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Risk–benefit analysis of micronutrients☆

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Abstract

Traditionally, different approaches have been used to determine the recommended dietary allowances for micronutrients, above which there is a low risk of deficiency, and safe upper levels, below which there is a negligible risk of toxicity. The advice given to risk managers has been in the form of point estimates, such as the recommended dietary allowance (RDA) and the tolerable upper level (UL). In future, the gap between the two intake–response curves may become narrower, as more sensitive indicators of deficiency and toxicity are used, and as health benefits above the recommended daily allowance are taken into account. This paper reviews the traditional approaches and proposes a novel approach to compare beneficial and adverse effects across intake levels. This model can provide advice for risk managers in a form that will allow the risk of deficiency or the risk of not experiencing the benefit to be weighed against the risk of toxicity. The model extends the approach used to estimate recommended dietary allowances to make it applicable to both beneficial and adverse effects and to extend the intake–incidence data to provide a range of estimates that can be considered by the risk manager. The data-requirements of the model are the incidence of a response at one or more levels of intake, and a suitable coefficient of variation to represent the person-to-person variations within the human population. A coefficient of variation of 10% or 15% has been used for established recommended dietary allowances and a value of 15% is proposed as default for considerations of benefit. A coefficient of variation of 45% is proposed as default for considerations of toxicity, based on analyses of human variability in the fate and effects of therapeutic drugs. Using this approach risk managers, working closely with risk assessors, will be able to define ranges of intake based on a balance between the risks of deficiency (or lack of benefit) and toxicity.

Keywords: Risk; Benefit; Risk assessment; Micronutrients

Abbreviations: AI, adequate intake; AR, average requirement; CV, coefficient of variation; DOH, Department of Health (UK); EAR, estimated average requirement; ED50, dose giving a 50% response; EVM, Expert Group on Vitamins and Minerals (UK); GSD, geometric standard deviation; IOM, Institute of Medicine (USA); LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; RDA, recommended dietary allowance; RNI, reference nutrient intake; PRI, population reference intake; SCF, Scientific Committee on Food (EU); SD, standard deviation; UF, uncertainty factor; UL, safe upper level, tolerable upper intake level; WHO, World Health Organization

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1. Introduction

Two different aspects need to be taken into account in determining the optimum range of intake of a nutrient; the minimum amount that is needed by the body for normal function (benefit) and the maximum amount that is compatible with normal function (risk). Such relationships can be expressed also as a risk–risk comparison, with the health risk arising from an inadequate intake being matched against the health risk from an excessive intake. Such a risk–risk comparison is also appropriate for assessment of effects produced at intakes above the traditional recommended daily intake (see below), where the "risk" relates to the absence of a reported additional benefit. A range of acceptable intakes would be that which provides a low incidence of adverse health effects arising from either too low an intake (deficiency or the absence of a health benefit) or too high an intake (toxicity).

Thus there are three intake–incidence relationships which need to be considered (Fig. 1). Adverse effects, due to a deficiency condition, would be present at very low intakes, and these would decrease in incidence and/or severity with increase in intake. A second intake–incidence curve may be present if there are additional benefits at intakes above those needed to prevent a deficiency condition, and the risk associated with the absence of such a health benefit would also decrease with increase in intake. In contrast, adverse effects due to excessive intake would show an increase in incidence and/or severity with an increase in intake. The relative positions and slopes of these curves may vary widely between different nutrients.

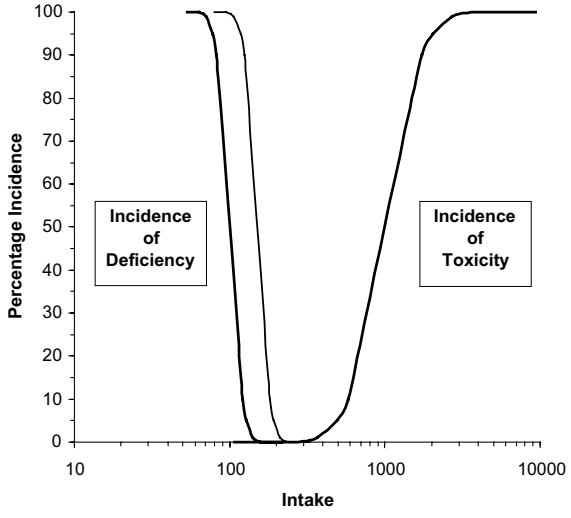

Fig. 1. Intake–incidence relationships for potential adverse health effects which may arise (i) at low intakes because of deficiency (shown as a thick line), or the absence of a health benefit (shown as a thin line at slightly higher intakes), and (ii) at high intakes because of the presence of toxicity, or unwanted adverse health effects.

Both curves can be considered to be the incidence of individuals "at risk", with the left-hand curve representing the decreasing risk of deficiency with increase in intake, and the right-hand curve being the increase in risk of toxicity with increase in intake. In relation to "benefit" there is an intake above which there is no significant increase in perceived benefit (or decrease in the signs or symptoms of deficiency), whilst for "toxicity" there is an intake below which there is no significant incidence of adverse effects. Establishing a safe upper level (UL) assumes the presence of a no-observed-adverse-effect level (NOAEL) in the dose–response, or intake–response, relationship. [In this paper the terms "intake" and "dose" are essentially interchangeable, with "intake" used when exposure is not controlled and "dose" used when the exposure is controlled, for example as part of an experimental study.] The difference between the recommended daily allowance and the upper level is the range over which the intake would be both adequate and without significant adverse health effects.

In this paper the methods that have been used traditionally for the estimation of adequate intakes and excessive intakes are presented. This is followed by a proposal for a combined risk–benefit analysis which can be used as the basis for advice to risk managers on the balance of the risk of deficiency and the risk of toxicity at different intakes.

2. Dietary reference standards—definitions and derivation

2.1. Dietary reference standards related to adequacy of nutrient intake

2.1.1. Nutrient requirements

Dietary reference standards related to adequacy of essential nutrient intake are based on the concept of nutrient requirement. For an essential nutrient a requirement may be defined as the lowest level of continuing intake that, for a specified criterion of adequacy, will maintain a defined level of nutriture in an individual (IOM, 1997). Requirements vary between individuals and every nutrient has a distribution of requirements (for any given criterion of adequacy) that is described by a median (estimated average requirement, EAR) and a standard deviation (SD) for different age and sex groups (Fig. 2).

The EAR (IOM, 1997; DOH, 1991), also referred to as the average requirement (AR) (SCF, 1993), is the daily intake value that is estimated to meet the requirement, as defined by a specified indicator of adequacy, in 50% of the individuals in a life stage or gender group (IOM, 1997).

The distribution of requirements is usually assumed to be normal, although evidence for this is limited for most nutrients, and a clear exception is known for iron

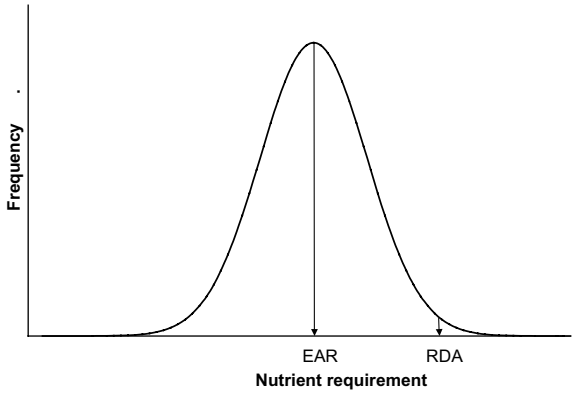

Fig. 2. A normal frequency of distribution of individual requirements for a nutrient. EAR represents the mean (median) requirement of the population. RDA represents the mean requirement plus 2 SD, i.e. that intake which meets the needs of almost all (97–98%) healthy people in a group.

requirements for menstruating women that are skewed towards higher values (SCF, 1993). In the absence of specific data on the distribution of requirements, the coefficient of variation (100 × SD/mean) of the requirement is assumed to be 10% (IOM, 1997) to 15% (SCF, 1993; DOH, 1991). The assumption of a value of 10–15% for the CV for the EAR is based on extensive data on the variation in basal metabolic rate, on a CV of 12.5% estimated for protein requirements in adults (IOM, 1997) and on the observation that many biological characteristics have a CV of about 15% (SCF, 1993).

2.1.2. RDA—recommended intakes

Once the requirement distribution is described, the recommended dietary allowance (RDA) is located at the point on the distribution at which intake is adequate for 97–98% of the population group. For most nutrients, assuming a normal distribution of requirements, the RDA can be calculated as the EAR + 2 SD of the requirement or, assuming a CV of 10% (or 15%):

$$\text{RDA} = 1.2 \text{ (or } 1.3) \times \text{EAR}$$

This requirement is referred to variously as the population reference intake (PRI) (SCF, 1993), the recommended dietary allowance (RDA) (IOM, 1997), and the reference nutrient intake (RNI) (DOH, 1991), and corresponds with the traditional term RDA. Throughout this document this value will be referred to as the RDA.

In the case of iron in menstruating women, for whom good data are available on the distribution of requirements, recommended intakes can be estimated directly from these data. For example, a PRI of 16 mg/day covers the requirements of 90% of the population while a PRI of 20 mg/day covers 95% of the population (SCF, 1993).

RDAs are established for a range of different age and gender groups, including infants, male and female children, adolescents and adults, and pregnant and lactating women. Because the requirements of individuals are not known, the RDA is used as the recommended intake level for all individuals, although it exceeds the requirements for almost all.

In practice, describing a requirement distribution and establishing an EAR is not always possible and thus sometimes nutrients have less precise estimates of recommended intake, e.g. adequate intake (AI) (IOM, 1997), 'acceptable range of intakes' (SCF, 1993) and 'safe and adequate intake' (DOH, 1991). Intakes so designated are generally based on observed intakes of apparently healthy populations.

