PSI) paradigm for each nutrient so that they can be allocated into three groups of risk. The PSI risk management model can be applied to different data sets and for adults and children.

A key aim of nutritional risk analysis is to provide clear, transparent and detailed documentation of the methods used to underpin any regulatory developments to set maximum levels of nutrients in food supplements. Further dialogue, exchanges of information and appropriate involvement of interested parties are critical to protect consumers both young and old, and to promote public understanding of the processes involved so as to enhance trust and confidence in the safety of the food supply.

Glossary of terms [1]

Adverse health effect

A change in morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.

A related substance

A constituent of food (other than a nutrient) that has a favourable physiological effect.

Essential nutrient

Any substance normally consumed as a constituent of food which is needed for growth and development and the maintenance of healthy life and which cannot be synthesises in inadequate amounts by the body.

Habitual intake

The long-term average daily intake of the nutrient substance.

Hazard

Inherent property of a nutrient or related substance to cause adverse health effects depending upon the level of intake.

Lifestage

Generally refers to pregnancy or lactation.

Nutrient

Defined by Codex *General Principles for the Addition of Essential Nutrients to Foods* (CAC/GL 09-1987) to mean any substance normally consumed as a constituent of food:

a) which provides energy; or
b) which is needed for growth and development and maintenance of healthy life; or
c) a deficit of which will cause characteristic biochemical or physiological changes to occur.

Nutrients and related substances (abbreviated to nutrient substances)

Regarded as inherent constituents of food that either are biologically essential or have a demonstrated favourable impact on health. They do not encompass food additives or substances such as food contaminants, pesticides, microbiological pathogens, or other food-borne hazards. National/regional regulatory authorities vary in their definitions for nutrient substances; however, scientific evidence to assess risk from such substances should in principle be equally relevant for all countries.

[1] Adapted from WHO/FAO (2006) and Codex Alimentarius (2010)

Risk

The probability of an adverse effect in an organism, system or (sub)population caused under specified circumstances by exposure to an agent.

(Sub)population

The collective inhabitants of a country or region and/or a subgroup thereof—used when the sentence may be applicable to the population as a whole and to subgroups of the population (e.g. as used in the definition of 'adverse health effect' above).

Subpopulation

A specified subgroup of a population—examples include children in a specified age range, pregnant women.

Upper level of intake (UL)

The maximum level of habitual intake from all sources of a nutrient or related substance judged to be unlikely to lead to adverse health effects in humans.

Abbreviations

ADI	Acceptable Daily Intake
AI	Adequate Intake
DRV	Dietary Reference Value
EC	European Commission
EFSA	European Food Safety Authority
ERNA	European Responsible Nutrition Alliance
EU	European Union
EVM	Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organisation
FNB	US Food and Nutrition Board
FSA	UK Food Standards Agency
GI	Gastrointestinal
GL	Guidance Level
HOI	Highest Observed Intake
ILSI	International Life Sciences Institute
IOM	US Institute of Medicine of the National Academy of Sciences
IU	International Unit
IUNA	Irish Universities Nutrition Alliance
IW	Intake of minerals from water
LOAEL	Lowest Observed Adverse Effect Level
MHI	Mean Highest Intake
MLS	Maximum level of a vitamin or mineral in a food supplement
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NDNS	UK National Diet and Nutrition Survey

NOAEL	No Observed Adverse Effect level
NRV	Nutrient Reference Value
PSI	Population Safety Index
RDA	Recommended Daily Allowance/Recommended Dietary Allowance
RE	Retinol Equivalents
RfD	Reference Dose
RNI	Reference Nutrient Intake
SACN	UK Scientific Advisory Committee on Nutrition
SCF	EU Scientific Committee on Food
SUL	Safe Upper Level
UF	Uncertainty Factor
UK	United Kingdom
UL	UL
WHO	World Health Organisation
WTO	World Trade Organisation

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1. Introduction

The subject of this report is the development of a science-based international approach to nutrient risk analysis. It is based primarily on the Codex Alimentarius "Nutrition risk analysis principles and guidelines for application to the work of the Codex Committee on Nutrition and Foods for Special Dietary Uses" (Codex Alimentarius 2010) and the report of a Joint FAO/WHO Technical Workshop on Nutrition Risk Assessment entitled "A model for establishing upper levels of intake for nutrients and related substances" (FAO/WHO 2006).

Vitamins and minerals are essential for normal growth and health, and for risk managers the estimation of optimal intake of a micronutrient in a given population is problematic, because different individuals have different requirements and intakes for any given nutrient as well as differences in susceptibility to adverse effects at very high intakes (Renwick *et al*. 2008). The key challenge for risk managers is to balance the risk of deficiency in some individuals with the risk of overconsumption in others in the same population. The risks of adverse effects of too little or too much are illustrated in Table 1.

Table 1. Risk of adverse effects of certain essential nutrients

	Too little	Too much
Calcium	Osteoporosis	Hypercalcaemia, kidney stones
Iron	Anaemia, impaired performance	Gastrointestinal side effects
Zinc	Growth failure	Affects copper status
Vitamin A	Growth abnormalities	Liver damage, teratogenic, brittle bones
Vitamin C	Scurvy, fatigue	Gastrointestinal side effects
Vitamin D	Skeletal deformities	Hypercalcaemia
Folic Acid	Megaloblastic anaemia, Neural tube defects	Masking of vitamin B_{12} deficiency

Part of the problem has been that nutritionists have in the past focused on preventing dietary deficiencies, requiring a particular set of clinical and statistical approaches, the main reference point for nutritional deficiencies being the concept of the Recommended Daily Allowance (RDA). In contrast, the study of adverse effects at high intakes has been within the province of toxicology, which has developed different tools and principles in order to establish a tolerable upper intake (UL), an intake that should avoid adverse effects.

Typically, expert committees establish Dietary Reference Intakes (DRIs), which are a set of reference intake levels for nutrients that can be used for planning diets and assessing nutrient inadequacies of individuals and groups. The DRIs are a quantitative set of Nutrient Reference Values (NRVs)

that include the RDA, adequate intake (AI), estimated average requirement (EAR) and the tolerable upper intake level (UL). Table 2 provides definitions for each of the DRIs and Table 3 outlines the appropriate use of each of these DRIs when planning diets, when assessing nutrient adequacy for groups and individuals and when assessing potential risk of adverse effects from excessive nutrient intake. Scientific recommendations on micronutrient intake therefore include advice on both the RDA and the maximum intake from all sources that can be consumed without significant risk of toxicity.

