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Guidelines
of the Scientific Committee on Food
for the development of tolerable upper intake levels
for vitamins and minerals

(adopted on 19 October 2000)

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FOREWORD

This opinion is one in the series of opinions of the SCF on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address: http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

These guidelines outline a framework of general principles for evaluation of the adverse effects of micronutrients in humans and for establishing upper levels of intake of micronutrients which are unlikely to result in adverse effects in the general population. It is recognised that these principles may have to be reconsidered in the light of experience obtained in the evaluation of individual micronutrients and of interactions with other micronutrients.

Vitamins and (essential) minerals are micronutrients which are essential components of the human diet and the human body. Like other chemical substances, micronutrients may have adverse effects if consumed in excessive amounts. However, when evaluating the adverse effects of micronutrients it is necessary to take into account that, in contrast to non-essential chemical substances, there is a (lower) level of intake below which risk of deficiency conditions or sub-optimal functioning arises. This aspect has been addressed by the Scientific Committee on Food in establishing the recommended daily intakes (SCF, 1993). The focus of this report is the evaluation of 'risk' although it is recognised that nutritional requirements will need to be taken into consideration when setting upper levels of intake. This will be done on a nutrient by nutrient basis.

A number of reports on upper levels of intake of nutrients have been consulted in the development of these guidelines (Bernier, 1995; Nordic Council of Ministers, 1995; Anon, 1996; FNB, 1997, 1998, 2000; Hathcock, 1997; Shrimpton, 1997; WHO, 1996).

2. DEFINITIONS

Tolerable upper intake level (UL) - the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. 'Tolerable intake' in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure. ULs may be derived for various lifestage groups in the population.

The UL is not a recommended level of intake. It is an estimate of the highest level of intake which carries no appreciable risk of adverse health effects. To establish whether an exposed population is at risk requires a risk assessment to determine what is the fraction (if any) of the population whose intake exceeds the UL and the magnitude and duration of the excessive intake.

To whom does it apply? – all groups of the general population (excluding those receiving the nutrient under medical supervision), including sensitive individuals, throughout the life stage - except in some cases discrete, identifiable sub-populations (e.g. those with genetic predisposition or certain disease states) that may be especially vulnerable to one or more adverse effects (FNB, 1997). The exclusion of such sub-populations will be considered on a nutrient by nutrient basis.

Adverse effect - change in morphology, physiology, growth, development or life span of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences (WHO, 1994). Decisions on whether or not any effect is adverse require expert judgement.

3. APPLICATION OF RISK ASSESSMENT TO NUTRIENTS

3.1. Special considerations for nutrients

Nutrients possess some characteristics which distinguish them from other food chemicals for the purpose of risk assessment. Nutrients are essential for human well-being within a certain range of intakes and there is a long history of safe consumption of nutrients at the levels found in balanced human diets. Additionally, for some nutrients there may be experience of widespread chronic consumption (e.g. from dietary supplements) at levels significantly above those obtained from endogenous nutrients in foods without reported adverse effects. Data on adverse effects of nutrients are also often available from studies in humans which helps to reduce the uncertainty factors. Furthermore, many nutrients are subject to homeostatic regulation of body content through adaptation of absorptive, excretory or metabolic processes, and this provides a measure of protection against exposures above usual intakes from balanced diets.

Where possible, ULs should be derived for total intake of nutrients from all sources. It should be noted that added nutrients may sometimes differ from endogenous nutrients in foods in a number of ways, e.g. chemical form, timing of intake and amount consumed in a bolus dose, and effect of the food matrix and interaction of the nutrient with other constituents of the diet.

3.2. Basic concepts

In general, the same principles of risk assessment apply to nutrients as to other food chemicals, but it must be recognised that nutrients possess some distinguishing characteristics, as outlined above.

Risk assessment is a systematic means of evaluating the probability of occurrence of adverse health effects in humans from an excess exposure to an environmental agent (FAO/WHO, 1995) (in this case nutrients in food and water, nutrient supplements and medicines). The hallmark of risk assessment is the requirement to be explicit in all of the evaluations and judgements that must be made to document conclusions.