2.1.3. Criteria of adequacy

When considering requirements it is important to keep in mind the question 'requirement for what?' A nutrient requirement is always related to a specified criterion of adequacy and this must be defined explicitly. Historically, criteria of adequacy that have been used for establishing nutrient requirements commonly included prevention of a clinical outcome of a nutrient deficiency, i.e. indicators at the lower end of the flow

Box 1. Indicators of adverse effects

Indicators of adverse effects, which may be used for the derivation of the UL and for the establishment of EAR and RDA, may range from biochemical changes without adverse health effects through to irreversible pathological changes in the functioning of the organism. It is possible to devise a sequence of indicators of hazard that are in increasing order of severity, i.e.

Biochemical changes within the homeostatic range and without indication of adverse sequelae

↓

Biochemical changes outside homeostatic range without known sequelae

↓

Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess

↓

Clinical symptoms indicative of a minor but reversible change

↓

Clinical symptoms of significant but reversible effects

↓

Clinical signs indicative of significant but reversible organ damage

↓

Clinical signs indicative of irreversible organ damage

chart in Box 1. However, over time these have been replaced by indicators of adequacy higher up this flow chart, including biochemical markers of nutrient function (e.g. maintenance of a defined level of physiological function, such as enzyme activity), and also by indicators of nutrient status or body stores (e.g. biochemical indicator of status/stores) and by nutrient balance. Thus, the severity of the 'adverse effect' arising from inadequate intakes depends on the criterion selected for establishment of requirements. The relationship of a given criterion of adequacy to a health outcome is not always clear. Selection of the criterion of adequacy is a significant point of difference between different review groups and leads to differences in EAR values and derived RDAs.

2.1.4. Benefits beyond the RDA

There is considerable evidence for health benefits of some nutrients at intake levels greater than the RDA. Examples include folate and reduced risk of foetal neural tube defects, cardiovascular disease, cancer and neurodegenerative disease, selenium and vitamin C and reduced risk of certain cancers, vitamin E and reduced risk of cardiovascular disease. While the evidence in many cases is promising, in only a few cases are the associations sufficiently substantiated or consistent to establish causality. It is likely that, in the future, the effects of nutrients on risk reduction of disease will be used increasingly to establish nutrient requirements. In principle, recommendations for intake of nutrients to achieve such benefits could be based on a similar approach to that for establishing the RDA.

2.2. Dietary reference standards related to excess of nutrient intake

2.2.1. Adverse health effects of nutrients—general concepts

An adverse health effect has been defined as any impairment of a physiologically important function that could lead to an adverse health effect in humans (IOM, 1998), and as any 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 (SCF, 2000a; WHO, 1994). Indicators of adverse health effects, which may be used for the derivation of the safe upper level or UL, range from biochemical changes without adverse health effects through to irreversible pathological changes in the functioning of the organism (Box 1). In practice, because of limited availability of data on adverse effects in humans, and since biochemical indicators of adverse effects are often not available, adverse effects selected for establishing ULs may cover the full range indicated in Box 1, including clinical outcomes.

There is an established paradigm for determining safe intakes of foreign compounds, such as food additives, based on the dose–response relationship for adverse effects in animals or humans (Edler et al., 2002). For most types of toxicity, from either foreign compounds or nutrients, there is believed to be a threshold dose (or intake) below which adverse health effects are not produced. Thresholds for any given adverse effect vary among members of the population. In general, there are insufficient data to establish the distribution of thresholds within the population for individual adverse effects, and uncertainty factors are used to allow for human variability (and for species differences when necessary) (Edler et al., 2002).

Application of this approach to the establishment of an UL for a nutrient has to take into account the fact that essential nutrients, e.g. vitamins and essential minerals, are subject to homeostatic control whereby the body content is regulated over a range of intakes. Homeostasis reduces the risk of depletion of body pools when intakes are low, but also reduces the risk of excessive accumulation when intakes are high. For a number of micronutrients the capacity for homeostasis may be exceeded by continuing high dietary intakes, which can lead to abnormal accumulation in tissues, or overloading of normal metabolic or transport pathways. A second difference is that the safe level for a foreign compound is chosen so that it applies to all life-stages, whereas the UL for nutrients may vary with age or for specific groups because of different balances between requirement and sensitivities to adverse effects (see below).

2.2.2. Tolerable Upper Intake Level (UL)—definition

Dietary reference standards for evaluating and managing the risk of excessive intakes of vitamins and minerals have been established recently for a number of vitamins and minerals and are referred to as tolerable upper intake levels (sometimes also called safe upper levels).

The UL is the maximum level of total chronic daily intake of a nutrient (from all sources, including foods, water and nutrient supplements) judged to be unlikely to pose a risk of adverse health effects to almost all individuals in the general population (SCF, 2000a). 'Tolerable' implies a level of intake that can be tolerated physiologically by humans. ULs may be derived for various lifestage groups in the population, e.g. adults, pregnant and lactating women, infants, children. The UL is not a recommended level of intake but is an estimate of the highest level of regular intake that carries no appreciable risk of adverse health effects.

The UL is meant to apply to all groups of the general population, including sensitive individuals, throughout

the lifestage. However, it is not meant to apply to individuals receiving the nutrient under medical supervision or to individuals with predisposing conditions which render them especially sensitive to one or more adverse effects of the nutrient, e.g. those with genetic predisposition or certain metabolic disorders or disease states.

2.2.3. Derivation of the UL

The UL can be derived for nutrients using the principles of risk assessment that have been developed for biological and chemical agents. *Risk assessment* is a process of evaluation including the identification of the attendant uncertainties, of the likelihood and severity of an adverse effect(s)/event(s) occurring in humans or the environment following exposure under defined conditions to a risk source(s) (Smith, 2002). In the context of this paper it is a systematic means of evaluating the probability of occurrence and severity of adverse health effects in humans from an excess exposure to nutrients from all sources (in food and water and nutrient supplements). In general, the same principles of risk assessment apply to nutrients as to other food chemicals.

The steps involved in the application of risk assessment principles to the derivation of ULs for nutrients, e.g. vitamins and minerals, are summarised in Fig. 3 and explained in more detail below. Complete risk assessment requires two additional steps not shown in Fig. 3:

(a) Exposure assessment—the quantitative or semi-quantitative evaluation of the likely exposure of man and/or the environment to risk sources from one or more media (Kroes et al., 2002); in this case the intake in human populations of the nutrient from food, water and nutritional supplements.

(b) Risk characterisation—the quantitative or semi-quantitative estimate, including attendant uncertainties, of the probability of occurrence and severity of adverse effect(s) in a given population under defined exposure conditions based on hazard identification, hazard characterisation and exposure assessment (Renwick et al., 2003); in this case the likelihood of occurrence of adverse effects associated with excessive intake of a nutrient and an indication of circumstances, if any, in which risk of adverse effects is likely to arise.

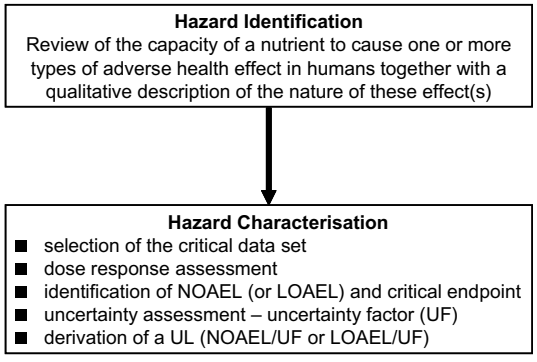

Fig. 3. Steps in the development of the UL (see text for explanation).

Hazard identification involves a review of the capacity of a compound to cause one or more types of adverse health effect together with a qualitative description of the nature of these effect(s) (Barlow et al., 2002). In this case it involves the collection, organisation and evaluation of all information pertaining to the capacity of the nutrient to cause one or more types of adverse health effect in humans.

Hazard characterisation involves the quantitative or semi-quantitative evaluation of the nature of the adverse health effects to humans following exposure to a risk source(s), including a dose–response assessment (Dybing et al., 2002). The UL is derived from the available dose–response data on the nutrient, taking into account the scientific uncertainties in the data.

Assessment of the dose–response curve, which is illustrated diagrammatically in Fig. 4, involves two key components:

(i) *Identification of the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) for the critical endpoint*: The NOAEL is the highest intake of a nutrient at which the adverse effect(s) of concern has not been observed. The NOAEL is identified from the dose–response data for the critical effect (which is usually the effect of relevance to humans which is produced at the lowest doses). If there are no adequate data demonstrating a NOAEL, then a LOAEL (the lowest intake at which an adverse effect has been demonstrated) may be used. Where different adverse health effects occur for a nutrient the NOAELs (or LOAELs) for these endpoints will differ. The critical

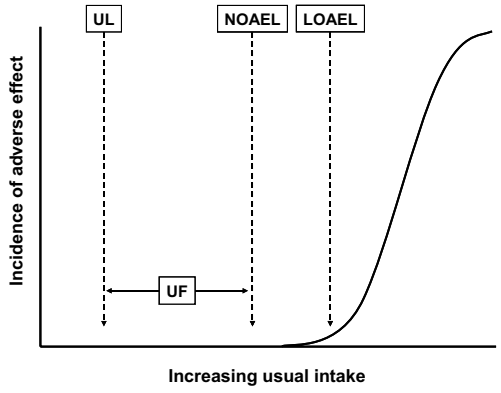

Fig. 4. Theoretical description of adverse health effects of a nutrient as a function of excessive intake. As intakes increase above the UL the uncertainty factor (UF) will be eroded and the risk of adverse effects may increase. The NOAEL is a point observation that is determined by the size of the study and the sensitivity of the methods used. A UF is applied to the NOAEL to derive the UL. An increased UF may be used if the study does not detect a NOAEL and the UL has to be based on the LOAEL.

effect is the adverse health effect exhibiting the lowest NOAEL (i.e. 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 health effects.