Table 2. Definitions of DRIs from Dwyer *et al*. (2014)

Term	Definition
Estimated average requirement (EAR)	The daily intake value that is estimated to meet the requirement for that nutrient, as defined by a specific criterion of adequacy or optimal health, in half of the apparently healthy individuals in a specific life stage and gender group
Recommended dietary allowance (RDA)	An estimate of the daily average intake level that meets the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group and assuming a normal distribution of requirements; mathematically derived from the EAR (RDA = EAR + 2 x SD)
Adequate intake (AI)	Reference intake level based on observed or experimentally determined approximations or estimates of observed median nutrient intakes by a group (or groups) of healthy people; used when there is insufficient evidence to calculate an EAR
Tolerable upper intake level (UL)	Highest average daily intake of a nutrient that is likely to pose no risk of adverse health effects for nearly all persons in the general population

Table 3. Use of the DRIs for assessing and planning intakes of apparently healthy individuals and groups (from Trumbo *et al.* 2013)

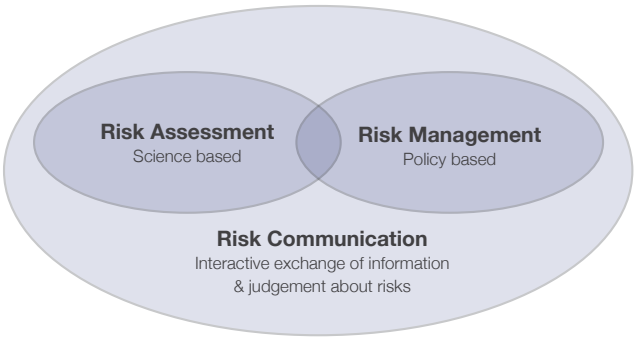
Type of use	For individuals	For groups
Assessment	EAR: use to examine the probability that usual intake is inadequate RDA: usual intake at or above this level has a low probability of inadequacy AI: usual intake at or above this level has a low probability of inadequacy UL: usual intake above this level has a potential risk of adverse effects	EAR: the proportion of a group with usual intake below this level estimates the prevalence of inadequate intakes in the group RDA: do not use to assess intakes of groups AI: mean usual group intake at or above this level implies a low prevalence of inadequate intakes UL: the proportion of a group with usual intakes above this level can estimate the percentage of the population at potential risk of adverse effects from excessive nutrient intake

Planning	EAR: do not use to set intake goals for an individual RDA: plan for this intake; usual intake at or above this level has a low probability of inadequacy AI: plan for this intake; usual intake at or above this level has a low probability of inadequacy UL: use to plan for usual intake below this level to avoid potential risk of adverse effects from excessive nutrient intake	EAR: use to plan for an intake distribution in which a low percentage of a group has intakes below the EAR; do not use the EAR to plan mean intakes, as this will lead to a 50% prevalence of inadequacy RDA: should not be used to plan intakes for a group AI: use to plan mean intakes; mean usual intake at or above this level implies a low prevalence of inadequate intakes UL: use in planning to minimise the proportion of the population at potential risk of excessive nutrient intake

As previously stated, the focus of this report is on nutritional risk analysis for vitamins and minerals. However, it is important to note that, unlike many constituents of foods and food supplements that are the subject of traditional food safety risk analysis (such as food additives, chemical (pesticide and veterinary drug) residues, microbiological pathogens, contaminants and allergens), micronutrients are biologically essential and favourable to health. Nutritional risk analysis therefore adds a new dimension to traditional risk analysis by also considering risks directly posed by inadequate intakes (Codex Alimentarius 2010). This report also mirrors the FAO/WHO (2006) and Codex principles and guidelines for the establishment of upper levels of intake of nutrients and to characterising such risk. The increasing use of fortified foods, food (dietary) supplements, specially formulated foods and so-called functional foods have the potential to increase the intake of nutrient substances for population groups around the world. In addition, there is growing interest in harmonising an international basis for determining safe levels of intake, and for models for nutrient risk assessment and risk management that can be useful at national and regional levels. The overall objectives are to protect the consumer, to ensure a safe food supply, to contribute to efforts to conduct scientific nutrient risk analysis and to facilitate trade.

2. Nutritional risk analysis

Figure 1. Components of risk analysis (based on FAO/WHO report 2006)

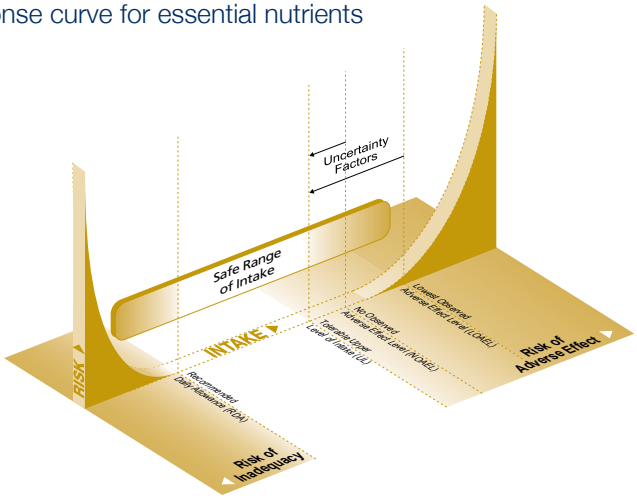


Nutritional risk analysis comprises three distinct but closely linked components as shown in Figure 1. For food regulators and policy makers, risk analysis provides a systematic and structured approach to assess public health and safety risks from food and food supplements, and a means to manage any characterised risk. Nutritional risk analysis addresses two key questions:

i. What is the nature and magnitude of the health risk?
ii. How should the risk be managed and communicated to those affected?

Nutritional risk analysis, therefore, considers the risk of adverse health effects from inadequate and/or excessive intakes of nutrients and related substances, and the predicted reduction in risk from proposed management strategies. As regards potential risks from foods and food supplements, Figure 2 intake data and the shape of the dose-response curve provide information on the cumulative risks of deficiency or toxicity and a safe range of intake. Typically, the entire risk analysis process is preceded by a problem formulation step. The objective is to foster interactions between risk managers and assessors to help ensure a common understanding of the problem and the purpose of the risk assessment (Codex 2010; FAO/WHO 2006).