A generic model for carrying out risk assessment for biological and chemical agents was agreed upon at the FAO/WHO Expert Consultation ‘Application of risk analysis to food standards issues’ in 1995 (FAO/WHO, 1995) and this model now constitutes the basis of discussions on risk assessment by the Codex Alimentarius Commission and the European Commission. A similar model for risk assessment of nutrients has been used recently in the US and Canada and has been described in detail (FNB, 1997, 1998, 2000).

The process of the risk assessment may be divided into a number of steps (FAO/WHO, 1995; FNB, 1997, 1998, 2000):

Step 1. Hazard identification - identification of known or potential adverse health effects of a given nutrient. It involves the collection, organisation and evaluation of all information pertaining to the adverse effects of a given nutrient. It concludes with a summary of the evidence concerning the capacity of the nutrient to cause one or more types of adverse effect in humans.

Step 2. Hazard characterisation – the qualitative and quantitative evaluation of the nature of the adverse effects associated with a nutrient; this includes a dose response assessment, i.e. determining the relationship between nutrient intake (dose) and adverse effect (in terms of frequency and severity).

Based on these evaluations, an UL is derived, taking into account the scientific uncertainties in the data. ULs may be derived for various life-stage groups within the population.

Step 3. Exposure assessment - evaluates the distribution of usual total daily nutrient intakes among members of the general population.

Step 4. Risk characterisation - analyses the conclusions from steps 1 through 3 and characterises the risk. Generally, risk is considered to be the probability of an adverse effect (and its severity). The risk will depend on the fraction of the population exceeding the UL and the magnitude and duration of the excessive intake. Scientific uncertainties associated with both the UL and the intake estimates are described so that risk managers understand the degree of scientific confidence they can place in the risk assessment.

3.3. Thresholds

For nutrients, no risk of adverse effects is expected unless a threshold dose (or intake) is exceeded (FNB, 1997).

Thresholds for any given adverse effect vary among members of the population. In theory, ULs could be established by defining some point in the distribution of thresholds that would be protective for some specified fraction of the population. However, in general, for nutrients

there are insufficient data to establish the distribution of thresholds for individual adverse effects.

Nevertheless, it is possible to derive ULs for which there is confidence that it lies very near the low end of the theoretical distribution of thresholds, thus protecting most of the general population, including the most sensitive (but excluding discrete sub-populations that may be especially vulnerable to one or more adverse effects).

3.4. Variability in the sensitivity of individuals to adverse effects

Adverse effects of nutrients are influenced by physiological changes and common conditions associated with growth and maturation that occur during an individual's lifespan. Therefore, where necessary, and to the extent possible, ULs are derived for each separate life-stage group, e.g. infants, children, adults, the elderly, and women during pregnancy or lactation. Even within relatively homogenous life-stage groups, there is a range of sensitivities to adverse effects, e.g. sensitivity is influenced by body weight and lean body mass.

The derivation of ULs for the normal healthy population, divided into various life-stage groups accounts for normally expected variability in sensitivity, but it excludes sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other considerations (including these would result in ULs which are significantly lower than are needed to protect most people against adverse effects of high intakes). Sub-populations needing special protection are better served through the use of public health screening, health care providers, product labelling, or other individualised strategies. The extent to which a sub-population becomes significant enough to be assumed to be representative of a general population is an area of judgement and of risk management and will be considered for individual nutrients.

3.5. Bioavailability

Bioavailability of a nutrient relates to its absorption and may be defined as its accessibility to normal metabolic and physiological processes. Bioavailability determines a nutrient's beneficial effects at physiological levels of intake and the nature and severity of adverse effects at excessive intakes. Because of the considerable variation in nutrient bioavailability in humans, bioavailability data for specific nutrients must be considered when deriving ULs. In particular, the chemical form of a nutrient may have a large influence on bioavailability and should be specified in deriving the UL. Other modulating factors include: nutritional status of the individual, nutrient dose, interaction with other dietary components and the food matrix (e.g. consumption with or without food).

