Eur J Nutr (2008) 47:17–25
DOI 10.1007/s00394-007-0691-6

ORIGINAL CONTRIBUTION

Andrew G. Renwick
Lars O. Dragsted
Reg J. Fletcher
Albert Flynn
John M. Scott
Sandra Tuijtelaars

Minimising the population risk of micronutrient deficiency and over-consumption: a new approach using selenium as an example

Received: 25 July 2007
Accepted: 30 November 2007
Published online: 14 January 2008

A.G. Renwick
School of Medicine
University of Southampton
SO16 7PX Southampton, UK

L.O. Dragsted
Institute of Human Nutrition
Faculty of Life Sciences
University of Copenhagen
Frederiksberg, Denmark

R.J. Fletcher
Kellogg's Company of Great Britain Ltd.
Swords (Co. Dublin), Ireland

A. Flynn
Department of Food and Nutritional Sciences
University College Cork
Cork, Ireland

J.M. Scott
School of Biochemistry and Immunology
Trinity College
Dublin, Ireland

S. Tuijtelaars, MSc
International Dairy Federation (IDF)
Brussels, Belgium

Abstract *Background* At the present time the recommended daily intake or allowance (RDA) and the safe upper level (UL) of intake of micronutrients are given as single values. The recommended daily intake is considered to cover the requirements of 97.5% of the population while the safe upper level is a value for the whole population. These values provide only limited guidance to risk managers. *Aim of the study and methods* A method has been developed recently which models the relationships between intake and risks of either deficiency or excess using an observed incidence for each effect and population distribution characteristics. Using this model it is possible to formulate advice to risk managers on the incidence (prevalence) of adverse effects, due to either deficiency or excess, at different levels of intake. Application of the model to the data used to derive the RDA and UL for selenium shows that it can predict the impact of changes in nutrient intake on the balance between benefit (absence of deficiency) and risk (development of toxicity). *Results and conclusions* Application of the model has illustrated the utility of this approach, but highlighted the need for a comprehensive evaluation of the data and a critical appraisal of the validity of the relationships that are analyzed. In addition, the derived incidences will usually relate to effects with different biological or health impacts, so that the final balance between benefit and risk should be developed by a dialogue between the risk assessor and the risk manager.

T. Wildemann (✉)
ILSI Europe a.i.s.b.l
83 Av. E. Mounier, Box 6
1200 Brussels, Belgium
Tel.: +32-2/771-0014
Fax: +32-2/762-0044
E-Mail: publications@ilsieurope.be

Key words risk-benefit analysis – micronutrients – selenium – recommended daily allowance – upper intake level – population-based analysis

Introduction

Vitamins and minerals are essential for normal growth and health, and because they are present at low concentrations in the diet they are known as micronutrients. For the risk manager, estimating the optimal intake of a micronutrient in a given population is problematic, because different individuals have different requirements and intakes for any given nutrient as well as differences in susceptibility to adverse effects at very high intakes. Few objective tools exist to help the risk manager balance the risk of

deficiency in some individuals, with the risk of overconsumption in others in the same population. Part of the problem has been that nutritionists have historically focused on preventing dietary deficiencies, requiring a particular set of clinical and statistical approaches; the main reference point for nutritional deficiency being the concept of the recommended daily intake or allowance (RDA). In contrast, the study of adverse effects at high intakes has been the province of toxicology, which has developed different tools and principles in order to set a tolerable upper intake level (UL), an intake that should avoid adverse effects. The main problem with the UL is that it provides risk managers with no indication of the magnitude of any adverse health impact when the intake exceeds the UL due to excessive intake from foods or food supplements. In addition, it is not possible to set a UL for some nutrients, such as sodium because there is a continuum of increasing risk with increasing intake over the normal range of intakes from foods.

This paper describes a new approach to the estimation of optimal intakes, which uses both of the above reference points to calculate a directly comparable measure of risk for both deficiency and over consumption. The detailed statistical methods have been previously reported [9]. This paper sets out to illustrate the approach using selenium as a case study.

Traditional methods for setting the recommended daily intake or allowance and the safe upper level

The amount of a micronutrient necessary for normal health varies slightly from person to person because of their different individual physiological and metabolic status. Thus some individuals may require low intakes for normal health, while others need higher intakes. This is taken into account in the recommended dietary allowances, which are established to cover the needs of 97.5% of the population. This is illustrated in Fig. 1.

The normal distribution given in Fig. 1 can also be plotted as a cumulative distribution, in which the total proportion of the population covered by any level of intake is plotted against the intake level. Figure 2 shows the cumulative distribution as the proportion of the population NOT covered by a particular level of intake, i.e. as the intake increases so a smaller and smaller proportion of the total population does not have their requirements met.

Micronutrients in the diet are consumed in small amounts, but it is possible to make preparations, such as tablets, capsules and drops, which contain vastly more than the recommended dietary allowance. When such preparations are consumed the risk to health changes; there is negligible likelihood of deficiency, but an increased risk of toxicity. Recommendations on micronutrient intake include advice on both the recommended dietary allowance and the maximum intake that can be taken without significant risk of toxicity.