Figure 2. Intake response curve for essential nutrients



Codex Principles and Guidelines on Nutritional Analysis provide a comprehensive list of considerations to be included in the formulation of the nutritional problem (Codex 2010). These include the priority it should be accorded, whether data are available to embark on the evaluation of nutritional risks, the relevant sources of intake, the identification of the (sub) population to be the focus of the risk assessment and the health endpoints to be considered, as well as the resources available and timelines for completion of the assessment.

2.1 Nutritional risk assessment

The principles for scientific risk assessment are shown in Table 4. In Steps 1 and 2, **Nutrient-related Hazard Identification and Hazard Characterisation**, the process begins with the identification of adverse health effects associated with the nutrient substance and makes use of human, animal and in vitro data. Each data source has both advantages and disadvantages. For example, animal data have the advantage of quite extensive and robust datasets and the disadvantage of requiring very uncertain and problematic extrapolation for application to humans. On the other hand, human data are often quite sparse for many nutrients, but they do have the advantage that little or no extrapolation is needed for decisions that are relevant for humans (Hathcock 2014).

Table 4. Principles for scientific risk assessment
Problem Formulation

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

A pivotal point in the risk assessment is the identification of the critical adverse health effect upon which the UL is based. The process involves the identification of a No Observed Adverse Effect Level (NOAEL) from human data if possible. If the data cannot support a NOAEL, a Lowest Observed Adverse Effect Level (LOAEL) may be established. Animal data are used only if appropriate human data are not available and also as a guide to search for a hazard that may be identified in human data. The uncertainties in the data are assessed and Uncertainty Factors (UFs) are applied to the identified toxicological thresholds, e.g. NOAEL or LOAEL. The numerical UF accounts for the scientific uncertainties, including inadequacies in the database, interspecies extrapolation, variability and differences in susceptibility of individuals, the nature and severity of the adverse effect and whether there are short-term or long-term effects. Scientific judgement is used in the choice of the UFs, and the UL is derived by dividing the NOAEL or LOAEL by the total product of the UFs. The selection of the UFs is critical when considering the potential effects for nutritional deficiency and excess. These quantitative evaluations of critical effects in the hazard identification and characterisation steps include the key activities shown in Table 5.

Table 5. Key activities in hazard identification and characterisation (FAO/WHO 2006)

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

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

2010). With this sanction, the HOI acquires global policy and regulatory importance because Codex is recognised as the pre-eminent international authority on food safety by the World Trade Organisation in its Sanitary and Phytosanitary (SPS) Agreement (WTO 2011).

In Step 3, **Nutrient-Related Intake Assessment**, the nutritional risk analysis requires an assessment of the current and potential intakes of vitamins and minerals from the various dietary sources. A fundamental problem is the adequacy of the information on nutrient intakes, and much greater attention needs to be paid to the acquisition, development and interpretation of intake data for essential nutrients for specific population groups (WHO 2002, FAO/WHO 2006). FAO/WHO (2006) recognised that the ability to acquire and maintain useful and up-to-date composition and intake data is a growing challenge because of the changing food supply and the increased use of fortified foods and food supplements. The uncertainties and biases in the estimation of habitual nutrient intake distributions to reflect the reality of the diverse patterns of intake and dietary contexts that exist are also major challenges. In situations where intake data are limited, mathematical modelling approaches can be used to handle uncertainties in the intake estimates and the potential impact of these uncertainties on risk characterisation.

Scientific committees draw on a wide array of available consumption data, including habitual or average intake of various population groups from conventional food, water, fortified food and food supplements. The variability of the magnitude of intakes can be assessed using intake percentiles, e.g. P5, P50, P95 and P97.5, to represent the spectrum of intakes from deficient up to high intake levels. Consumption data are derived from household surveys, 24-hour and 48-hour recalls etc. In fact, data from many days are needed to estimate accurately intakes for individuals, because day-to-day variation in nutrient intake can be quite large (FAO/WHO 2006). The best intake data (used later in the risk management model in Section 4_) is based on the use of four- or seven-day weighed dietary records as the sources of the best available data. The objective in the dietary intake assessment is to provide clear, transparent and detailed documentation of the approaches used.

National diet and nutrition surveys are the best sources of information, despite the fact that many of them have been conducted with different methodologies and may not be up to date. A pragmatic approach adopted by the European Commission (EC 2007) in their orientation on setting maximum and minimum amounts of vitamins and minerals in foodstuffs is to use the best available data. The most complete data are often from countries considered to be “mature” markets for both food supplements and fortified foods (e.g. the UK National Diet and Nutrition Surveys (UKNDNS) (UK Office for National Statistics 1998, 2000, 2003; UK Food Standards Agency 2000) and the North/South Ireland Food Consumption Survey (Irish Universities Nutrition Alliance 2001). Population-based surveys such as the National Health and Nutrition Examination Survey (NHANES) in the USA are also used for monitoring nutrient intakes and identifying shortfalls and excesses within the US population (Dwyer et al. 2014). In population monitoring and surveillance, the goal is to obtain an estimation of usual intakes that reflect long-term chronic exposure to the nutrients in question. In the NHANES surveys, data before 2002 were based on a single-day 24-hour recalls of food, beverage and self-reported supplement use over the past 30 days. Because this methodology may have overestimated both the number of very low and very high intakes, the NHANES data collected after 2002 are based on two separate 24-hour food and supplement intake recalls.

This methodology gives better estimates of the distribution of usual intakes (US Department of Agriculture 2009, 2010); US Centers for Disease Control and Prevention 2014). In addition, specific nutrients can be assessed on a case-by-case basis by means of validated national data for specified population groups. In practice, for countries where robust, regional intake data are not readily available, the best solution is often to utilise methodologies and data from different parts of the world in order to provide the most appropriate and valid picture of intakes from foods, supplements and, where applicable, water. Some risk assessments provide the entire distribution of intake, while others provide only the mean and the 95 or 97.5 percentile intakes.