(ii) *Uncertainty assessment*: There are usually several scientific uncertainties associated with extrapolation from the observed dose–response data to the general population (e.g. inadequacy of the data on variability between individuals) and several judgements must be made in deriving an uncertainty factor (UF) to account for these uncertainties. In general the approach is "The larger the uncertainty, the larger the UF and the lower the UL". For foreign compounds default uncertainty factors are usually used to allow for human variability (factor = 10) and for species differences (factor = 10) (Edler et al., 2002), thereby achieving an overall uncertainty factor (sometimes referred to as a safety factor) of $10 * 10 = 100$. The UF used in setting ULs is lower with higher quality data and when the adverse effects are extremely mild and reversible. For example, for magnesium an UF of 1.0 was applied to the NOAEL for osmotic diarrhoea, because the effect is relatively mild and reversible, and the large database relating magnesium intake to this adverse effect in humans was adequate to cover the range of interindividual variation in sensitivity (SCF, 2001a). In contrast, for vitamin B6 an UF of 4 (for a LOAEL) was used since the adverse effect (neurotoxicity) is potentially severe, there were only limited data available, mainly from inadequate studies of insufficient duration, relating vitamin B6 intake level to this adverse effect in humans, and a clear NOAEL could not be established (SCF, 2000b).

The UL is calculated by dividing the NOAEL (or LOAEL) by the UF (Fig. 4). Thus, the UL value is less than the experimentally derived NOAEL, unless the UF is 1.0. In practice, the derivation of a UL has to consider also nutritional needs, because the derived UL should not be lower than the recommended intake.

ULs are derived for different lifestage groups, e.g. infants, children, adults, the elderly, and women during pregnancy or lactation, using relevant data or, in the absence of data for a particular lifestage group, by extrapolating from the UL for other groups, e.g. on the basis of body weight. ULs have been derived for a number of vitamins and minerals (references to SCF, 2000a,b,c,d, 2001a,b,c, 2002/3; IOM, 1997, 1998, 2000a,b, 2001, 2002; EVM, 2003). Experience has shown that it is not always possible to establish a UL for a micronutrient using a purely science-based risk assessment approach. Such a situation can arise for different reasons:

- evidence of the absence of any adverse health effects even at high intakes e.g. vitamin B1 (SCF, 2001b);
- absence of evidence of any adverse effect (this does not necessarily mean that there is no potential for adverse effects resulting from high intake), e.g. biotin (SCF, 2001c);
- evidence of adverse effects but insufficient data on which to base a dose–response assessment e.g. β-carotene (SCF, 2000c), manganese (SCF, 2000d).

3. Application of dietary reference standards in estimating prevalence of health effects of nutrients

3.1. Assessment of adequacy of nutrient intake in populations

Because of the high between-person variability in intake of nutrients it is not useful to attempt to define the prevalence of inadequacy of nutrient intakes in a population in terms of the mean intake. For example, a mean population intake equal to the RDA may occur in the presence of inadequate intakes in a significant proportion of the population (Murphy and Poos, 2002). This is because the variance of nutrient intake typically exceeds the variance of nutrient requirement and thus the mean usual nutrient intake of a group must exceed the RDA to have a low prevalence of inadequate nutrient intake. For example, both the mean (2.0 mg) and median (1.5 mg) daily intakes of dietary riboflavin in Irish women exceed the RDA (1.3 mg), but approximately 21% have intakes below the EAR (1.1 mg) (O'Brien et al., 2001).

The proportion of the population for which intake is inadequate may be estimated using the EAR cut-point method, originally proposed by Beaton (1994) and adopted by the US FNB (IOM, 2000). This method requires knowledge of the EAR and the distribution of habitual nutrient intakes and has been shown to be effective in obtaining a realistic estimate of the prevalence of dietary inadequacy (Carriquiry, 1999) (Appendix A).

The percentage of the population with an habitual daily nutrient intake that is lower than the EAR is taken as an estimate of the percentage of the population with inadequate intakes. For example, at a median intake equal to the EAR, 50% of a population group will have intakes that are inadequate for the prevention of adverse effects/maintenance of benefit (Fig. 5).

In principle, the prevalence of inadequacy of nutrient intake for potential health benefits beyond the RDA could also be estimated using this approach, e.g. the prevalence of folate intakes that are inadequate for maintenance of low plasma homocysteine.

It is generally assumed that the intakes of vitamins and minerals are not related to the daily requirements, as happens for calories, and that the average requirements for vitamins and minerals, except iron, are symmetrically distributed (SCF, 1993; IOM, 1997). In the

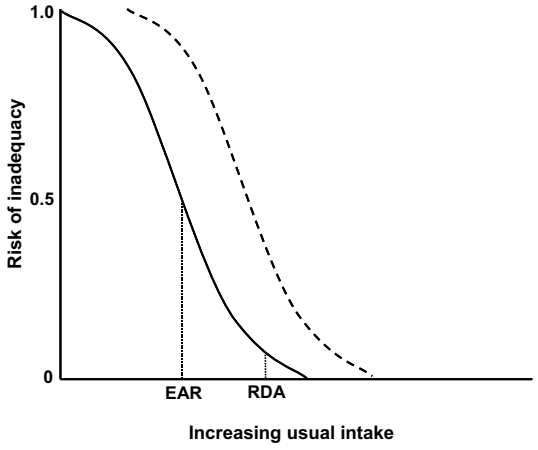

Fig. 5. Theoretical description of beneficial health effects of a nutrient as a function of level of intake. Solid line—risk of inadequacy for the criterion used to establish the RDA; as intake decreases below the RDA there is an increase in the risk of adverse effects due to inadequate intake. At an intake equal to the EAR, 50% of the population will have intakes that are inadequate for the prevention of adverse effects or maintenance of benefit. The dashed line represents the risk of inadequacy of nutrient intake for a health benefit (e.g. disease risk reduction) not included in the derivation of the RDA.

case of iron, use of the cut-point method would lead to an underestimate of the prevalence of inadequacy in menstruating women due to the skewed distribution of iron requirements (IOM, 2000). The SD of the habitual daily intakes of vitamins and minerals are generally greater than 30% of the mean (O'Brien et al., 2001; Hannon et al., 2001) and are almost always more than twice the commonly assumed SD of requirement of 10–15% of the mean.

The number of days over which nutrient intake is estimated is important in establishing habitual intake (Bingham et al., 1995), but intake estimates may be imprecise due to under-reporting of intakes of certain foods, and uncertainty in the values of nutrients in foods.

The prevalence of inadequacy of intake of a nutrient in a population cannot be estimated using the less precise estimates of recommended intake, e.g. nutrients with adequate intake (AI) (IOM, 1997), 'acceptable range of intakes' (SCF, 1993) or 'safe and adequate intake' (DOH, 1991), because the relationship of such reference values to the requirement for the nutrient is not known.

3.2. Assessment of risk of excess nutrient intake in populations

The UL is a dietary reference standard which can be used for both the evaluation and management of risk of excessive intake of vitamins or minerals in individuals or populations. The UL is not in itself an indication of risk, but rather an intake that is without appreciable risk. However, the UL can be applied to data derived from intake assessment (e.g. the distribution of usual total daily nutrient intakes among members of the general population) to identify those individuals or population groups potentially at risk and the circumstances in which risk is likely to occur. The UL does not give any indication of the magnitude of any risk associated with intakes that exceed the UL.

Members of the population with usual intakes of a nutrient below the UL are at no appreciable risk of adverse health effects due to over-consumption, while individuals with intakes above the UL may be at some (unquantified) risk, the magnitude of which depends on the magnitude and duration of the excess. Because the UL is derived using an appropriate UF the risk of adverse effects in the population is much lower at intakes in excess of, but close to, the UL than at intakes around the NOAEL (or LOAEL) (Fig. 4). Because it is not known which individuals are most sensitive, it is necessary to interpret the UL as applying to all individuals.

Estimation of the prevalence of nutrient intakes in excess of the UL is affected by under-reporting of food intakes, by the duration of intake measurement, with short studies overestimating the long-term incidence, and by uncertainty in the concentrations of nutrients in foods.

3.3. Comparison of the approaches used to assess adequacy and toxicity

A comparison of the current approaches used to establish nutritionally adequate and nutritionally excessive intakes is given in Appendix B.

4. Description of an approach and model for risk–benefit analysis

4.1. The limitations of the current approaches to provide suitable advice

The current approaches, with the establishment of recommended minimum daily intakes (such as the RDA) and maximum intakes (such as the UL), provide risk managers with point estimates at the lower and upper end of the range of intake values which should be both nutritionally adequate and non-toxic. However, often the criteria for adequacy and toxicity differ in both nature and severity. In addition, as assessment methods for both adequacy and toxicity (or beneficial and adverse effects) become more varied (Box 1), there may be very different adverse health consequences at intakes below the RDA compared with above the UL. The current approaches do not give advice that would allow the

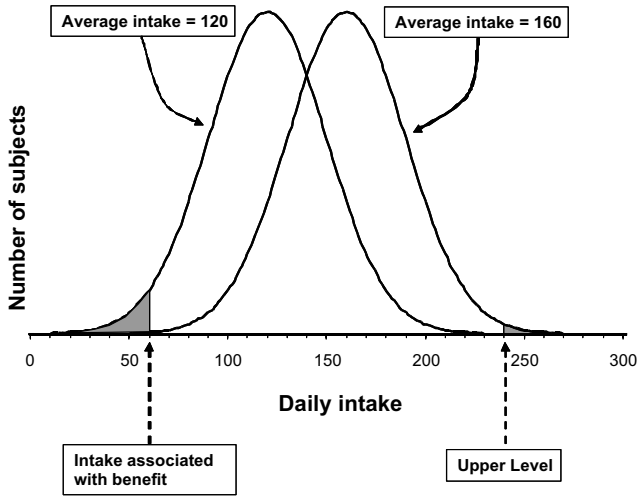

Fig. 6. The influence of an increase in average daily intake (with the same variability in intake) on the proportions of the population with insufficient or excessive intake. The shaded area on the left is the proportion that would not receive a benefit at the lower intake distribution, while the shaded area to the right is the proportion that would be at risk of toxicity at the higher intake distribution.

risk manager to weigh the consequences of a change in intake that altered the proportion of the population that would have either "inadequate" or "excessive" intakes. For example, the risk manager may want to permit increased average intakes if there was a clear benefit, such as the prevention of a common disease, but this might increase the numbers of subjects with intakes above the UL. This is illustrated by the hypothetical example in Fig. 6, in which the usual intake, with an average of 120 units per day results in a proportion of the population with intakes below that associated with a perceived benefit, but an increase in the average intake to 160 units per day, for example by fortification, would lead to a small proportion having an intake above the UL.