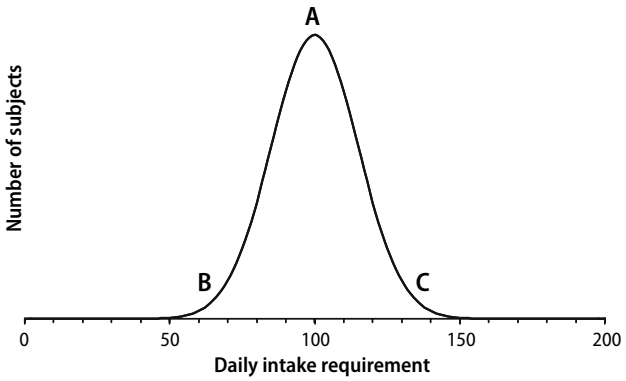

Fig. 1 The distribution of intake requirements of a micronutrient necessary for normal health. The *X*-axis shows the different requirement levels and the *Y*-axis shows the numbers of subjects with that level of requirement. Most individuals have a requirement at or close to the average (Point *A*, set at 100 in this theoretical example), and there are very few individuals with very low requirements (Point *B*) or very high requirements (Point *C*). In consequence, the numbers of subjects at low and high levels tail off to give the shape shown which is known as a normal or Gaussian distribution. The variation between individuals, which is described as the CoV, has been set at 15% in this figure

Traditionally, safe upper levels have been determined from analysis of data on the levels of intakes

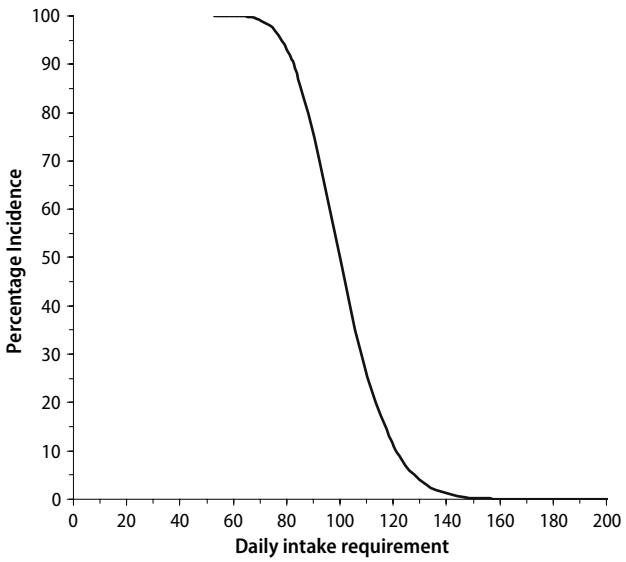

Fig. 2 The cumulative distribution of intake requirements of a micronutrient necessary for normal health. The *X*-axis shows the different daily intake requirement levels and the *Y*-axis shows the cumulative proportion of the population with a requirement greater than that level of intake. In this example, essentially 100% of the population requires more than 50 units, while the needs of essentially the whole population are met by an intake of 150 units

that cause toxicity, with the lowest dose causing toxicity divided by a suitable safety factor. Using the example illustrated in Fig. 3a, a safe upper level of 200 or 500 units might have been set based on findings that 10% of subjects showed a mild adverse effect at an intake of 5,000 units and that none of a group showed effects when given 2,000 units/day with the application of an uncertainty factor of 10. Such incidence data may be converted to a distribution curve if the extent of human variability is known or can be predicted (Fig. 3b).

The population distribution model

Thus there are two curves that need to be considered for essential nutrients, i.e. that related to the risk of insufficiency (Fig. 2) and that related to the risk of toxicity at high intakes (Fig. 3b). This is shown in Fig. 4, which for the example chosen shows a clear separation between the decreasing risk of deficiency and increasing risk of toxicity as the daily intake increases, and it would be a relatively simple matter to set a recommended dietary allowance and a safe upper level [9].

More sensitive indicators of deficiency and considerations of health benefits above the recommended daily allowance will have the effect of moving the benefit curve to the right. In contrast, more sensitive indicators of toxicity will move that curve to the left. In consequence, the separation between the two intake-response curves (Fig. 4b) may become narrower in the future. Under these circumstances the curves may not allow easy definition of a range of intake that is both beneficial and safe (Fig. 5a). Under these circumstances it would be helpful to be able to advise risk managers on the predicted incidences of both an absence of benefit and at the same time the risk of toxicity for specific levels of daily intake (Fig. 5b). For example the predicted incidences of a lack of benefit and of toxicity are about 50 and 0.0008% at a daily intake of 100 units but 0.00015 and 0.07% at a daily intake of 200 units.

A major advantage of this approach is that risk managers can be informed of the change in predicted incidences with change in intake and also the nature of the adverse effect that was modelled to produce the graphs, i.e. the consequences of an inadequate intake (lack of benefit) and of toxicity. Such information will provide a secure basis for the formulation of dietary advice, the consequences of fortification and the influence of different amounts in supplements.