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

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

2.2 National/regional reports on nutrient risk assessment

Over the last 20 years, the tolerable upper intake level (UL) and scientific risk analyses have become the internationally accepted ways to evaluate the safety of the essential nutrients, and to underpin regulatory approaches to setting maximum levels of vitamins and minerals, where appropriate, in fortified foods and food supplements. Several international organisations and numerous national scientific committees have developed recommendations for UL values. The three national authoritative bodies included in the FAO/WHO model in 2006 were:

EFSA/SCF
European Food Safety Authority, European Union, and the former Scientific Committee on Food, European Commission (EFSA 2006)

IOM
Institute of Medicine of the National Academies, United States of America and Canada (IOM 1997, 1998, 2000, 2001, 2010)

EVM
Expert Group on Vitamins and Minerals, Food Standards Agency, United Kingdom (EVM 2003)

The UL values may be expressed in terms of total dietary intake (i.e. from all dietary sources including conventional foods, fortified foods and food supplements), as in the case of the IOM and EFSA risk assessments, or for long-term supplementary amounts as in the case of the EVM, referred to as the safe upper level (SUL) for supplementary use. These UL and SUL values have been accepted by FAO/WHO and by the Codex Alimentarius Commission. These international organisations provide a collection of standards, codes and practical guidelines, such as a nutritional risk analysis, which act as a global reference point for national food control agencies, for consumers, food producers and processors and for international trade. Their main aims are to help all nations to join the international community in formulating and harmonising food and food supplement standards and ensuring their global implementation. The Codex standards have also become the benchmarks against which national food measures and regulations are evaluated within the legal parameters of the World Trade Organisation Agreements (WTO 2011).

The UL risk assessment model therefore has widespread scientific and policy support around the world. All these UL methods used emphasise the concept of quantitative risk assessment, but disparities in the selection and interpretation of available scientific literature on safety and the approaches to handling uncertainty have sometimes led to large differences in the UL values for various nutrients. Appendix I shows the levels established by the three assessment committees. For example, the SCF/EFSA were requested by the European Commission to provide scientific opinions on ULs for 29 nutrients listed in Annex I of the Food Supplements Directive (European Parliament and of the Council 2002). This request resulted in specific numerical ULs being established for 16 nutrients. Some of the remaining nutrients showed extremely low or non-existent adverse effects, even at very high levels of intake, and for some, lack of sufficient scientific data did not permit the derivation of a numerical UL. Where ULs have not been established, the SCF/EFSA have provided qualitative risk characterisation for the specific nutrients. In contrast, other expert scientific risk assessment committees such as IOM and EVM have set numerical values, and all these UL values should be taken into account in the development of risk management models. The terms of reference for the three national/regional reports are summarised by FAO/WHO (2006).

It is important to recognise that the ULs represent an intake that can be consumed daily over a lifetime without significant risk to health according to the available scientific evidence. Table 6 illustrates what ULs are and what they are not.

Table 6. Characteristics of Upper levels (ULs)

ARE:
• Based on scientific risk assessment's assumptions and uncertainties. • Not only safe, but safe by a comfortable margin. • Defined and identified to reflect safety of chronic intakes. • Values that take account of identified sensitive populations.
ARE NOT:
• Thresholds for adverse effects. • "Safety limits". • Applicable to temporarily elevated intakes.

2.3 Nutritional risk management

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

2.4 Nutritional risk communication

The risk communication section of the Codex Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius is generally applicable to nutritional risk communication (Codex Alimentarius Commission 2010). These principles were set out by the Codex Alimentarius Commission in 2007. In this document, Codex states that the three components of risk analysis should be documented fully and systematically in a transparent manner, and that, while respecting legitimate concerns to preserve confidentiality, documentation should be accessible, as far as possible, to those not directly engaged in the process and to all interested parties in all aspects

of the process. Adapting the Codex working principles to nutritional risk analysis, nutritional risk communication should:

i. Promote awareness and understanding of the specific issues under consideration during the nutritional risk analysis

ii. Promote consistency and transparency in formulating nutritional risk management options/ recommendations

iii. Provide a sound basis for understanding the nutritional risk management divisions proposed

iv. Improve the overall effectiveness and efficiency of the nutritional risk analysis

v. Strengthen the working relationships among participants

vi. Foster public understanding of the process, so as to enhance trust and confidence in the safety of the food supply

vii. Promote the appropriate involvement of all interested parties

viii. Exchange information in relation to the concerns of interested parties about the risks associated with food

The risk analysis process as a whole should be a continuing process that takes into account all newly generated data so that food standards and related texts are reviewed regularly and updated as necessary to reflect new scientific knowledge and other relevant information.

3. Global regulatory approaches to the setting of maximum amounts of vitamins and minerals in food supplements

Regulatory authorities around the world need to ensure that levels of micronutrients in the total diet are safe, and that the cumulative intake from all sources does not lead to excessive intakes and any adverse effect in the population, including sensitive groups such as children, the elderly and women during pregnancy and lactation.

If regulatory maximum levels of vitamins and minerals in food supplements (and in fortified foods) are considered to be appropriate, the general approaches are based on scientific risk analysis promulgated by FAO/WHO (2006) and the Codex Alimentarius Commission (2010). For example, in Europe, the criteria to be taken into account for the establishment of the maximum amounts of vitamins and minerals in fortified foods and food supplements are set out in Regulation (EC) 1925/2006 (European Parliament and of the Council 2006), which makes provision for the harmonisation of the conditions for the voluntary addition of vitamins and minerals and of certain other substances to foods (often referred to informally as food fortification) and in Directive 2002/46/EC (European Parliament and of the Council 2002) on the approximation of the laws of European Union (EC) Member States relating to food supplements that harmonise specific rules on vitamins and minerals in these products. Both these legal acts aim to provide a high level of consumer protection and to ensure the effective functioning of the internal market. The key legal criteria in Europe for setting maximum amounts in fortified foods and food supplements are shown in Table 7. These criteria are considered requisite for the risk management policy to be used in the forthcoming EU-wide harmonisation of the maximum levels.

Table 7.

European regulatory approaches to the setting of maximum amounts of vitamins and minerals in food take due account of:
• Upper safe levels vitamins and minerals by scientific risk assessment based on generally accepted scientific data. • Intake of vitamins and minerals from other dietary sources. • Reference intakes of vitamins and minerals for the population.

Another good example is the establishment of maximum levels (MLs) by the Association of Southeast Asian Nations (ASEAN 2013), which are based on the risk assessment component derived from the FAO/WHO model (2006) and the Codex Alimentarius Commission Principles and Guidelines (2010). The ASEAN general principles are based on the risk management component

and the Population Safety Index (PSI) methodology described in Section 4 of this report, and in the report "Risk management approaches to the setting of maximum levels of vitamins and minerals in food supplements for adults and children aged 4–10 years" (Food Supplements Europe 2014). This new report updates the previously published report by the European Responsible Nutrition Alliance (ERNA 2004), which is quoted in the ASEAN General Principles.