The difference in approach between establishing an RDA and a UL means that any risk–benefit analysis is based on different criteria and approaches. A harmonised and consistent approach is necessary if the optimum range of intakes is to be established. The following text is structured to describe how different aspects of the intake–incidence data for either the benefit or toxicity can be taken into account by suitable modelling, and how the output of the model can be used to provide usable advice for risk managers.

Because the UL is a point estimate it does not allow the risk manager to estimate the magnitude of the health risk at the top end of the intake distribution curve.

4.2. General approach and model for hazard characterisation.

There is a common currency in the proposed approach since the decreasing risk of one adverse health effect (deficiency) is balanced against an increasing risk of another adverse health effect (toxicity). Therefore this combined analysis and comparison is really a risk–risk comparison, rather than a risk–benefit analysis. However, the decrease in the risk of deficiency with increase in intake can be regarded as an increase in "benefit" and the analysis can be considered as a risk–benefit analysis, and this term has been used also in this paper because of its wide recognition.

In a combination risk–benefit analysis, the intake–response data for the benefit should be represented as the decreasing risk of deficiency, or decreasing risk of absence of the health benefit, with increase in dosage. In general, it is assumed that within each individual there are thresholds in the curves for the relationships between the intake and the magnitude of the response for both benefit and adverse effects. The intake–incidence relationships for the absence of benefit and adverse effect should be plotted as the change in risk with increase in intake. The slope of any relationship between intake and incidence, either deficiency or adversity, will depend on the coefficient of variation of susceptibility within the population. Such variation can be modelled using either a normal or log-normal distribution; the latter is usually considered to represent biological variability. For either a normal or a log-normal distribution there is no value associated with a zero incidence, other than either an infinite intake for a benefit which shows a negative slope (everyone would have an adequate intake), or zero intake for toxicity which shows a positive slope (no-one would have excessive intake).

Extrapolation more than 2 standard deviations away from the mean or median would be a method of providing an estimate of the intake relevant to low percentages of the population. Extrapolation should be as the intake–incidence curve, rather than the curve for the relationship between intake and magnitude of response. In these circumstances the mathematical model would be of variability in the intakes required to produce the same magnitude of response in the human population rather than variability of the magnitude of the response within the human population for a given intake. Extrapolation of incidence data avoids one of the main criticisms of extrapolation outside the actual data, because it will not develop estimates that may be incompatible with the biology of a system, for example, an increase in liver weight that exceeded body weight. Intake–incidence extrapolation would estimate the proportion of the population that might show some predefined alteration of liver function, such as a 5% increase in liver weight or an increase in serum transaminase levels that exceeded the normal range (see Box 1).

The optimum intake can be defined as "the intake at which there are equivalent risks of both inade-

quacy and toxicity''. If the data on both risk and benefit were

(a) of equal quality,
(b) related to hazards of comparable severity and
(c) were equally well defined,

then the optimum intake on a population basis would be that which minimised both the absence of benefit and the presence of the toxic effect.

Under these circumstances, the optimum intake would be the position at which the intake–incidence curves for deficiency and adverse effects cross (Fig. 7).

In reality the optimum intake would usually need to allow for differences in the nature of the different health effects. For example, the mathematically derived optimum intake could represent a balance between the absence of a marginal benefit and serious toxicity, or between the absence of a clear benefit related to a serious health problem and a poorly defined or minor adverse effect at higher intakes. Such considerations are not a normal part of risk assessment, and require a societal perspective to determine the most acceptable balance. An additional difficulty with an optimum intake is that it does not give practical advice for risk managers, because even if the population average intake was at the optimum there would be a wide range of intakes within the population, and the optimum estimate provides no information on the risks associated with other intakes (see later).

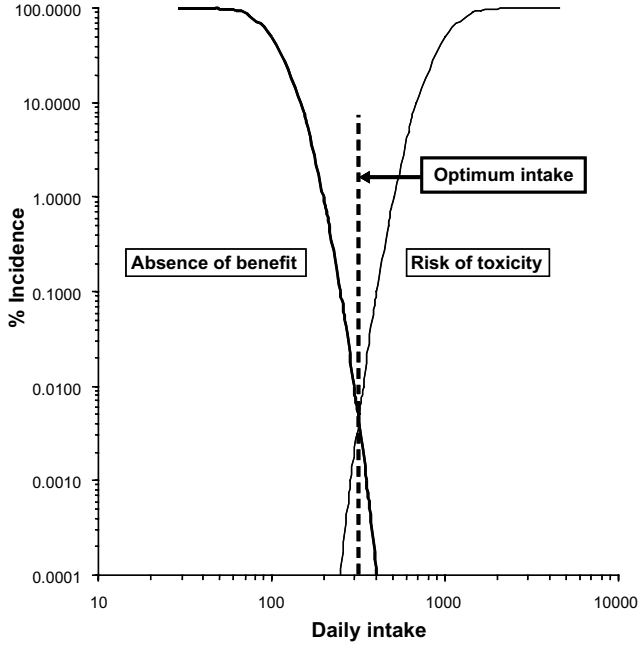

Fig. 7. Intake–incidence relationships extrapolated to low incidences in order to define the optimum intake. The optimum nutritional intake would be that which maximises benefit and minimises toxicity, when all variables have been taken into account.

4.3. Mathematical considerations

A major problem for risk–benefit analysis of micronutrients is the absence of comprehensive intake–response or intake–incidence data that can be used as the input to the mathematical model. The following text describes an approach that could be adopted practically in the absence of comprehensive intake–response data. The incorporation of predicted human variability and uncertainties will require a mathematical expression of the magnitude of the uncertainty which is then incorporated into the model. Following the general description of the method there are examples of how uncertainties could affect the outcome.

Determination of the shape and position of the intake–response curves will usually be based on data related to effects produced by a single dosage or intake level, or by a small number of intake levels that may not be sufficient to define directly the position or slope of the intake–response or intake–incidence curve. The intake–incidence relationship for an adverse or beneficial effect can be defined based on the intake required to give a 50% response and the standard deviation (SD—for a normal distribution) or the geometric standard deviation (GSD—for a log normal distribution). The position and shape of the intake–incidence curve can be calculated from limited data as outlined below and in Appendix C.

Human variability in susceptibility is indicated by the extent of the differences in the intakes required in different individuals to produce the same response, which can be any predetermined response that provides reliable response data.

Ideally, suitable data for modelling would be obtained from studies in which the same subjects were given a range of daily intakes and their individual intake–response relationships, which related the magnitude of response to the dosage or intake, were determined. The individual intake–response curves would then be analysed to define the intake necessary in each person to give the same magnitude of response. The population distribution of the different intakes necessary to produce the same magnitude of response would usually be a normal or log-normal distribution (Fig. 8).

Data on differences in response to the same dose in different subjects will identify sensitive and less sensitive subjects. However the magnitude of the difference, and therefore the CV for differences in response, will depend on the dose selected for study. Such data will be less valid than differences in the dose necessary to produce the same response. For intake–incidence data the incidence refers to the cumulative numbers of ''responders'', i.e. those who will give the same predetermined magnitude of response at that particular intake (Fig. 9).

In reality, the type of information that may be available to be used as a basis for determining the position of

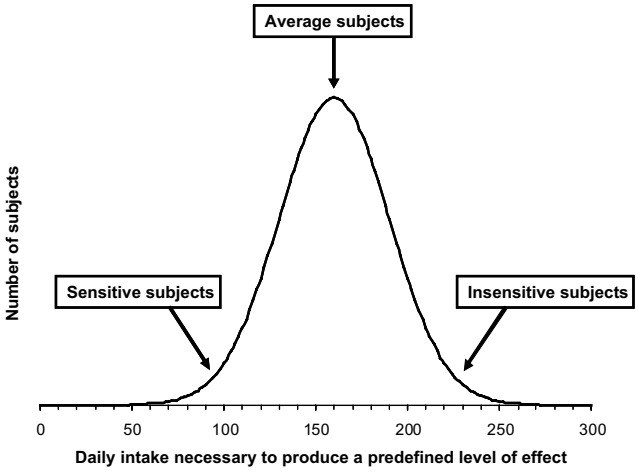

Fig. 8. Hypothetical distribution of sensitivity within the human population, showing the number of subjects showing a predefined level of response, such as a 10% change in an enzyme activity, at different levels of daily dosage. Sensitive subjects will produce the response with low intakes while less sensitive subjects require higher intakes to show the same response.

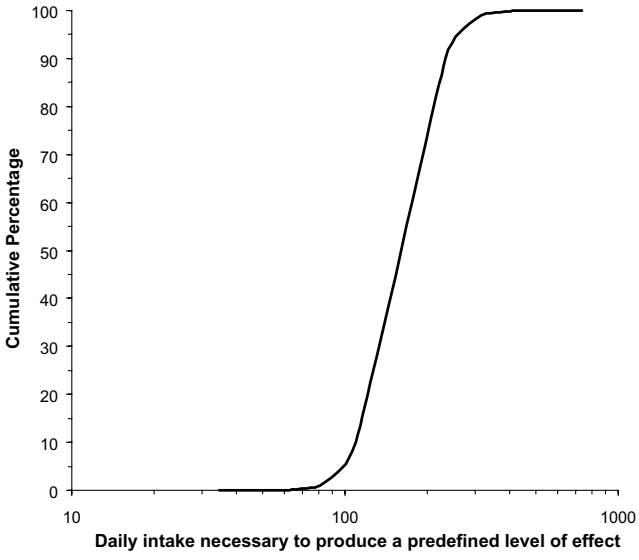

Fig. 9. Hypothetical cumulative distribution of sensitivity within the human population, showing the cumulative percentage of subjects giving a predefined level of response, such as a 10% change in an enzyme activity, at different levels of daily dosage (based on Fig. 8).

the intake–response data (for either benefit or adversity) is likely to be the results from a single dose study in which a given percentage of the population showed a response. For example the best data available on a nutrient effect may be that a dose of 100 mg produced a change that exceeded the normal range (for example in an enzyme activity) in 10% of the population. Such incidence data can be used to derive the mean for a normal distribution providing that an estimate is made concerning the coefficient of variation within the population. Information on, or an assumption about, the variability in the population is also essential for extrapolation away from the median.