4. STEPS IN THE DEVELOPMENT OF THE UL

4.1. Hazard identification

This step outlines the adverse health effects that have been demonstrated to be caused by the nutrient.

Human studies provide the most relevant data for hazard identification and, when they are of sufficient quality and extent, are given the greatest weight. Other experimental studies (*in vivo*

and *in vitro*) may also be used. Six key issues that can be addressed in the data evaluation of human and animal studies are:

- ***evidence of adverse effects on humans:*** all human, animal and *in vitro* published evidence addressing the likelihood of a nutrient eliciting an adverse effect in humans is examined. Not all demonstrable structural or functional alterations represent adverse effects; some alterations may be considered of little or self-limiting biological importance. Decisions on which observed effects are ‘adverse’ are based on scientific judgements.
- ***causality:*** it is important to determine whether there is a causal relationship established by the published human data. Criteria for judging the causal significance of an exposure-effect association indicated by epidemiological studies have been adopted in various reports (e.g. NRC, 1982, 1989; Department of Health, 1998). These include demonstration of a temporal relationship, consistency, strength of association (narrow confidence intervals for risk estimates), a dose-response relationship (a biological gradient), specificity, biological plausibility, and coherence.
- ***relevance of experimental data:*** for example, animal data - all animal data should be considered, taking into account interspecies differences, and explicit reasons given for excluding data not considered relevant to human risk; route of exposure - ingestion exposure is more relevant than other routes; duration of exposure and relevance of exposure to dietary intakes by human populations (e.g. chronic daily versus short-term bolus exposure).
- ***mechanisms of adverse effects:*** knowledge of the molecular or cellular events underlying the adverse effect can assist in dealing with the problems of data interpretation.
- ***quality and completeness of the data base***
- ***identification of distinct and highly sensitive sub-populations:*** these may or may not be included in the derivation of the UL, subject to judgement applied on a case by case basis.

4.2. Hazard characterisation

This step includes dose response assessment which addresses the relationship between nutrient intake (dose) and adverse effect (in terms of intake and severity) and involves a number of key components (FNB, 1997):

- ***data selection:*** the data evaluation process results in the selection of the most appropriate or critical data set(s) for deriving the UL. Selecting the critical data set includes the following considerations:
 - ⇒ human data are preferable to animal data. Human studies should be considered in relation to hazards identified in animal studies.
 - ⇒ in the absence of appropriate human data, information from an animal species whose biological responses are most like those of humans is most valuable.
 - ⇒ if it is not possible to identify such a species or to select such data, data from the most sensitive animal species, strain, or gender combination are given the greatest emphasis.