The main purpose of the ASEAN General Principles is to establish maximum daily intake levels of vitamins and minerals in health supplements so that normal use of the products under the instructions of use provided by the manufacturers will be safe for the consumers. The General Principles state that there is no scientific basis for the use of RDA/Recommended Dietary Intake (RI) in establishing MLs, and the ASEAN risk managers used the scientific risk assessments carried out by EFSA, IOM and EVM, as summarised in Appendix I of this report. For nutrient intake data, ASEAN used appropriate foreign values and country exposure assessments and consumption surveys. In the ASEAN risk management model, the mean highest intakes (MHIs) refer to the mean of the highest intakes of a nutrient from foods at the 95 or 97.5 percentile intakes. The ASEAN risk managers also decided to use the Highest Observed Intake (HOI) risk assessment process for those nutrients with no reported adverse effects (ASEAN 2013).

4. Risk management approaches to the setting of maximum levels of vitamins and minerals in food supplements for adults (Food Supplements Europe 2014)

The proposed risk management model for setting maximum levels of nutrients in food supplements in adults applies the principles of quantitative and qualitative risk assessment taking into account the legal criteria based on the European Regulations and set out in Table 7.

The model includes:

- Calculation of a Population Safety Index (PSI) for each nutrient
- Taking into account the contribution to total nutrient intake from all sources including conventional foods, fortified foods and food supplements
- Evaluation of the risk management options for current and future intakes of nutrients from all sources
- Categorisation of nutrients into three groups of risk using quantitative and qualitative information
- Proposals for maximum safe levels for each nutrient in food supplements (MLS) for adults

The risk management model takes into account the risk assessments from several authoritative groups of scientific assessors including EFSA/SCF, IOM and EVM. For the EFSA and IOM risk assessments, the UL is defined as the maximum level of habitual intake from all sources of a nutrient judged to be unlikely to lead to adverse health effects in humans. The EVM risk assessment is based on the UL method, but the scientific committee assigned the term Safe Upper Level (SUL) because the levels refer to long-term supplementary use, not total intakes (see Appendix I).

4.1 Nutrients that do not represent a risk to human health (no UL established)

When authoritative risk assessments show no adverse effects in healthy individuals, that there are no safety concerns about a nutrient, and when a UL cannot be established, these nutrients (vitamins B_1, B_2, B_{12}, biotin, pantothenic acid, vitamin K and chromium (trivalent form) are placed in Group 1, and no further risk management measures are required. Since there is no scientific basis for establishing a maximum level for these Group 1 nutrients, the European Commission orientation paper (2007) concluded that, because of the lack of evidence of adverse effects, a proportionate risk management approach, in line with the principles of better regulation, would be not to establish maximum amounts for these nutrients.

Table 8. Guidance on upper safe levels for nutrients with no established ULs

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

Nutrient GROUP 1	Adults
Vitamin B_1 (mg) Thiamin	100
Vitamin B_2 (mg) Riboflavin	40
Biotin (µg)	900
Vitamin B_{12} (µg) Cobalamin	2000
Pantothenic acid (mg)	200
Vitamin K (µg)	1000
Chromium III (mg)	10
* Based on UK EVM Guidance Levels (GLs) for supplementation (equivalent to FAO/WHO Highest Observed Intake (HOI))	

In the risk assessments carried out by EFSA and the IOM, no data were found to identify any hazard related to high intakes of thiamin, riboflavin, vitamin B_{12}, biotin and pantothenic acid. The standard position of these authorities is that a UL cannot be set if a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) cannot be identified owing to the absence of an established adverse effect or hazard. Interestingly, the EVM did not define the HOI or any similar concept, but it did identify advisory or guidance levels (GLs)[2], and these are analogous to the definition of HOI. In the development of regulatory values, it is argued that no maximum levels should be set for nutrients with no established adverse effects or safety concerns and where no UL could be established. Nonetheless, it is acknowledged that some policymakers and regulatory authorities prefer to establish maximum levels for all the nutrients, and hence any maximum value could be based on the HOI risk assessment method (FAO/WHO 2006; Hathcock and Kriengsinyos 2011).Table 8 shows information on the establishment of GLs by the EVM (2003) and upper safe levels for supplements for the Group 1 nutrients. These levels can be used as guidance when a risk manager needs scientific advice concerning an upper safe intake.

[2] Guidance levels (GLs) represent an approximate indication of levels that would not be expected to cause adverse effects but have been derived from limited data and are less secure than Safe Upper Levels (SULs), which are established based on adequate data (i.e. NOAEL or LOAEL). Guidance was given by the EVM (2003) on safe levels of intake when the establishment of an SUL was not possible

4.2 Characterising risk for Group 2 (low risk of exceeding the UL) and for Group 3 (potential risk at excessive intakes) using the Population Safety Index (PSI)

The fundamental risk management question is how to establish an objective process to determine how large the margin of safety is now and is likely to be in the future, allowing for different dietary contexts, new research findings and their application to food and food supplement products entering the food supply. The PSI paradigm describes a process by which vitamins and minerals with ULs can be allocated into categories of risk. The concept of characterising risk using the PSI is set out in the following equation, and the PSI calculations for adults are shown in Table 9.

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

Table 9. PSI calculations for characterising risk (Food Supplements Europe 2014)

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

For adults, the UL from all sources is established by SCF/EFSA when available; otherwise, the IOM UL values are used. The MHI is the "mean highest intake" from food sources (includes fortified foods but excludes food supplements) based on the 97.5 percentile (P97.5) mean intake data of male adults. The intakes in males are all higher than the equivalent intakes by female adults, and hence the calculation introduces a small precautionary measure. The IW is the estimated intake of minerals from water drawn from EFSA (2006) and EVM (2003). The RDA value—now referred to as the Nutrient Reference Value (NRV) or Reference Intake (RI) is the labelling Recommended Daily Allowance sources from Annex XIII of Regulation EU No 1169/2011 (European Parliament and of the Council 2011). The labelling RDAs are for the whole population and are generally significantly higher than the reference nutrient intakes (RNIs) for a particular population group. The higher labelling RDA denominator is used in the calculation because the value is consistent across all 28 EU Member States, whereas RNI values vary considerably. The use of the labelling RDA not only provides a fixed point on the intake curve (see Figure 2) but also adds a substantial precautionary measure. The PSI model provides a process by which the vitamins and minerals can be allocated into categories of risk. The model assumes that where the PSI of a nutrient is higher than around 1.5, i.e. where there is a margin of safety of 1.5 times the RDA between the P97.5 intake of food (including fortified foods) plus the estimated intake from water (where appropriate) and the UL, the chance of exceeding the UL is low (Group 2). Where the PSI is 1.5 or below, i.e. the P97.5 of intake from food (including fortified foods) plus the estimate of intake from water is either above the UL or less than 1.5 times the RDA below the UL, there is a potential risk of exceeding the UL (Group 3). In other words, the characterising factor for Group 2, the "low risk" of exceeding the UL "is a PSI greater than around 1.5", and for Group 3, the "potential risk at excessive intakes" is a PSI of around 1.5 or less. Group 2 includes some nutrients as special risk management cases, e.g. potassium, vitamin C, magnesium and folic acid, either because no UL was established by SCF/EFSA or, as in the case of magnesium, the UL of 250 mg/day refers to supplemental sources of readily dissociable magnesium salts and the UL of 1000 µg/day is for supplemental folic acid. Similarly, Group 3 contains manganese as a special case because SCF/EFSA could not establish a UL (ERNA 2004, Food Supplements Europe 2014).