Such a calculation is best done assuming a log-normal distribution. Normal distributions are described by means, standard deviations and coefficients of variation (CV), whereas log-normal distributions are best described by medians, and geometric standard deviations (GSD). This adds complexity to the calculation, which would require conversion of data expressed in terms of a normal distribution, into a log-normal distribution (Appendix C).

The proposed approach is illustrated by Fig. 10 which represents the graphs that would be obtained from data for both absence of benefit and risk of toxicity. For illustrative purposes, the benefit has an ED50 (dose giving a 50% response) of 100 mg with a CV of 15% and the toxicity with an ED50 of 1000 mg and a CV of 45%. The optimum intake would be where the lines cross.

The position of the optimum is dependent on both the ED50 values and the CVs (or GSDs) that are used to calculate each curve. In consequence this approach to risk–benefit analysis is sensitive to the position and nature of the dose–incidence relationships. The model can be used to fit any value of ED50 and any CV or GSD value and therefore data on the particular micronutrient under evaluation can be used when available. In the absence of such data a default value for the CV has to be used (see below).

4.3.1. The effect of the ED50 on the optimum intake

Fig. 11 shows the relationships when the dose required to produce a beneficial effect is decreased from

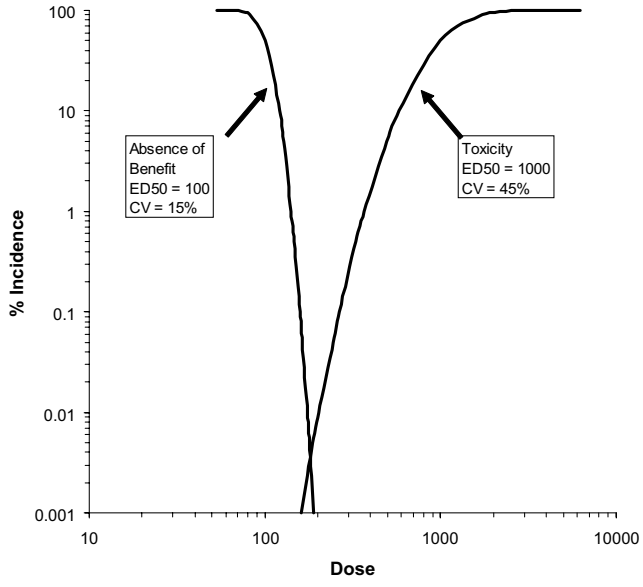

Fig. 10. Comparisons of differences in the dose–incidence relationships for the absence of benefit (ED50 = 100; CV = 15%) and the production of toxicity (ED50 = 1000; CV = 45%).

100 to 50 (shown as a thin line) and when the dose required to produce an adverse effect is increased from 1000 to 2000 (also shown as a thin line).

The consequence of a reduction in the dose required to produce a beneficial effect is to move the optimum dose from a value of just over 300 down to approximately 210. When the dose required to produce an adverse effect is increased from 1000 to 2000 the optimum dose increases to about 430. It is interesting to note that a 2-fold change in either ED50 does not result in a 2-fold change in the optimum, but rather a change that reflects the shift in balance of benefit and risk. This is one of the main advantages of undertaking a mathematically modelled risk–benefit analysis rather than a more simplistic NOAEL approach.

4.3.2. The effect of the CV on the optimum intake

The position of the optimum is dependent on the CV (or GSD) for each curve. Actual data on the variability in sensitivity to either the beneficial or toxic effect of a particular micronutrient could be incorporated into the model. In reality such information will almost never be available, and application of the model will require the selection of suitable default values for the CV for both the benefit and toxicity curves. The CV selected to reflect human variability would also be used to derive the ED50 from the available incidence–response data (see Appendix C).

A CV of 15% has been used by the SCF to establish the RDA for benefit considerations, although a value of 10% is used by the IOM in the USA for the same purposes. The use of 15% for benefit has a history of use for extrapolation from the median to the 95th percentile. The use of a CV of 15% for any benefits above the RDA would indicate acceptance of the same assumptions that were inherent in its selection for estimating the RDA (see Section 2.1.1).

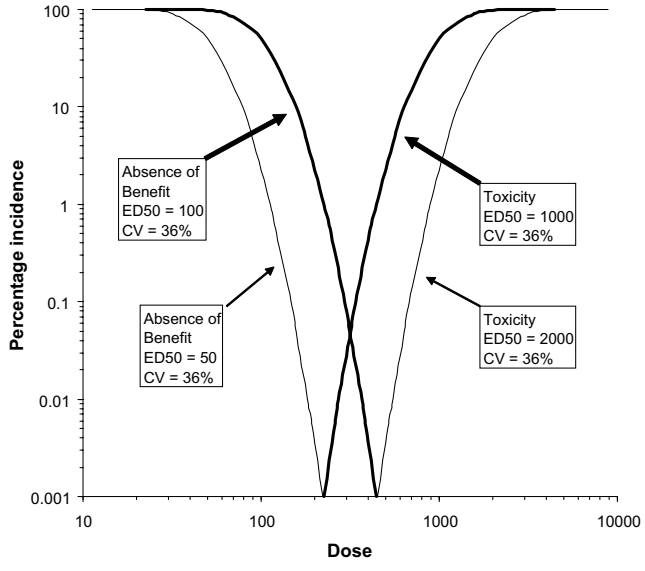

Fig. 11. The effect of 2-fold changes in the ED50 for either benefit or toxicity on the position of the optimum. For ease of interpretation the CVs for both the benefit and toxicity have been set at the same value (36%).

The selection of a suitable CV for the variability in toxicity is more problematic, because variability in sensitivity to toxicity would not be linked to simple basal metabolic rate or protein requirement (as is assumed in the value of 15% for adequacy). The CV for toxicity would not necessarily be related to nutritional aspects, and variability in response would result from the micronutrient producing adverse effects similar to those produced by non-nutrient chemicals. An analysis of human variability in the elimination of foreign compounds (kinetics) and response to therapeutic drugs (dynamics) in healthy people (Renwick and Lazarus, 1998) gave average CV values of 38% for kinetics and 51% for dynamics, so that a composite value of 45% could be considered to represent the likely human variability in overall response to an external dose. Recent meta-analyses of human variability for a variety of pathways of xenobiotic elimination (Dorne et al., 2001a,b, 2002, 2003a,b, 2004a,b) have shown that the CVs in healthy adults are about 29% for monomorphic pathways of metabolism, about 45% for polymorphic pathways of metabolism (non-phenotyped subjects) and about 20% for renal excretion. Greater variability might be expected for the general population, which would include the elderly. An overall CV of 45% would be reasonable to reflect the likely human variability in both kinetics and dynamics at the high intakes that could be associated with toxicity. Although there is no precedent for using 45% as the CV for toxicity, this is a scientifically supportable value, and the use of a higher value for toxicity compared with benefit will be precautionary, because it will give a lower optimum and therefore a lower upper limit on any range selected from the risk–benefit comparison (see later). It should be recognised that the selection of this value is no more arbitrary than the values traditionally used as uncertainty factors in the determination of a UL.

Fig. 12 shows two sets of data to illustrate the influence of the CV on the shape of the dose–incidence curves. The coefficient of variation associated with the beneficial effect has been reduced from an arbitrary 30% to 15% indicating lower variability within subjects (equal to the variability assumed in the current method of calculating RDAs). The coefficient of variation associated with toxicity has been increased from an arbitrary 30% to the proposed default value of 45% (to be consistent with the variability inherent in the activity of non-nutrients). The consequence of these changes is that the optimum is reduced from about 310 (when both curves have CVs of 30%) to about 180 (when the CVs are 15% and 45% for benefit and toxicity).

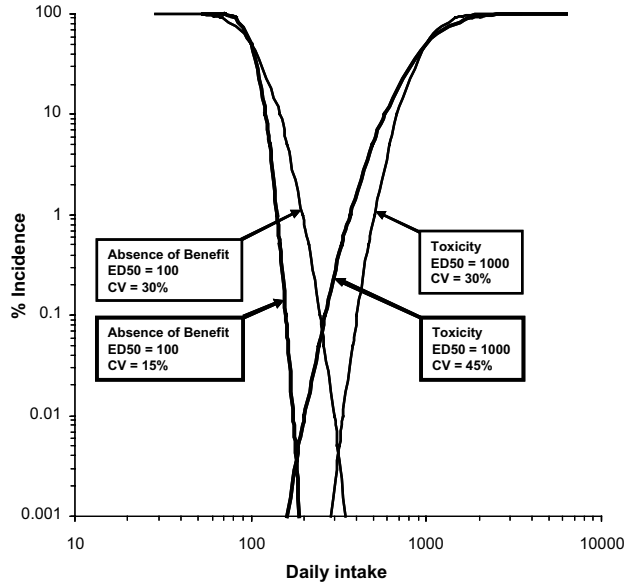

Fig. 12. The effect of changes in the CVs for both benefit and toxicity on the slope of the intake–incidence curve and on the position of the optimum. For illustrative purposes, the thin lines are plotted with equal CV values (30%) and the thick lines are plotted using the proposed default CV values of 15% for absence of benefit and 45% for presence of toxicity.

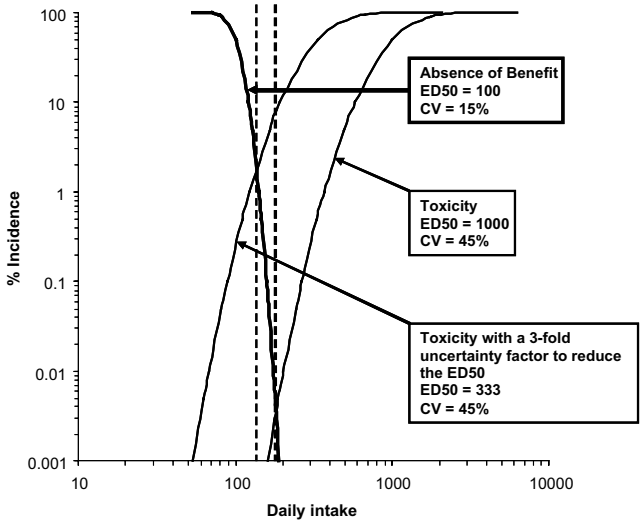

Fig. 13. The effect of a 3-fold reduction in the ED50 for toxicity on the position of the optimum which is indicated by the vertical dashed lines (compared with Fig. 12).