- ⇒ the route of exposure that most resembles the route of expected human intake is preferable. This includes considering the digestive state (e.g. fed or fasted) of the subjects or experimental animals. Where this is not possible, the differences in route of exposure are noted as a source of uncertainty.
 - ⇒ the critical data set defines the dose-response relationship between intake and the extent of the adverse effect known to be the most relevant to humans. Data on bioavailability need to be considered and adjustments in expressions of dose response are made to determine whether any apparent differences in dose response between different forms of a nutrient can be explained.
 - ⇒ the critical data set should document the route of exposure and magnitude and duration of intake, and the intake that does not produce adverse effects as well as the intake which produces adverse effects.
- **identification of NOAEL (or LOAEL) and critical endpoint:** the no observed adverse effect level (NOAEL) is the highest intake of a nutrient at which no adverse effects have been observed. The NOAEL can be identified from evaluation of the critical data set. If there are not adequate data demonstrating a NOAEL, then a lowest observed adverse effect level (LOAEL - the lowest intake at which an adverse effect has been demonstrated) can be used. Where different adverse effects (or endpoints) occur for a nutrient the NOAELs (or LOAELs) for these endpoints will differ. The critical endpoint is the adverse effect exhibiting the lowest NOAEL (e.g. the most sensitive indicator of a nutrient's adverse effects). The derivation of a UL based on the most sensitive endpoint will ensure protection against all other adverse effects.
 - **uncertainty assessment:** there are usually several scientific uncertainties associated with extrapolating from the observed data to the general population and several judgements must be made in deriving uncertainty factors to account for the individual uncertainties. The individual uncertainty factors may be combined into a single composite uncertainty factor for each nutrient and applying this (composite) uncertainty factor to a NOAEL (or LOAEL) will result in a value for the derived UL that is less than experimentally derived NOAEL, unless the uncertainty factor is 1.0. The larger the uncertainty, the larger the uncertainty factors and the lower the UL, which represents a lower estimate of the threshold above which the risk of adverse effects may increase. In the application of uncertainty factors there should be cognisance of nutritional needs, e.g. the derived UL should not be lower than the recommended intake.
 - Because imprecision of the data, lack of data and adequacy of the data on variability are major limitations of risk assessment, uncertainty factors are used. Considerable scope must be allowed for the application of scientific judgement in making the final determination of uncertainty factors. Since data are generally available in human populations, and since studies on human populations may cover part of the variability inherent in the population, the data on adverse effects of nutrients may not be associated with the same uncertainties as with non-essential chemical substances resulting in uncertainty factors for nutrients typically less than 10. The uncertainty factors are lower with higher quality data and when the adverse effects are extremely mild and reversible. The availability of toxicokinetic data in humans may permit a lower uncertainty factor. In general, when determining an uncertainty factor, the following potential sources of uncertainty are considered:
 - ⇒ *interindividual variation and sensitivity:* a small uncertainty factor is used if it is judged that little population variability is expected for the adverse effect, and a

larger uncertainty factor (close to 10) may be used if variability is expected to be great (NRC, 1994).

- ⇒ *experimental animal to human*: an uncertainty factor is generally applied to the NOAEL to account for the uncertainty in extrapolating from animal data to humans. A larger uncertainty factor may be used if it is believed that the animal responses will underpredict average human responses (NRC, 1994).
- ⇒ *LOAEL to NOAEL*: if a NOAEL is not available, an uncertainty factor may be applied to account for the uncertainty in deriving a UL from the LOAEL. The size of the uncertainty factor involves a judgement based on the severity and incidence of the observed effect at the LOAEL and the steepness (slope) of the dose response.
- ⇒ *subchronic NOAEL to predict chronic NOAEL*: when data are lacking on chronic exposures, scientific judgement is necessary to determine whether chronic exposure is likely to lead to adverse effects at lower intakes than those producing effects after subchronic exposures.

- **derivation of an UL**: the UL is derived by dividing the NOAEL (or LOAEL) by the (composite) uncertainty factor. ULs are derived for different life-stage groups using relevant data. In the absence of data for a particular life-stage group, extrapolations are made from the UL for other groups on the basis of known differences in body size, physiology, metabolism, absorption and excretion of a nutrient. When data are not available for children and adolescents, extrapolations are made on the basis of body weight using the reference weights in the Appendix. It should be noted that derivation of a UL does not take into account possible adverse effects of acute bolus dosages. This issue will be addressed separately for individual nutrients, where relevant.

4.3. Characterisation of risk

This may include a description of the scientific uncertainties associated with the UL estimates in order to indicate the degree of scientific confidence that can be placed in these estimates. It may also include an estimate of intake for population groups, where data are available, as well as an indication of the margin between recommended or actual intakes and the UL, and an indication of circumstances, if any, in which risk is likely to arise.

It should indicate whether sub-populations having distinct and exceptional sensitivities to the adverse effects of the nutrient have been excluded, and whether more research is needed. For nutrients for which there are no, or insufficient, data on which to base the establishment of a UL, an indication should be given on the highest level of intake where there is reasonable confidence in data on the absence of adverse effects.

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APPENDIX

Reference body weights 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