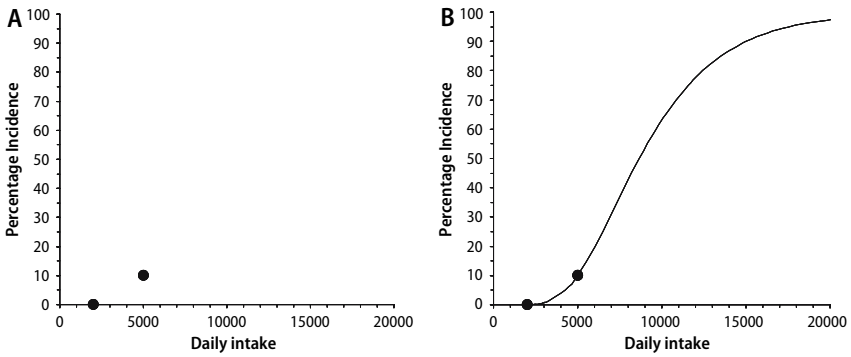

Fig. 3 The setting of a safe upper intake level for a micronutrient. In the example given there are data showing that 10% of subjects show an adverse effect, or potentially adverse change, at a daily intake of 5,000 units, and that no adverse response was found in a group given 2,000 units per day (Graph **A**). Such data can be converted into a distribution curve (Graph **B**) if the CoV for inter-individual variability in susceptibility to the effect is either known or is assumed. The graph shown on the right assumes a CoV of 45%

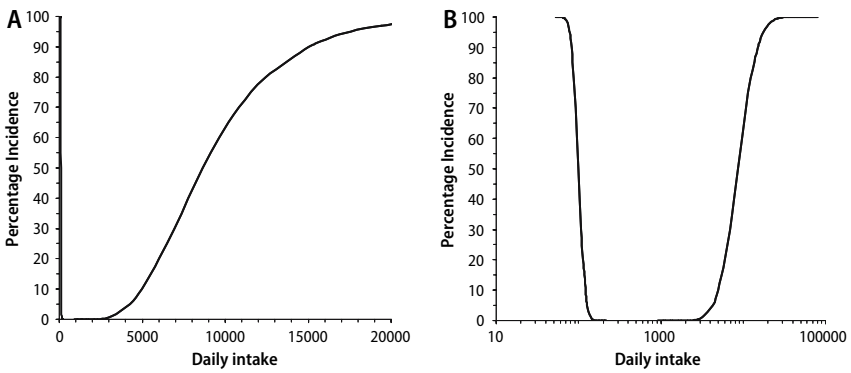

Fig. 4 The relationships between daily intake and the risk at very low intake (the absence of the essential benefit) or high very intake (the risk of toxicity). Using a linear scale (Graph **A**) the curve for the risk of absence of benefit (Fig. 2) is very close to and barely separated from the *Y*-axis and most of the graph only represents clearly the curve for toxicity (Fig. 3b). This can be avoided if the daily intake axis is given on a logarithmic scale (Graph **B**)

Application and data requirements of the population distribution model

The model requires only limited data, since it plots the change in incidence of a defined effect against intake, rather than the change in severity of an effect as the intake changes. The only information necessary is

(1) the intake causing the defined biomarker of a beneficial effect, such as a 20% change in an enzyme activity,
(2) the intake causing the defined adverse effect, such as an adverse effect on liver function,
(3) the coefficient of variation (CoV) for the change in beneficial effect with intake and
(4) the CoV for the change in adverse effect with intake.

There is a history of use of a CoV of 15% for essentiality when the RDA is established (see above), while a CoV of 45% was proposed for toxicity by Renwick et al. [9] based on a meta-analysis of human pharmaceutical data. The rationale is explained in more detail in Renwick et al. [9], but in essence assumes that supra-nutritional intakes will be handled by non-specific elimination pathways; the choice of a higher CoV for adverse effects than for benefits has the advantage of making the model more conservative in relation to the prevention of possible adverse effects.

Risk:benefit analysis for selenium as a worked example

The following text describes the basic input information, the intake-incidence modelling, and the format of advice that could be provided to the risk-manager. To allow comparisons with the traditional approaches, the data used for modelling are those that were used to establish the RA and the UL in the IOM evaluation; the impact of recent findings and other data on the application of the model are discussed later.

Selenium was selected for analysis of the utility of the model, since the database illustrates both the advantages and limitations of the model.

Essentiality and benefit

Frank deficiency of selenium is associated with Keshan disease, which is a form of cardiac myopathy. The minimum intakes necessary to prevent this condition have not been defined, and therefore this effect cannot be used either to set an RDA or for mathematical modelling. The requirement and recommended intakes are not based on prevention of this adverse effect but on the optimization of plasma glutathione peroxidase—a selenium-dependent enzyme.

There have been two studies that have provided useful and largely comparable data on plasma glutathione peroxidase.

A study of the effects on plasma glutathione peroxidase of supplements from 0 to 90 μg/day given for 8 months to Chinese adult men, aged 18–42 years, reported that similar enzyme activities were found after administration of supplements of 30, 60 and 90 μg/day given as selenomethionine [15]. In consequence, 30 μg/day was chosen as the minimum average requirement from this study. After allowing for the intake of 11 μg/day from the diet and the difference in body weight between Chinese and North American males, the Food and Nutrition Board of the Institute of Medicine in the USA [6] calculated that this was equivalent to 52 μg/day. It should be noted that this value was based on small groups of men (8–9) with a restricted age range.