Comparison of the dose–incidence curves in Fig. 12, which use different CV values, illustrates that the model is sensitive to the CV, because the reduction in the CV for benefit and the increase for toxicity means that the optimum intake is reduced to a lower value. In other words the greater variability in susceptibility to the toxic effect has resulted in a lower or more cautious optimum intake.

The influences of the slopes of both of the dose–incidence curves and the position of the ED50 values would affect not only the optimum intakes, as illustrated in Figs. 11 and 12 but also the ranges of intakes that could be abstracted from the curves and could form the basis of advice to risk managers (see Section 5).

4.3.3. Incorporation of uncertainties

In reality the ideal situation, in which both the incidence and the variability in susceptibility in humans are known, will never occur and uncertainties will be an inherent part of any risk–benefit analysis (just as they are for any separate assessment of either risk or benefit). Uncertainties may include the nature of the hazard, the adequacy of the data and the inherent uncertainties related to whether the available data reflect all possible benefits, a well as all potential hazards. Such uncertainties can be incorporated by application of an uncertainty factor to the ED50 value, which has the effect of moving the dose–incidence curve.

This is illustrated in Fig. 13, in which the dose–incidence for toxicity has been shifted by the application of an uncertainty factor to the ED50 compared with the data in Fig. 12. In this case an uncertainty factor of 3 has been applied so that the dose–incidence relationship is taken to occur with a 50% response at 333 instead of 1000. This change has the effect of moving the optimum dose level from 180 (see Fig. 12) to approximately 120, i.e. a <3-fold difference in dosage.

A major problem for any risk–benefit analysis arises when there are no or insufficient hazard identification studies in either animals or humans. In classic risk assessment of non-nutrients this is taken into account by the use of uncertainty factors, but application of the usual large defaults to the ED50 for a micronutrient could frequently result in an ''optimum intake'' in which a large proportion of the population would suffer deficiency in order to allow for the uncertainties of the database. In other words incorporation of the usual uncertainty factors giving a one-sided precautionary approach could result in significant adverse health effects in the population due to deficiency.

Perceptions of data inadequacy will differ depending on whether the inadequacy relates to the perceived benefit or the potential toxicity. For example, the ability to detect an effect in a human study depends on the group size investigated and the presence of a type 1 error (a failure to detect an effect which should be there). This type of error would have more serious consequences in relation to not detecting a form of toxicity compared with not detecting an additional benefit over and above the recommended daily allowance or recommended nutrient intake.

The total absence of an appropriate study would have different consequences. For example, the absence of a study showing a benefit in reducing cardiovascular risk from a micronutrient could be considered less severe

than the absence of an adequate toxicity study defining chronic toxicity or reproductive toxicity. The way that database inadequacies would be taken into account would depend on whether the inadequacy related to the perceived benefit or the hazard. If the inadequacy related to the benefit, theoretically this could be taken into account by moving the intake–response for benefit to the right, thereby giving an optimum intake higher than would otherwise occur. In contrast, if the database inadequacy related to the adverse effects produced by high intakes, then the intake–response for toxicity would need to be moved to the left to give a lower optimum intake.

Fig. 14 illustrates the impact of incorporating a 10-fold uncertainty factor to the dose response for toxicity because of database inadequacy in relation to toxicity testing. Although in the data used for illustration the optimum intake is reduced by a factor of about 2 rather than 10, the shift would produce a significant incidence of individuals lacking benefit, in order to compensate for the uncertainty arising from the inadequacy of the database.

Database inadequacies may relate to size and statistical power of the available studies, the sensitivity of the measurements to detect the effect (benefit or hazard), and the ability of the studied individuals to reflect the human population (for example sexes, life stages etc.).

4.3.4. Consideration of the nature of the effect—comparing like with like

The dose–incidence relationships for different measurements related to the same underlying effect depend on the sensitivity of the measurement method, and the relationship between that measurement and the ultimate response. For example changes in enzyme activity may be used as biomarkers of either inadequacy (for example erythrocyte superoxide dismutase) or of toxicity (for example elevated serum transaminases with liver toxicity). The intake–responses for sensitive biomarkers of deficiency will be detectable at intakes at which a frank deficiency syndrome is no longer apparent. Biomarkers of adverse toxic effects will be detectable at intakes at which frank toxicity (for example pathological changes) is not produced. Consequently the intake–incidence for any level of response to the biomarker compared with the frank effect will occur at different intakes (Fig. 15).

Incorporation of differences between biomarkers and frank effects could be undertaken by application of adjustment factors to the ED50 in an attempt to be consistent in the severity of the absence of benefit and the presence of toxicity. However the relative ranking of different forms of toxicity contains societal rather than scientific issues, and therefore should be a task for the risk manager, and could be done when considering the suitable range of intakes (see later).

4.3.5. Use of data from different species

In most cases data relating to nutritional benefits will be obtained from studies in humans whereas data on hazards associated with excessive intake may be derived from human studies and/or animal studies. There is an established risk assessment paradigm using uncertainty factors to extrapolate from animal dose–response data to determine safe intakes for humans in relation to exposure to non-nutrient chemicals. In this approach the NOAEL in animals is usually divided by an uncertainty factor of 100 comprising a 10-fold factor to allow for possible species differences and a second 10-fold factor

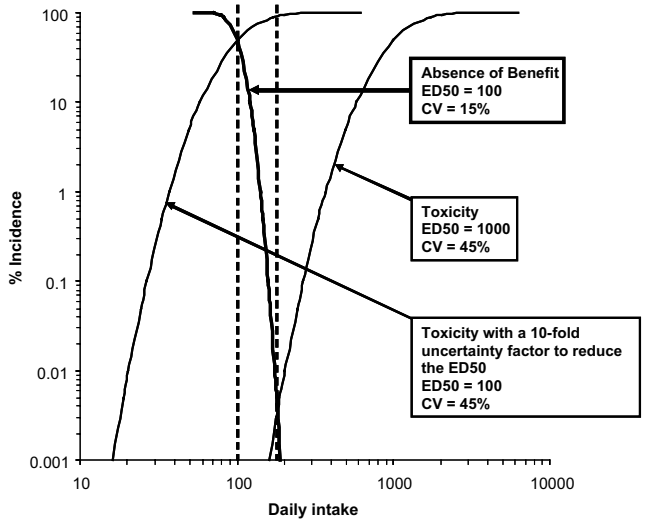

Fig. 14. The effect of application of a 10-fold uncertainty factor to the ED50 for toxicity on the basis of database deficiencies (compared with Figs. 12 and 13).

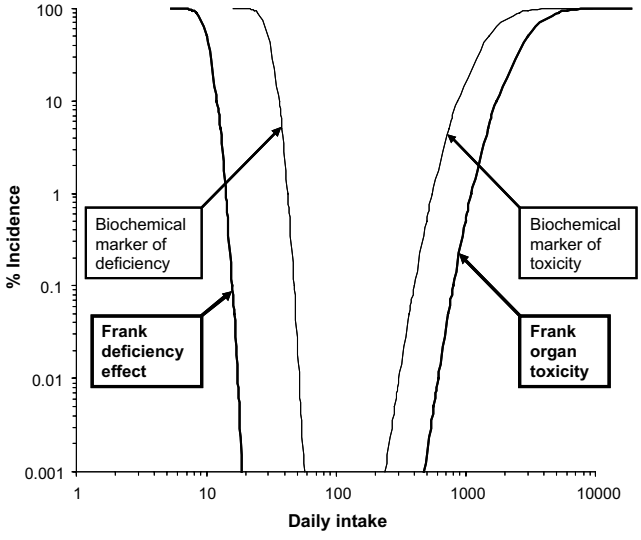

Fig. 15. The intake–incidence relationships for sensitive biomarkers compared with frank effects. This illustration assumes that the biochemical markers have different ED50 values to more serious effects, but that there is similar variability (15% for benefit and 45% for toxicity).

to allow for human variability. Because human variability is taken into account by the mathematical model, the animal dose–response data could be divided by a factor of 10 to allow for differences in sensitivity.

The normal starting point for risk assessment based on animal data is the NOAEL, which is a dose that does not give a measurable response in the test species. A no-response or no-incidence of response intake cannot be fitted to the model. Therefore in a practical approach, the LOAEL from the animal study, which would define the incidence of an adverse effect in a group of animals, could be divided by a default interspecies uncertainty factor of 10 to give a "human equivalent LOAEL". This value could then be modelled assuming the default CV of 45% to provide a predicted human incidence curve based on the animal data. An alternative and more scientific method would be to analyse the animal dose–incidence relationship mathematically and to select a starting point, such as a critical effect size, from the fitted data (see Edler et al., 2002), then to divide this by the 10-fold interspecies factor, and then to apply the human CV to model the curve.

The interspecies factor of 10 could be modified on the basis of available scientific data, or understanding of the basic biology of the adverse effect produced at high intakes. It is clear from the curves in Fig. 14 that the application of a 10-fold interspecies uncertainty factor would have a major impact on determining the upper bound of any advice to risk managers. In this respect the model proposed is no different to the current methods for derivation of ULs which are single point estimates.

4.3.6. Consideration of population subgroups

Data on population subgroups were considered when available by the SCF (EU), EVM (UK) and IOM (USA) in the determination of ULs, and in some cases a subgroup was the basis for the determination of the tolerable upper intake level for the general population. Potential adverse health effects produced by inadequate dietary intakes were not considered as a part of a formal risk–benefit analysis, but were taken into account such that the uncertainty factor selected was tempered by a realisation that application of high uncertainty factors, particularly those related to database inadequacies, could have resulted in the generation of adverse health effects due to deficiency, rather than protection from adverse health effects due to excess.