4.3 Allowing for future intakes of vitamins and minerals

To gain a measure of potential changes in consumer food preferences, food supplement use and the increased fortification of food products that might develop, a comparison was made of dietary surveys undertaken in the United Kingdom over a period of 15 years (UK Office for National Statistics 2003). Based on these intake data, the proposed risk management model assumes a precautionary risk management factor of a 50% increase in dietary intake for all the vitamins from foods, including fortified foods, and a 10% precautionary risk management factor for minerals. These precautionary factors represent the biggest changes over the 15-year period, i.e. based on an actual increase in vitamin C intake of 36% rounded up to 50% and 8% for calcium rounded up to 10%. In fact, many of the micronutrient intakes declined over this period, demonstrating the need to monitor suboptimal and inadequate nutrient intakes of (sub)population groups.

These precautionary factors have been used where possible to estimate proposed maximum levels in food supplements (MLS) using the following equations:

For vitamins: **MLS = UL – (MHI x 150%)**

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

5. Proposed maximum safe levels (MLS) in food supplements for adults

The summary tables 10 and 11 for Group 2 and Group 3 nutrients, respectively, are based on both quantitative and qualitative risk management assessments. The proposed model and MLS for food supplements take into account the contributions to total nutrient intake from conventional foods, fortified foods and food supplements using the best available data for a European context (Food Supplements Europe 2014). Theoretical models have also been proposed for setting maximum amounts of vitamins and minerals in fortified foods (Flynn *et al*. 2003, Rasmussen *et al*. 2006, Kloosterman *et al*. 2007). Reassuringly, those models have also resulted in three categories.

Table 10. Proposed maximum safe levels (MLS) in food supplements for adults (Food Supplements Europe 2014)

Setting daily maximum supplement levels (MLS) for adults		
GROUP 1 No evidence of risk to human health at levels currently consumed	No further risk management measures required	
GROUP 2 Low risk of exceeding UL	Nutrient	Proposed MLS
	B_6	18 mg
	C	1700 mg
	D	83 µg
	E	270 mg
	Nicotinamide	820 mg
	Molybdenum	350 µg
	Phosphorus	1250 mg
	Selenium	200 µg
	Magnesium	250 mg
	Folic Acid	600 µg
	Potassium	1500 mg

Because of the large differences in scientific opinions on the derivation of the ULs/SULs for the nutrients there is a need for a systematic reassessment of their safety. For the nutrients vitamin B6, pyridoxine, vitamin E, molybdenum, phosphorus and magnesium, the IOM ULs are significantly higher than those established by EFSA risk assessments, which could result in a higher MLS.

Table 11. Proposed maximum safe levels (MLS) in food supplements for adults (Food Supplements Europe 2014)

GROUP 3	Case-by-case qualitative risk characterisation	
Potential risk at excessive intakes	Nutrient	Proposed MLS
	Vitamin A	1200 µg
	Beta-carotene	7 mg
	Calcium	1000 mg
	Copper	2 mg
	Fluoride	3.5 mg
	Iodine	200 µg
	Iron	20 mg
	Manganese	4 mg
	Zinc	15 mg

Because of the large differences in scientific opinions on the derivation of the ULs/SULs for the nutrients there is a need for a systematic reassessment of their safety. For the nutrients copper, iodine, iron, manganese and zinc, the IOM ULs are significantly higher than those established by EFSA risk assessments, which could result in a higher MLS.

of risk similar to those characterised in this report. In Europe, the methodologies for setting maximum levels of vitamins and minerals in fortified foods are still being developed, including the decision about how to present the values, i.e. per weight or per energy of the food consumed (e.g. per 100 g, per quantified serving, or per 100 kcal. Typically in the EU, the amounts of nutrients added to food products are based on the quantitative criteria for making nutrient content claims. The proposed maximum levels for vitamins and minerals include the overages, which are the amounts over the declared values on product labels. The use of micronutrients in fortified foods and food supplements poses several technological challenges. For example, the stability of vitamins is influenced by several factors: temperature, moisture, oxygen, light, pH, oxidising and reducing agents, presence of metallic ions (e.g. iron and copper), presence of other vitamins and components, and various combinations of the above. Vitamin deterioration takes place naturally during storage of foods and food ingredients, losses occur during processing and preparation, and the factors that affect the degradation of vitamins are the same whether the vitamins are naturally occurring or are added to foods or food supplements (Berry Ottaway 1993). Shelf-life and stability data provide the necessary information for labelling purposes. Regulatory bodies set tolerances for nutrient values declared on a label, and the nutrient content should not deviate substantially from labelled values to the extent that such deviations could lead to consumers being misled. Control authorities ensure compliance with national legislation.

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

The basic principle is that the most sensitive members of the general population must be protected from the adverse effects of high nutrient intakes. Some sensitive subpopulations can have responses (in terms of incidence, severity or both) to the nutrient, and those responses may be different from those expected at different life stages or with different physiological status. Even within relatively homogeneous life stage groups, there can be a range of sensitivities to adverse effects, e.g. sensitivity is influenced by bodyweight, lean body mass and extent of adiposity.