The second study was performed in New Zealand and involved mixed groups of about ten men and women (aged 17–59 years) administered supplements over the range 0–40 μg/day given as selenomethionine for 20 weeks [5]. Analysis of the study data by the IOM [6] concluded that plasma glutathione peroxidase activity was increased by supplementation in the

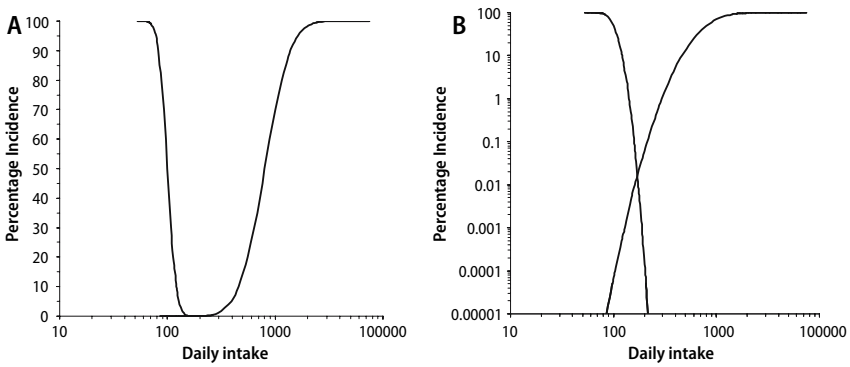

Fig. 5 The relationships between daily intake and the risk at very low intake (the absence of the essential benefit) or high very intake (the risk of toxicity) for a micronutrient for which toxicity occurs at intakes only slightly above those producing the benefit (from Fig. 2). Advice to risk managers could take the form of a description of the narrow range of beneficial and safe intakes (from graph **A**) or an estimate of the risks associated with different intakes (from graph **B**)

range 10–40 μg/day, but that there was no difference between doses. In consequence, and after allowing for dietary intake of 28 μg/day, an estimated average requirement was derived at 38 μg/day based on the lowest dose given.

The IOM [6] derived an average requirement from these two studies of 45 μg per day based on this biochemical effect. Although the database refers to experiments with selenomethionine no differentiation between selenium species is made for the average requirement.

Adverse effects at high intakes

The data most useful for relating high intakes to adverse effects comes from four studies by Yang and colleagues [13, 14, 16] in China and by Longnecker et al. [8] in the USA.

The studies by Yang et al. [13, 14, 16] built on an early publication [12] in which a 50% incidence of hair and nail loss and mottling of teeth was noted in a population of 248 subjects from the five most heavily affected villages with daily intakes in the range of 3,200–6,690 μg. Subsequent studies focused on the lowest intakes associated with adverse effects. Yang et al. [16] correlated biomarkers of selenium exposure with estimates of dietary intakes.

The subsequent study [13] related the presence of adverse effects to biomarkers of exposure, particularly whole blood selenium concentrations. The distribution of selenosis in 349 adults indicated that the first case diagnosed had a blood selenium concentration of 1.02 mg/l. Prolonged clinical symptoms were found in five subjects who had blood concentration of 1.05 to 1.85 mg/l. No clinical signs of selenosis were reported in those with blood concentrations below 1.0 mg/l; a 3–7% incidence of severe clinical effects was noted at higher blood concentrations, but without a clear concentration–response relationship.

A subsequent study [14] on the five subjects with the persistent clinical symptoms showed that these were lost when the dietary intake was decreased to about 800 μg/day.

The study by Longnecker et al. [8] compared the health status of 142 subjects in two cohorts with different dietary selenium intakes. There were no significant signs or symptoms in relation to selenium intake and the authors concluded that there was no evidence of toxicity from selenium in subjects whose intakes were up to 724 μg/day.

Finally, the cancer prevention study by Clark et al. [2] found no evidence of selenium toxicity in the group of 653 subjects given 200 μg/day as a supplement. A slightly higher number of treated subjects (21 subjects) complained of gastrointestinal upset compared with the placebo group (14 subjects), but this was not considered to be a significant treatment-related difference.

The IOM in the USA [6] set a tolerable upper intake level for selenium of 400 μg/day for adults. No differentiation was made between different selenium species.

Modelling of the data

Essentiality and benefit

The estimated average requirement from the studies on plasma glutathione peroxidase activity was approximately 45 μg per day, and this value can be used as an estimate of the ED50 for this effect (i.e. the dose or intake giving a 50% response). The CoV has not been defined for this effect and the proposed default value of 15% has been assumed. The graphical representation of the modelled incidence distributions is given in Fig. 6.

Adverse effects

Although there is an extensive database on adverse effects in humans, it is difficult to convert the data into incidences associated with specific intakes. Part of the difficulty arises from the nature of the intake estimations, which are ranges arising from dietary intake, and partly from the focus of studies on small numbers of individuals with adverse effects.