Population subgroups may need to be considered in relation to both the benefit and the possible adverse effect. In many cases the benefit over and above that normally associated with basic nutritional requirements may relate to a specific subgroup, for example, folate in pregnancy. Similarly the adverse effects may relate to a subgroup, which may not necessarily be the same group as that receiving the benefit, for example, folic acid and the elderly. The presence of subgroups in the population in relation to either benefit or adverse effects may require separate analyses of the risk–benefit considerations for each specific subgroup. Such analyses may require different ED50 values or CVs for either the benefit or toxicity, as appropriate.

In consequence the advice to risk managers may take the form of advice for the general population, general advice combined with specific advice in relation to those groups who may receive an additional benefit, and/or other advice related to individuals who may be at enhanced risk from the normal or slightly elevated intakes.

5. Risk characterisation and formulation of advice for risk managers

5.1. Conversion of the intake–incidence data and the optimum intake into a range of intakes

The analyses described above provide a method of developing intake–incidence data and of calculating the optimum intake. However it must be recognised that a single value (the optimum) would not provide usable health advice either for nutritionists or for risk managers.

An inherent part of the risk–benefit analysis will be that the intake–incidence curves will inevitably relate to different effects of different severity, and possibly even apply to different subgroups of the population. In consequence simply reporting the intakes associated with a 5% incidence (or any other preselected incidence) of both the benefit and toxicity based on the estimated intake–incidence analyses may be unacceptable to either nutritionists or risk managers or both.

The advice to risk managers should be open-ended and sufficient for them to take all relevant issues into account. The task of the risk manager will be to select a point along the intake–incidence curve that gives an acceptable incidence, after allowing for the nature of the effect, the reliability of the associated database, and the size and nature of the population potentially affected.

Therefore an essential part of the advice to risk managers will be an adequate descriptive narrative about the nature of the adverse health effects based on the data that were used to derive the intake–incidence curves. This will allow the risk manager to weight the acceptability of any incidence against the severity of the effect. For example a risk manager might be willing to accept an incidence of 5 in 100 for a change in an enzyme activity that is a very sensitive indicator of deficiency or potential toxicity, but an incidence of only 1 in 100,000 or less for a deficiency symptom like scurvy or frank toxicity such as liver failure. Such decisions contain societal elements for which the scientifically trained risk assessor, such as a

toxicologist, epidemiologist etc., does not have the necessary expertise or experience. In addition, risk managers would have to consider the practicability of any range of intakes that they proposed.

In consequence, the advice to risk managers cannot be in the form of a single recommended range of intake, but has to be presented as a series of possible lower and upper intake ranges, from which the risk manager can select the one that is most appropriate after taking all aspects into account. The most effective way to present the options to the risk manager is in tabular form. A simple table would show the incidences of insufficiency (whether deficiency or the absence of a benefit) and of toxicity in relation to a particular database. An example is given in Table 1, for a nutrient that shows a clear deficiency syndrome at low intakes, with a marginal beneficial effect at slightly higher intakes (for which a high incidence of "lack of benefit" might be acceptable), and clear organ toxicity, for which only a low incidence of "toxicity" would be acceptable. The range of possible incidences presented in Table 1 has been tailored to what is likely to be useful to the risk manager, but additional values could easily be calculated by the risk assessor if required.

Table 2 provides a generic analysis of the intake–incidence curves for a benefit (calculated using a CV of 15%) and for toxicity (calculated using a CV of 45%) that could be used as the basis for formulating advice on the predicted intakes associated with different incidences of deficiency and of toxicity. This is in the form of a grid so that risk managers can select the cell that is most appropriate taking into account the nature of the effects (both beneficial and toxic) and the reliability of the data. The table expresses the intakes as a multiple of the ED50 value for each effect considered. For example if the risk manager considered the absence of benefit to be serious and intended that only 1 in 1000 people would not to benefit, but that the toxicity was even more severe and only 1 in 1,000,000 should show toxicity then the selected cell from Table 2 would show "$1.59A$–$0.13B$" where A is the ED50 for the absence of benefit and B is the ED50 for toxicity. The extent of separation of the two ends of the range will depend on the values of A and B. For example if A is 10 mg/day and B is 1000 mg/day, the acceptable range would be 15.9–130 mg/day. Depending on the incidences selected by the risk manager there could be an overlap in the estimates, for example if A is 10 mg/day and B is 100 mg/day the range would be 15.9–13.0, in other words the upper end of the range is below the lower end. In such cases it is not possible to define an intake that provides the degrees of protection that the risk manager would wish, and the compromises necessary will be transparent.

Some micronutrients may have a number of intake–incidence curves for both the absence of different benefits and the presence of different types of toxicity. Under

Table 1
The format of advice to risk managers for a nutrient that shows a deficiency syndrome (with an estimated ED50 of 50 mg/day), a marginal benefit (with an estimated ED50 of 75 mg/day) and clear toxicity (with an estimated ED50 of 1000 mg/day)

Intake (mg/day)	Incidence of deficiency	Incidence of not experiencing the additional health benefit	Incidence of toxicity
50	1 in 2		
57	1 in 5		
61	1 in 10		
64	1 in 20		
68	1 in 50		
71	1 in 100		
75	1 in 300	1 in 2	
85	1 in 5000	1 in 5	
91	1 in 25,000	1 in 10	
96	1 in 200,000	1 in 20	
102	1 in 1,000,000	1 in 50	
106	<1 in 1,000,000	1 in 100	
119		1 in 1000	<1 in 1,000,000
130		1 in 10,000	1 in 1,000,000
160		<1 in 1,000,000	1 in 100,000
200			1 in 10,000
270			1 in 1000
290			1 in 500
370			1 in 100
490			1 in 20

The incidences have been estimated using a log-normal population distribution model (see Appendix C), and with human variability represented by the proposed default CVs of 15% for deficiency and marginal benefit, and 45% for toxicity. Compound-specific CV values should be used when suitable data are available.

Table 2
Analysis of intake–incidence curves and the abstraction and formulation of advice for risk managers

Incidence of deficiency or absence of benefit	Incidence of toxicity								
	1:10	1:20	1:50	1:100	1:500	$1:10^3$	$1:10^4$	$1:10^5$	$1:10^6$
1:10	1.21*A*–0.58*B*	1.21*A*–0.49*B*	1.21*A*–0.41*B*	1.21*A*–0.37*B*	1.21*A*–0.29*B*	1.21*A*–0.27*B*	1.21*A*–0.20*B*	1.21*A*–0.16*B*	1.21*A*–0.13*B*
1:20	1.28*A*–0.58*B*	1.28*A*–0.49*B*	1.28*A*–0.41*B*	1.28*A*–0.37*B*	1.28*A*–0.29*B*	1.28*A*–0.27*B*	1.28*A*–0.20*B*	1.28*A*–0.16*B*	1.28*A*–0.13*B*
1:50	1.36*A*–0.58*B*	1.36*A*–0.49*B*	1.36*A*–0.41*B*	1.36*A*–0.37*B*	1.36*A*–0.29*B*	1.36*A*–0.27*B*	1.36*A*–0.20*B*	1.36*A*–0.16*B*	1.36*A*–0.13*B*
1:100	1.41*A*–0.58*B*	1.41*A*–0.49*B*	1.41*A*–0.41*B*	1.41*A*–0.37*B*	1.41*A*–0.29*B*	1.41*A*–0.27*B*	1.41*A*–0.20*B*	1.41*A*–0.16*B*	1.41*A*–0.13*B*
1:500	1.54*A*–0.58*B*	1.54*A*–0.49*B*	1.54*A*–0.41*B*	1.54*A*–0.37*B*	1.54*A*–0.29*B*	1.54*A*–0.27*B*	1.54*A*–0.20*B*	1.54*A*–0.16*B*	1.54*A*–0.13*B*
$1:10^3$	1.59*A*–0.58*B*	1.59*A*–0.49*B*	1.59*A*–0.41*B*	1.59*A*–0.37*B*	1.59*A*–0.29*B*	1.59*A*–0.27*B*	1.59*A*–0.20*B*	1.59*A*–0.16*B*	1.59*A*–0.13*B*
$1:10^4$	1.74*A*–0.58*B*	1.74*A*–0.49*B*	1.74*A*–0.41*B*	1.74*A*–0.37*B*	1.74*A*–0.29*B*	1.74*A*–0.27*B*	1.74*A*–0.20*B*	1.74*A*–0.16*B*	1.74*A*–0.13*B*
$1:10^5$	1.89*A*–0.58*B*	1.89*A*–0.49*B*	1.89*A*–0.41*B*	1.89*A*–0.37*B*	1.89*A*–0.29*B*	1.89*A*–0.27*B*	1.89*A*–0.20*B*	1.89*A*–0.16*B*	1.89*A*–0.13*B*
$1:10^6$	2.03*A*–0.58*B*	2.03*A*–0.49*B*	2.03*A*–0.41*B*	2.03*A*–0.37*B*	2.03*A*–0.29*B*	2.03*A*–0.27*B*	2.03*A*–0.20*B*	2.03*A*–0.16*B*	2.03*A*–0.13*B*

The curves for the benefit and toxicity can be analysed based on the estimated ED50 and the CV, as described in Appendix C and illustrated by Figs. 10–15. The incidence of the inadequacy or absence of a beneficial effect will be 50% when the intake equals the ED50 and will decrease as the intake increases; in contrast for toxicity the incidence will decrease as the intake decreases. This table presents the incidences at different fractions of the ED50 values for benefit and risk calculated using a log-normal population distribution model (see Appendix C). In order to make the table generally applicable the ED50 value for benefit is given as *A*, and the ED50 value for toxicity is given as *B* (these values could be in mg/day or mg/kg body weight per day). Human variability has been incorporated into the calculations by using the proposed default CVs of 15% for deficiency and marginal benefit, and 45% for toxicity. The table gives the intake values corresponding to fractions of *A* and *B* for different incidences of benefit and toxicity over the range 1:10 down to 1: 1,000,000.The use of this grid requires the risk manager to choose a cell that represents the correct balance of incidences based on the weight of all of the evidence for both deficiency (or absence of benefit) and toxicity.
For example if

(a) the risk of deficiency related to irreversible neuronal damage with an ED50 of 1 mg/day and

(b) the toxicity was an elevation of serum transaminases indicative of liver damage, but without other signs and symptoms of hepatotoxicity with an ED50 of 200 mg/day and

(c) the databases for both incidence–response relationships (efficiency and toxicity) were of equal strength and validity, then the risk manager *may* select the cell which allows only a 1 in 100,000 risk of the deficiency but a 1 in 100 risk of enzyme changes.