Major physiological changes in the velocity of growth and in endocrine status occur during childhood and adolescence. The onset of puberty is an extremely anabolic period that is influenced by a marked rise in hormonal activity, which results in a number of physical changes that characterise adolescence. These changes have been well documented and their timing, rates and extent are highly variable (Tanner *et al.* 1965; Zlotkin, 2006). Over several decades there has been a progressive increase in the heights and weights of children that is associated with trends towards earlier puberty. The enormous variability in the rate and timing of the adolescent growth spurt influences the nutritional requirements of children at different ages and their adaptability to nutrient deficiencies and excess. For the purposes of setting maximum levels in fortified foods and food supplements for children, this report focuses on the younger age groups: 4–6 years and 7–10 years. Thereafter, safety issues for older and post-pubertal children have to take into account their increasing speed of growth and the adolescent growth spurt, where nutritional needs are similar to adults. Moreover, nutritional status and intakes of nutrients tend to deteriorate in older children aged 11–14 years and 15–18 years (Scientific Advisory Committee on Nutrition (SACN) 2008), which means that any risk management measures will have to take into account the risk of suboptimal intakes and deficiencies as well as excess in older children. The reasons for selection of a children's age range of four to ten years relate to the age ranges of reference bodyweights as shown in Table 12, the availability of nutrient intake data (UK Office for National Statistics 2000; Flynn et al. 2009), the age ranges for UK Dietary Reference Values (UK Department of Health 1991), the EFSA opinions on ULs for vitamin D (EFSA 2012) and DRVs for vitamin C and manganese (EFSA 2013a, 2013b), which summarise AIs for age groups four to six years and seven to ten years. Moreover, the IOM (1997) described early childhood as ages four through eight years, and determined that the adolescent age group should begin at nine years.

The scientific data on nutrient requirements, absorption, metabolism and excretion of nutrients in children is extremely limited. Hence, dietary requirements and ULs for children are extrapolated from adult requirements and from adult ULs, respectively. These extrapolations are usually made on the basis of bodyweights by means of either reference bodyweights (SCF 1993) or metabolic bodyweights, BW0.75 (EFSA 2006; FAO/WHO 2006). The large differences in bodyweights between younger and older children shown in Table 12 can markedly influence the magnitude of the UL.

Table 12. Reference bodyweights of population groups in Europe (SCF, 1993)

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

The PSI risk management paradigm and methodology can also be applied to children aged 4–10 years. The extrapolated ULs can be derived from the EFSA and IOM adult values and MHI and IW data can be obtained from some dietary surveys. This exercise has been carried out for the first time, and maximum levels of vitamins and minerals in food supplements for children aged 4–10 years have been proposed for the ongoing dialogue with the regulatory authorities in the European Commission (Food Supplements Europe 2014). In the Food Supplements Europe risk management model, the children's ULs that are used in the PSI calculations are for the lowest age group aged 4–6 years, whereas the highest 97.5 percentile intakes from UK NDNS data for male children aged 4–10 years are applied, together with the labelling RDA. The use of these sources of data introduces substantial precautionary measures into the risk management process and the proposed maximum levels for children. To illustrate the extrapolations of data from adults to children based on bodyweights the following equation can be used:

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

Based on a reference bodyweight for adults of 70 kg and a child weighing 20 kg, the child's UL for a 4–6 year old would be estimated to be 29% of the adult value, whereas for a 7–10 year old child weighing 28.5 kg, the UL would be 41% of the adult UL. In addition, the adult ULs already have built-in precautions for chronic exposure. For children, the imprecision of the data available, lack of data and adequacy of the data on variability are major limitations for risk assessors and risk managers. Therefore considerable scientific judgement is used to develop ULs for children, especially when the critical endpoints and uncertainty factors relate to adults. Nevertheless, ULs

for children have been established on the basis of known differences in body size, physiology, metabolism, absorption and excretion of a nutrient. However, Zlotkin (2006) identified specific examples of the difficulties in deriving a UL for children from inadequate data and uncertain uncertainty factors (sic) from adult risk assessment data and its subsequent use as a safety benchmark. The overall conclusion was that, when intakes exceed the extrapolated UL by a relatively small amount, the significant uncertainties surrounding the derivation of the children's UL makes it likely that intakes are not the problem, rather the application of a UL with inadequate data. For some nutrients, the narrow range between the RDA and UL may be unjustified, especially when there is a lack of demonstrated adverse effects at current intakes above the UL. Zlotkin (2006) also identified plausible arguments indicating that the setting of adult ULs for zinc, retinol and folic acid may be too low.

It should be noted that, in Europe and elsewhere, market practices for food supplements differentiate between products intended for adults and children, whereas when foods are fortified, the issues are complicated by the fact that many foods with added nutrients are consumed both by adults and by children.

7. Discussion and conclusions

As previously stated, risk assessment and risk management for nutrients differ from other substances in foods because vitamins and minerals are essential for human life, and consequently, adverse effects can result from suboptimal intakes and deficiencies as well as from excessive intakes. Risk assessment provides a systematic means to evaluate the probability of the occurrence of adverse health effects in humans due to excessive intake. The risk depends on the fraction of the population exceeding any defined upper level and mainly accounts for the most sensitive hazardous effect. Risk management draws together the information on the range of safe intake—sometimes referred to as the "acceptable" range of oral intake (AROI) (WHO 2002)—and involves the establishment of the risk to the population habitually exceeding the UL.

Insights into population micronutrient intakes and evaluation of too low or too high intakes are required to determine whether there are potential problems regarding inadequacy or excessive intakes. The need for regulation of specific nutrients depends on the severity of the adverse effects and on the estimates of the prevalence of too low or too high population intakes. Too low population intakes are evaluated against an Estimated Average Requirement (EAR) or, more commonly, the Recommended Daily Allowance (RDA). Too high population intakes are evaluated against a UL. For the purposes of nutritional risk management, the convenient set points to determine the safe range of each nutrient are for the upper end, the UL, and for the lower end, the labelling RDA. These set points are used in the proposed risk management model for setting maximum levels of vitamins and minerals in food supplements for adults, as described in Section 4 of this report.

It should be emphasised that the RDAs and ULs are determined by two completely different scientific conceptual approaches, and that the two values are used only as indicators to establish the extent of the range of safe intake and to help categorise nutrients on the basis of the risk associated with exceeding their ULs. In other words, where the UL and RDA are closer together, the safe range of intake is relatively small; where they are further apart, the safe range of intake is relatively large. The use of the labelling RDA as the denominator in the PSI calculation in the risk management model, described in Section 4 and utilised by ASEAN complies with the legal criteria used in Europe, namely that due account must be taken of the reference intakes of vitamins and minerals for the population (European Parliament and of the Council 2002, 2006), and helps to establish the breadth of the range of safe intakes, as well as a process for risk characterisation.