It can be concluded that the intake–response relationship should encompass the following points

(1) an incidence of <1 in 653 (<0.15%) for any effect at a supplemental intake of 200 μg/day [2]

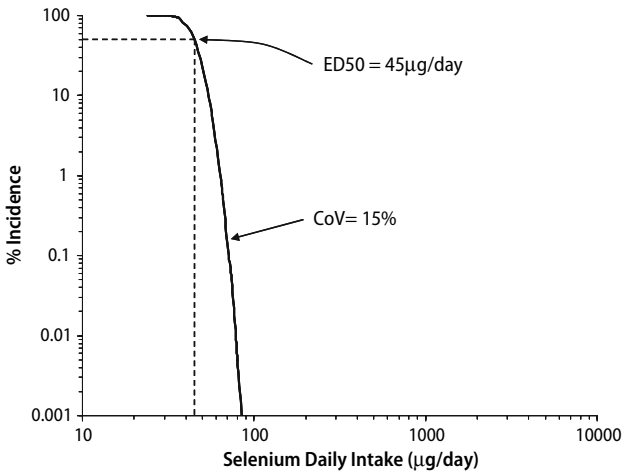

Fig. 6 Population distribution for the absence of benefit (optimization of glutathione peroxidase) for different levels of selenium intake

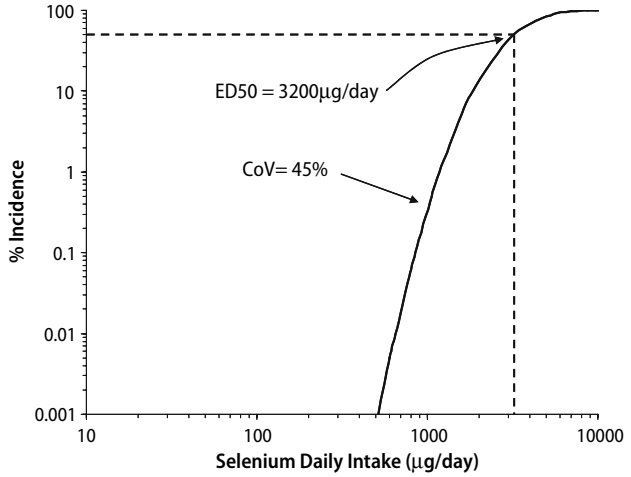

Fig. 7 Population distributions for frank selenosis associated with high levels of selenium intake

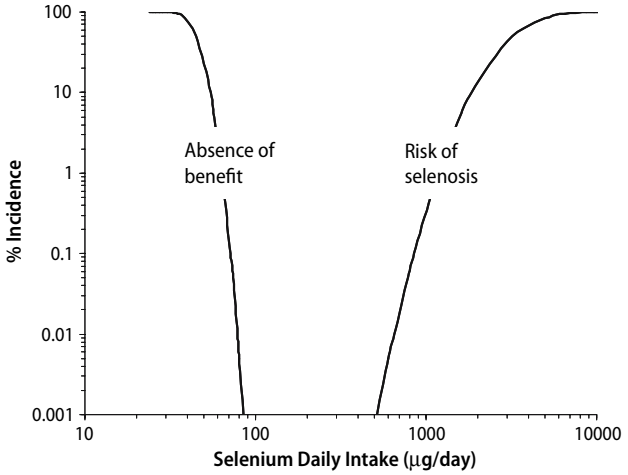

Fig. 8 Population distribution modelling of the data that were used as the basis of setting the RDA and the UL for selenium

(2) an incidence of <1 in 142 (<0.7%) based on no significant signs or symptoms in 142 subjects whose intakes were up to 724 µg/day [8]
(3) an incidence of 1 in 248 (0.4%) for signs and symptoms of selenosis at 910 µg/day [13, 16]
(4) an incidence of 50% for hair and nail loss and mottling of teeth at 3,200 µg/day [12].

It should be recognized that these values are conservative as they represent the lower end of the intake ranges for each group showing these characteristics. The CoV has not been defined for any of these effects and a default value of 45% as proposed by Renwick et al. [9] has been used. Modelling an ED50 of 3,200 µg/day for frank selenosis yields the intake incidence relationship shown in Fig. 7.

The modelled incidences are in excellent agreement with the reported data for all intake levels. The model predicts that the incidence at 910 µg/day would be about 0.16%, which is very close to observed incidence. The incidences at the intakes in the studies by Longnecker et al. [8] (724 µg/day) and Clark et al. [2] (200 µg/day) would be too low to detect in the group sizes studied. The model is consistent with the loss of symptoms in the five subjects when their intake decreased to 800 µg/day.

The overall risk:benefit balance for the effects that have been used as the basis of setting the RDA and the UL is illustrated in Fig. 8. It is clear from this that there is a reasonable range of intakes, from about 90 to 500 µg/day, that would give a very low (<0.001%) incidence of either inadequate intake or selenosis.

Such a graphical presentation of the information from the model would be difficult for a risk manager to use. The paper of Renwick et al. [9] proposed the development of tabulated incidence data and this is discussed further below, after a consideration of less well substantiated findings.