This selection would correspond to a range of 1.89*A*–0.37*B*, which equals ((1.89 × 1)–(0.37 × 200) mg/day), or (1.89–74 mg/day), or rounding the results the optimum range would be set at 2–75 mg/day.

these circumstances each curve would need to be analysed separately and a suitable range of values provided, as indicated in Tables 1 and 2. The most sensitive effects (the benefit curve that is at the highest intakes and the toxicity curve that is at the lowest intakes) may not always be the most important for risk assessment because of the weighting given to different effects when the risk manager selects an acceptable incidence for each effect. For example, the risk manager may accept only a 1 in 10,000 incidence of a serious toxic effect, and the resulting intake value may be lower than that for a 1 in 100 incidence of a less serious effect that occurred at lower doses.

Obviously the type of advice given in Table 2 requires sophisticated understanding over a wide range of expertise for successful implementation. A clear, comprehensive and comprehensible descriptive narrative on the strengths and weakness of the data for the consequences of both deficiency (or lack of benefit) and toxicity will be essential. Selection of the most suitable cell from Table 2 (or from a matrix developed using compound-specific CV values) will probably involve scientific, clinical and societal judgements, and will require extensive discussions between risk assessors and risk managers.

6. Conclusions

It is clear from the analyses presented above that the method is responsive to both the position of the intake–response relationships and to the extent of variability within the population. In addition the approach combines benefit and adverse effect data to define a range of "acceptable" intakes. One consequence of the model is that a simple numerical change in the position of one intake–response curve, for example a 3-fold reduction in the ED50 for toxicity due to the application of an uncertainty factor, does not produce an equivalent 3-fold change in the optimum balance between benefit and risk. A further advantage of the model is that the incidence of the deficiency effect (i.e. that effect used for intake–incidence modelling) can be estimated for intakes below the lower end of the recommended range. Similarly the incidence of the adverse effect, which was used to determine the ED50 for toxicity, can be estimated for intakes that exceed the upper end of the recommended range.

Application of the mathematical model allows scientific judgement to inform the derivation of the optimum range of intakes of a nutrient. It should be recognised however, as with all mathematical models, that the precision of the resulting estimate is dependent on the precision of the data that enter into the analysis; in this particular case the intake–response data for the beneficial and adverse effects. The approach does not resolve problems associated with inadequate data, as described above in relation to the establishment of a UL using the traditional approach.

The main problem with the implementation of the approach will not be derivation of suitable defaults for the likely variability within the human population, but rather how to weight and move the intake–response relationships in relation to the adequacy of the database.

Application of the model will require a closer integration of risk assessment and risk management than is usual, because the output of the approach is not a simple point estimate but is essentially a continuum, along which a decision has to be made based on scientific, medical and societal judgements.

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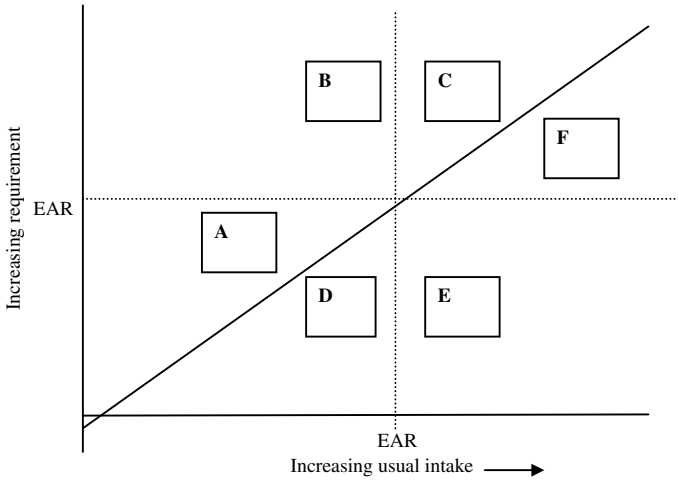
Appendix A. Illustration of the EAR cut-point method of estimating prevalence of inadequacy of nutrient intake in a population



When usual intake vs. requirement for individuals in a population is plotted (a joint distribution plot) those individuals with co-ordinates on the 45-degree line have usual intakes that equal their individual requirements. Those above the 45-degree line (in areas *A*, *B* and *C*) have usual intakes less than their individual requirements (i.e. have inadequate intakes) and those below the 45-degree line (in areas *D*, *E* and *F*) have usual intakes that are greater than their individual requirements (i.e. have adequate intakes).

Individuals in area *D* have usual intakes <EAR but greater than their own individual requirements (i.e. have adequate intake) while individuals in area *C* have intakes >EAR but less than their individual requirements. Under certain conditions (see below) the number of individuals in area *C* approximates the number in area *D*. Thus, $A + B + D = A + B + C$ = number of individuals with intakes <EAR. Thus, the prevalence of inadequate intakes in a population (i.e. the proportion of individuals with intakes <EAR) can be estimated if the distribution of usual intakes is known (e.g. from a food consumption survey).

The conditions under which this approximation is reliable are:

1. usual intakes are independent of requirements (true for micronutrients);
2. distribution of requirements is symmetric (not necessarily normal) (assumed to be true for all micronutrients except iron in menstruating women);
3. variance of distribution of requirements is small relative to variance in usual intakes (observed CV of usual intakes is generally greater than the assumed CV of 10–15% for requirement (O'Brien et al., 2001)).

Appendix B. Dietary reference standards for nutrient adequacy and excess—similarities and differences

Nutrient adequacy	Nutrient excess
RDA = estimate of the upper end of the distribution of requirements for a specific function in a population group	UL = estimate of an intake that would not produce a specific adverse effect in a population group
Generally the distribution of requirements is not known	Generally the distribution of sensitivity within the population is not known
Midpoint of the range (EAR) estimated from the observed data on dose–response	Indication of lower end of the range (NOAEL or LOAEL) obtained from the observed data on dose–response
Upper end of the range (RDA) estimated assuming a normal distribution with a CV of 10–15%: RDA = EAR + 2 SD = EAR × 1.2 or 1.3	Lower end of the range (UL) estimated by application of an uncertainty factor (UF): UL = NOAEL/UF
RDA protects about 97–98% of the general population—almost all	UL is considered to protect essentially 100% of the general population
RDA does not protect individuals with requirements more than 2 SD greater than the EAR—excludes 2–3% of the general population	UL is considered to protect the most sensitive individuals in the general population
RDA does not apply to individuals receiving the nutrient under medical supervision or to individuals with predisposing conditions that increase requirements for the nutrient, e.g. those with genetic predisposition or certain metabolic disorders or disease states	UL does not apply to individuals receiving the nutrient under medical supervision or to individuals with predisposing conditions which render them especially sensitive to one or more adverse effects of the nutrient, e.g. those with genetic predisposition or certain metabolic disorders or disease states
RDA derived for nutrient intake (not absorbed nutrient) and thus includes an assumption of bioavailability	UL derived for nutrient intake (not absorbed nutrient) and thus includes an assumption of bioavailability
RDA cannot be used to estimate prevalence of nutrient inadequacy in a population	UL cannot be used to estimate prevalence of nutrient excess in a population
EAR used as a cut-point to estimate the proportion of the population with inadequate intake: Prevalence of inadequacy = (%<EAR)	UL is a point estimate of intake above which individuals will be at some (unquantified) risk of receiving a potentially toxic intake

Appendix C. Conversion of data from a normal to log normal distribution

Conversion of a normal coefficient of variation (CV) into a log geometric standard deviation (log GSD) requires the calculation of sigma, in order to convert the normal CV onto a log scale.

$$\text{sigma} = (\ln(\text{CV}^2 + 1)^{0.5}$$

$$\text{GSD} = e^{\text{sigma}}$$

The log-normal distribution can be analysed in Excel by the statistical function NORMSINV followed by the fraction of the population under consideration.

For example, if the data related to a 10% incidence, then NORMSINV of 0.1 is −1.2816, whereas if the value corresponded to 5% of the population NORMSINV of 0.05 would be −1.6449.

% of distribution	NORMSINV
5	−1.6449
10	−1.2816
20	−0.8416
30	−0.5244
40	−0.2533
50	0.0000
60	0.2533
70	0.5244
80	0.8416
90	1.2816
99	2.3263

The log of the dose adjustment necessary to move from the nth percentile (e.g. the 10th percentile) to the median value is derived by multiplying the log GSD by the NORMSINV value for that percentile (e.g. −1.2816). The ratio of the *n*th percentile to the median (for which NORMSINV = 0) is given by 10 raised to the power of the product of log GSD and NORMSINV for that percentile.

$$\text{Ratio of doses at median and } n\text{th percentile} = 10^{(\text{logGSD} \times \text{NORMSINV})}$$

For example, if a dose of 100 mg were to produce a response in 10% of the population and the coefficient of variation was assumed to be 36%, then

$$\text{sigma} = (\ln(0.36^2 + 1))^{0.5} = 0.34909$$

The GSD is the exponent of this, which is 1.41778, and the log of the GSD is 0.15161.

The NORMSINV value for 10% (or a fraction of 0.1) is −1.2816 and the product of the log GSD $(0.15161) \times -1.2816 = -0.19430$.

The antilog of -0.19430 is $10^{-0.19430} = 0.6393$

In consequence the dose at the median of the population would be the dose administered to the 10th percentile, e.g. 100 mg ÷ 0.6939 = 156.4 mg. The mathematical model would therefore be based around an ED50 of 156.4 and a coefficient of variation of 36%.

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