Some countries in Europe and around the world have proposed that the maximum amounts in fortified foods and in food supplements should be based on, or limited to, fractions or multiples of the RDA. However, the FAO/WHO (2006) model for establishing upper levels of intake for nutrients and related substances and the Codex Alimentarius Commission Principles and Guidelines for Nutritional Risk Analysis (2010) as well as the European legislation require the establishment of maximum levels based on scientific risk assessment. Appendix II sets out why the RDA-based maximum levels, which are considered unscientific and arbitrary. In Europe, the use of an RDA-

based approach to setting maximum levels has been rejected by the European Commission and condemned by the European Court of Justice. Furthermore, it is essential to go beyond the standard micronutrient RDA methodology and paradigm, which focus on vitamins and minerals and prevention of deficiencies, to one that reflects recent scientific research on longer-term health benefits (Hanekamp and Bast 2007).

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

The setting of upper safe levels by risk assessors and the setting of maximum levels in fortified foods and food supplements by risk managers builds in levels of precaution and provides a framework within which the consumer can make an informed decision about intake, having confidence that harm should not ensue. The upper safe levels set in risk assessments tend to be conservative, and it is possible that for some vitamins and minerals, e.g. vitamin B6 and vitamin C, larger amounts could be considered for shorter-term consumption because the available data are limited and relate to differing time periods. As a consequence of the limited data, risk assessors build in uncertainty factors and apply the precautionary principle of allowing for the variable quality of information and for risk managers to weigh up the different safety margins between necessity and adverse effects. As the markets, and hence the exposures, vary over time, risk managers will need to monitor changing patterns of addition of nutrients to different foods and the use of food supplements in order to review the risk management options (Verkaik-Kloosterman et al. 2012). There will also be a need for regular review of the scientific basis for the establishment of lower and upper safe intakes of micronutrients, particularly for those nutrients with narrow safe ranges of intake. The recent risk reassessments for vitamin D and for beta-carotene illustrate this point (IOM 2010, EFSA 2012a, 2012b). Any changes in either RDAs or ULs will also impact on the risk management options.

Risk assessors are often faced with inadequate or limited data, insufficient dose-response or exposure data and variability and sensitivity of individuals or certain population groups (World Health Organisation 2002, 2006; Dufour et al. 2010). Risk assessments such as those by EFSA (2006), IOM (1997, 1998, 2000, 2001) and EVM (2003) set a safe upper level (SUL) or UL, where

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

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

The information about, and process for derivation of, proposed maximum levels for adults have been made as transparent and explicit as possible to stimulate further consultation and dialogue between regulators, risk assessors, the academic community and industry. The rationale and data presented in this study identify the sources of the ULs, the intake data relevant to the calculation of the PSIs, the proposed maximum levels of vitamins and minerals in food supplements (MLS) and the development of suitable approaches to setting maximum levels in fortified foods. Despite the inconsistencies in the various datasets, the risk management model does permit the characterisation of the nutrients into three groups of risk. Quantitative and qualitative approaches have been used to propose maximum levels that would not be expected to result in adverse effects. Because of the increased interest in, and availability of, fortified foods and food supplements, it is critical to undertake appropriate risk management measures to ensure consumer protection.

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

of the risk management model described in this paper depends on the availability of the input data, particularly data on nutrient intakes from food consumption surveys. Currently, such intake data are sparse. However, the PSI methodology can be applied to several different sets of nutrient intake data, including those for children. In the current paper the method for establishing maximum levels of vitamins and minerals in food supplements in adults has been applied using the most comprehensive intake data from the UK and Ireland. The overall purpose of the study is to contribute towards the development of a scientifically-based process for the setting of maximum levels of essential nutrients in fortified foods and food supplements. Consultation and dialogue between the various interested parties are critical to ensure that proportionate measures are used to protect consumers and to facilitate informed choice.

8. Appendices

Appendix I

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

Nutrient	Unit	SCF/EFSA total intake (UL)	IOM total intake (UL)	EVM for long-term supplementation (SUL)[a]
Vitamin A	µg	3000	3000	1500 (G, T)
Beta-carotene	mg	Below 15	Not set	7 (not for smokers)
Vitamin D[b]	µg	50→100	50→100	25 (G)
Vitamin E[c]	mg	300	1000	540 (800 IU)
Vitamin K	µg	Not set	Not set	1000 (G)
Thiamin (B_1)	mg	Not set	Not set	100 (G)
Riboflavin (B_2)	mg	Not set	Not set	40 (G) (43T)
Nicotinamide Nicotinic acid	mg mg	900 10	35[d] –	500 (G) (560T) 17
Pantothenic acid	mg	Not set	Not set	200 (G) (210T)
Pyridoxine (B_6)	mg	25	100	200 (short term)[e] 10 (long term)
Folic acid	µg	1000 (+dietary folate)	1000 supp. (+200 diet)	1000 (G) (1500T)
Vitamin B_{12}	µg	Not set	Not set	2000 (G)
Biotin	µg	Not set	Not set	900 (G) S (970T)
Vitamin C	mg	Not set	2000	1000 (G)

Calcium	mg	2500	2500	1500 (G)
Magnesium	mg	250 as supplement	350 as supplement+ diet	400 (G)
Iron	mg	Not set	45	17 (G)
Copper	mg	5	10	1 (10T)
Iodine	µg	600	1100	500 (G) (940T)
Zinc	mg	25	40	25 (42T)
Manganese	mg	Not set	11	4 (G) (9–12T) 0.5 (G) for older people
Potassium	mg	Not set	Not set	3700 (G)
Selenium	µg	300	400	350 (450T)
Chromium (trivalent)[f]	mg	Not set	Not set	10 (G, T)
Molybdenum	µg	600	2000	Not set
Fluoride	mg	Not set	10	Outside terms of reference
Phosphorus	mg	Not set	4000	250 (G) (2400T)

[See key below.]

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

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

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

[c] D-α-tocopherol equivalents/day.

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

[e] Implied in text of report.

[f] Picolinates are excluded.

Appendix II

Why Recommended Daily Amount (RDA)-based upper safe levels are not scientific or appropriate to establish maximum levels of vitamins and minerals in food supplements (Food Supplements Europe 2014).

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

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

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

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

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

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

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

8. The use of RDA-based safe upper limits in food supplements could be misleading to consumers and promote hypothetical safety concerns about a particular vitamin or mineral. An interesting example is the fact that the natural amounts of vitamin B_{12} in conventional foods, such as liver and some shellfish, can be many multiples of the RDA.

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ISBN: 978-1-9995992-5-6

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