Other possible beneficial and adverse effects of selenium that were not used as a basis for the RDA or UL

The less substantiated effects for both benefit (possible anti-cancer effect) and toxicity (change in prothrombin) for selenium have been modelled in order to show the utility of the population distribution method when more sensitive biomarkers, or other data, result in a considerable narrowing of the apparent range of adequate and safe intakes, and more difficult risk management decisions. Modelling of these data should not be taken as support by the authors for the validity of the data used, or that the findings represent cause and effect relationships.

A potential anti-cancer effect of selenium supplementation was reported in a study on 1,312 patients with a history of basal or squamous cell skin cancer, who received either placebo or 200 µg/day for a period of up to 10.3 years [2]. Treatment did not decrease the incidence of these skin cancers but was associated with significant reduction in total cancers, total carcinomas and lung cancer (the validity of this observation is discussed below under advice to risk managers). The risk ratios for these secondary endpoints were about 0.5 in the treatment group and the incidences of total cancers were 29/653 in the treatment group and 57/659 in the control group. Therefore these data could be claimed as showing an additional benefit at about 200 µg/day (the dietary intake was not reported). The incidence of the potential anti-cancer effect at 200 µg/day is approximately a reduction of 28 (57–29) in 650 subjects, or

4.3%. Conversion of this to a risk of lack of benefit is difficult because only about 30% of the population is likely to develop cancer during their lifetime, so that about 1.3% (4.3% of 30%) of the general population might be considered as not getting the anti-cancer benefit at the dose of 200 μg/day. Another difficulty is generalization of an effect derived from data for an approximately 10 year intervention to a lifetime intake. Ignoring this issue and converting directly the percentile reportedly experiencing a benefit into an ED50 (see appendix C of Renwick et al. [9] for details) requires an assumption about the CoV. The ED50 derived from an incidence of 1.3% at 200 μg/day equals 143 μg/day. However, the reported anti-cancer effect is controversial. Subsequent reanalyses of the data from Clark et al. [2] have not confirmed the initial findings, and there may even have been an increase in the risk of certain skin cancers [3, 4]. In contrast to the data of Clark et al. [2], recent analysis of data from a number of trials has shown an inverse association between higher blood selenium concentrations and adenoma risk [7]. Thus the current information indicates that prostate cancer may be potentially responsive to selenium whereas there is no evidence that any female-specific cancer responds beneficially to selenium. Thus the cancer risk may vary between the genders leading to a need for gender-specific modelling. A further study of selenium and diabetes risk using the Clark-cohort has indicated an adverse effect, possibly also dose-related which would need to be considered in any overview of the benefits and risk of selenium supplementation [10].

In relation to adverse effects, the study of Yang et al. [13] reported less severe effects which included a 45% incidence of prolonged prothrombin time in subjects with whole blood selenium concentrations of 1.0–1.49 mg/l, corresponding to an intake of about 850 μg/day or more and a decrease in blood glutathione at similar concentrations. The ED50 for this effect, calculated as described in appendix C of Renwick et al. [9], equals 897 μg/day.

The data for modelling of these additional effects is shown in Fig. 9. The modelling of these data clearly illustrates the problem that will be faced increasingly by risk assessors and risk managers as more sensitive effects (either beneficial or adverse) are detected. The clear overlap of the data makes the formulation of advice more difficult, as indicated below.

The impact of data on biomarkers of exposure on modelling decisions

The form of selenium that is ingested is an important issue in the interpretations of the RDA, the UL and the outputs from the proposed model in relation to human intake data. The main form used in supplements is selenomethionine, while that in the diet is mainly present in organic forms such as selenomethionine and selenocysteine. These forms of selenium have a higher bioavailability than selenite and greater effects on biomarkers such as plasma selenium, selenoproteins and glutathione peroxidase [1, 11]. Other organic and inorganic forms may have different bioavailabilities and ideally data should have been modelled for each selenium species separately. However, any information of speciation included in modelling has to be provided in the papers that are the source of the data that are modelled. The data modelled here for both beneficial and adverse effects are all for organic forms of selenium of direct relevance to normal dietary exposures. Speciation and bioavailability may be even more important for other micronutrients, and would be a critical consideration if the form used to define the beneficial or adverse effect differed from that ingested in the diet.

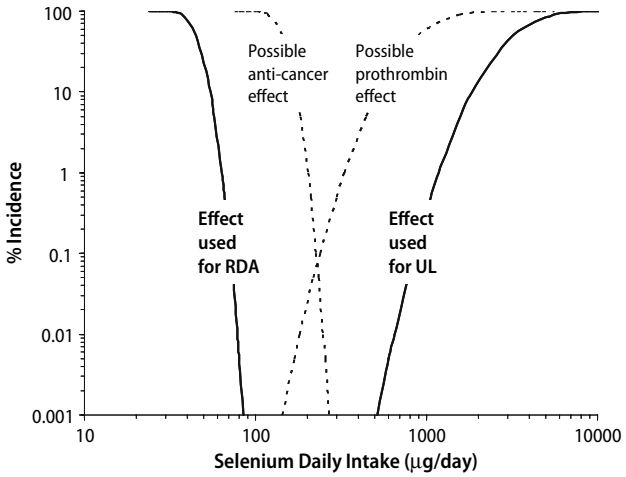

Fig. 9 Comparisons of the population distribution modelling of the data that were used to set the RDA and the UL for selenium with data for other effects. The *lines* for other effects are shown as *dotted lines* to indicate the unproven nature of the reported incidence data used for modelling

Formulation of advice for risk managers

The graphical forms are not user-friendly advice for risk mangers, and a better way to present the data would be as a table relating intakes to possible effects. In addition to the intakes and incidences, given in the table below, it would be necessary to provide the risk manager with a detailed description of the clinical data and modelling that is relevant to each endpoint.

In the example of selenium, the potential health consequences of inadequate or excessive intakes are not equivalent. The benefit relates to the optimization of an enzyme activity, and the actual health conse-

Table 1 The relationship between intakes and the reported and/or suspected adverse effects of selenium

Intake in μg/day	Percentage incidence calculated from model			
	Glutathione peroxidase deficiency	Absence of chemoprevention effect	Decreased prothrombin time	Frank selenosis
20	>99.999	>99.999	<0.0001	<0.0001
50	33.0	>99.999	<0.0001	<0.0001
100	<0.0001	99.997	<0.0001	<0.0001
200	<0.0001	26.0	0.025	<0.0001
300	<0.0001	0.04	0.54	<0.0001
400	<0.0001	<0.0001	3.00	<0.0001
500	<0.0001	<0.0001	8.7	0.0008
600	<0.0001	<0.0001	17.5	0.0049
700	<0.0001	<0.0001	28.2	0.020
800	<0.0001	<0.0001	39.5	0.062
900	<0.0001	<0.0001	50.3	0.158
1,000	<0.0001	<0.0001	60.0	0.34
1,200	<0.0001	<0.0001	75.1	1.12
1,400	<0.0001	<0.0001	85.0	2.72
1,600	<0.0001	<0.0001	91.1	5.33

quences of a sub-optimal intake are not known. In contrast the modelled adverse effect is for frank selenosis which is a serious effect affecting the quality of life of the individual.

Considering first the data in Table 1 for glutathione peroxidase and frank selenosis, risk management decisions would be relatively easy since a very low incidence of lack of benefit and of lack of toxicity would occur over the range 100–500 μg/day. For such clearly separated intake-response relationships, mathematical modelling is unlikely to be a major advantage over the setting of an RDA and UL, unless the intake data show a proportion of the population with intakes outside this range. In addition, although a clear description of the nature of each response should be provided to the risk manager, the fact that the benefit is a biochemical marker while the adverse effect is a clinical syndrome would not be of great significance, because both lack of benefit and toxicity can be avoided.

Consideration of the other reported effects for benefit and toxicity would result in a considerable overlap, with no dose level that would give a negligible absence of the benefit (cancer prevention) and absence of an effect on prothrombin time. In such circumstances, advice to risk managers should describe the strength of the evidence for causality and the consistency of the evidence. In addition, the nature and magnitude of the effect reported and its potential health impact should be defined.

In the case of selenium, the primary endpoint in the study of Clark et al. [2] was unaffected, but there appeared to be a possible beneficial effect on total cancers, total carcinomas and lung cancer. This was the response, which was taken at face value and modelled above, but the findings are controversial and the risk manager should be informed of the strength of any association that is modelled. In principle only clearly established "cause and effect" relationships should be used for modelling (or for setting the RDA or UL using the traditional approaches). Risk assessors should also provide risk managers with a critical assessment of the strengths and weaknesses of the different databases as well as the nature of the adverse effect.

Discussion

A problem with point estimates, such as the RDA or UL is that they tend to be regarded as "break points", with a dramatic change in risk as intake levels fall below the RDA or above the UL. A major advantage of the modelling of incidence data is that it removes this simplistic interpretation of the risks or lack of them. The model by Renwick et al. [9] provides a valuable additional method to compare benefits (or the risk of absence of benefit) against the risks of adverse effects at high intakes (toxicity). However, it is a quantitative method that does not remove the need for critical decisions that are essential for any risk assessment. These include considerations of

(1) causality (between exposure and effect),
(2) the nature of the effect and its health impact,
(3) the strength of any reported association,
(4) study design and adequacy,
(5) inter-species extrapolation (which is possible using this model—see [9],
(6) the applicability of the human data used in the model to the whole human population.

The main advantages of modelling the available data relate to

(1) its ability to define the incidence of deficiency effects both above and below the RDA,
(2) definition of the incidence of adverse effect at intakes both below and above the UL,
(3) interpretation of the health impact of an estimated range of intakes, for example the normal intakes of vitamin A cover a range over which there may be an increasing incidence of adverse effects on bone metabolism,
(4) interpretation of the health consequences of fortification or supplementation,
(5) prioritization of research based on the modelling of effects with poor data in order to determine if the effect could become of critical importance if subsequent studies validated the initial observations,

(6) its ability to model incidences in population subgroups, providing that suitable data are available.

With a risk:benefit comparison both the incidence of each effect and the nature and potential health impact need to be considered. The paper of Renwick et al. [9] presented a method to compare incidences only and left it to the risk assessor to explain the nature of the effects to the risk manager. A full risk:benefit analysis would also compare the nature and severity of effect using some "common currency". There is a long history of assessment of risk and benefits for medicines using methods that "score" the potential health impact of different effects and the duration of time. These numerical health scores, such as QALYs (quality of life adjusted years) could be combined with the quantitative incidences described in this paper to develop a purely numerical risk:benefit. Such mathematical analyses will appear to remove subjective judgements, but in reality expert judgement will be needed to decide which data are sufficiently credible and robust for mathematical modelling, while there is a significant subjective element to the establishment of QALYs for different effects.

Replacement of point estimates, such as the RDA and UL, in the formulation of health-related advice results in greater complexity, but offers a number of advantages. The distributional analysis proposed by Renwick et al. [9] and exemplified here with selenium represents a practical first step along the road to a full quantitative risk:benefit analysis that incorporates both the incidence and the nature of the adverse effects that would occur at different intakes.

Acknowledgments This work was commissioned by the Addition of Nutrients to Food Task Force of the European branch of the International Life Sciences Institute (ILSI Europe). Industry members of this task force are Ajinomoto, Akzo Nobel Functional Chemicals, BASF, Campina, Coca-Cola European Union Group, DSM, Friesland Foods, GlaxoSmithKline, Groupe Danone, Kellogg, Kraft Foods, Nestlé, PepsiCo International, Redbull, and Unilever. For further information about ILSI Europe, please call +3227710014 or email info@ilsieurope.be. The opinions expressed herein are those of the authors and do not necessarily represent the views of ILSI Europe.

References

1. Burk RF, Norsworthy BK, Hill KE, Motley AK, Byrne DW (2006) Effects of chemical form of selenium on plasma biomarkers in a high-dose human supplementation trial. Cancer Epidemiol Biomarkers Prev 15:804–810
2. Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Lesher JL Jr, Park HK, Sanders BB Jr, Smith CL, Taylor JR (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional prevention of cancer study group. JAMA 276:1957–1963
3. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF Jr, Slate EH, Fischbach LA, Marshall JR, Clark LC (2002) Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the nutritional prevention of cancer trial. Cancer Epidemiol Biomarkers Prev 11:630–639
4. Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA, Combs GF Jr, Park HK, Gross EG, Graham GF, Stratton MS, Marshall JR, Clark LC (2003) Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. J Natl Cancer Inst 95:1477–1481
5. Duffield AJ, Thomson CD, Hill KE, Williams S (1999) An estimation of selenium requirements for New Zealanders. Am J Clin Nutr 70:896–903
6. Institute of Medicine NAoSU (2000) Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. National Academy Press, Washington
7. Jacobs ET, Jiang R, Alberts DS, Greenberg ER, Gunter EW, Karagas MR, Lanza E, Ratnasinghe L, Reid ME, Schatzkin A, Smith-Warner SA, Wallace K, Martinez ME (2004) Selenium and colorectal adenoma: results of a pooled analysis. J Natl Cancer Inst 96:1669–1675
8. Longnecker MP, Taylor PR, Levander OA, Howe M, Veillon C, McAdam PA, Patterson KY, Holden JM, Stampfer MJ, Morris JS (1991) Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. Am J Clin Nutr 53:1288–1294
9. Renwick AG, Flynn A, Fletcher RJ, Muller DJ, Tuijtelaars S, Verhagen H (2004) Risk-benefit analysis of micronutrients. Food Chem Toxicol 42:1903–1922
10. Stranges S, Marshall JR, Natarajan R, Donahue RP, Trevisan M, Combs GF, Cappuccio FP, Ceriello A, Reid ME (2007) Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. Ann Intern Med 147:217–223
11. Xia Y, Hill KE, Byrne DW, Xu J, Burk RF (2005) Effectiveness of selenium supplements in a low-selenium area of China. Am J Clin Nutr 81:829–834
12. Yang GQ, Wang SZ, Zhou RH, Sun SZ (1983) Endemic selenium intoxication of humans in China. Am J Clin Nutr 37:872–881
13. Yang G, Yin S, Zhou R, Gu L, Yan B, Liu Y, Liu Y (1989) Studies of safe maximal daily dietary Se-intake in a seleniferous area in China. Part II: Relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine. J Trace Elem Electrolytes Health Dis 3:123–130
14. Yang G, Zhou R (1994) Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J Trace Elem Electrolytes Health Dis 8:159–165
15. Yang GQ, Zhou R, Yin S, Gu L, Yan B, Liu Y, Liu Y, Li X (1987) Human selenium requirements in China. In: Combs GF JR, Levander OA, Spallholz JE, Oldfield JE (eds) Selenium in biology and medicine. Avi, New York, pp 589–607
16. Yang G, Zhou R, Yin S, Gu L, Yan B, Liu Y, Liu Y, Li X (1989) Studies of safe maximal daily dietary selenium intake in a seleniferous area in China. I. Selenium intake and tissue selenium levels of the inhabitants. J Trace Elem Electrolytes Health Dis 3:77–87