Risk-benefit analysis of micronutrients

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Risk-benefit requires

1. A common method of dose-response assessment to describe the relationships between the intake and the beneficial and adverse responses

2. A common currency to describe the health impacts of the beneficial and adverse responses – i.e. to allow one effect to be weighed against the other (e.g. quality of life years)
The traditional approaches

Deficiency

Recommended dietary allowance

No observed adverse effect level

Toxicity

Daily intake of vitamin or mineral

How is the **Recommended Dietary Allowance (RDA)** determined?

Population distribution of requirements for a nutrient

2 standard deviations

Estimated average requirement - EAR

Recommended dietary allowance - RDA
The traditional approach to setting an upper level

Deficiency

Tolerable Upper Intake Level after allowing for uncertainties

Recommended dietary allowance

Toxicity

Daily intake of vitamin or mineral

Need to ensure that setting the upper intake level does not produce deficiency

For some micronutrients point estimates for “absolute sufficiency for all” or “absolute safety” are not realistic possibilities.

A “common method” of dose response assessment is essential for comparisons of “adequacy” and “safety”.

A simple “common method” of dose response assessment would be to model population distributions of defined magnitude of responses of benefit and adversity.
Increasing the average intake means that fewer individuals are at risk of not getting the benefit but more individuals are at risk of toxicity.

A population distribution can be used to describe the consequences of an increase in intake.

- Average intake = 120
- Average intake = 180
Choice of population distribution model

Unimodal does not allow for variation due to polymorphisms

Normal (Gaussiam) distribution

- Can give meaningless values e.g. negative requirement
- The differences above and below the mean are different e.g. if mean is 100 and SD is 40 then +2SD = 180 (1.8-fold) and -2SD = 20 (5-fold)

Lognormal distribution

- Better reflects human variability in biochemical and physiological differences.
- The fold-differences above and below the mean are the same.
- Cannot give negative values.
### Choice of population distribution model

**Polymodal**

- Can allow for variation due to polymorphisms

A polymodal model could be useful if

- The incidence of the polymorphism is defined
- The magnitude of the difference in sensitivity is defined
- The subgroup cannot be given specific advice because they cannot “self-recognise”

In application of the risk-benefit model - data on sub-groups are best analysed separately and given as specific advice to the risk manager

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A simple lognormal distribution is proposed as the default model but more appropriate models could be applied if suitable data were available

Application of a lognormal distribution model to data on either benefit or toxicity requires only limited data

The model is used to fit the change in the incidence of a predetermined level of response with change in intake and NOT the change in the magnitude of the effect with change in intake

In consequence the model can be extrapolated over a wide range without producing biologically implausible effects (e.g. a liver size that would be incompatible with life)
Define the dose-response data as *dose-incidence* data i.e. as the incidence of a pre-determined level of response at different doses.

The incidence at higher or lower intakes will depend on the coefficient of variation (CV) within the exposed group of interest - humans.

The minimum information necessary to model the data are:
- the incidence of the pre-determined response at one dose level and
- the selection of a suitable CV to represent human variability.
Most human variability is represented by a log-normal population distribution model.

The selection of the appropriate CV (coefficient of variation) is the only assumption that is required.

Species differences can be taken into account if animal data have to be used for toxicity.
Choice of CV to represent human variability

**Benefit**
There is a history of use of a CV of 15% by the SCF and of 10% by the IOM to convert the EAR into an RDA.

This is based on nutritional considerations such as variations in energy requirements and metabolic rates.

**Toxicity**
Occurs at high intakes which may saturate homeostasis and normal physiological and nutritional processes and the nutrient may be metabolised and excreted like a foreign compound.

Data on human variability in drug kinetics and dynamics indicate a suitable default would be a CV of about 45%.

The model compares the health “risk” due to the absence of a benefit with the risk due to the presence of toxicity.
- The model can define the **optimum intake** if the 2 effects are of similar severity - BUT
- The nature of the benefit and toxicity may be very different.
The acceptability of any particular balance of the risks of lack of benefit and presence of toxicity is a risk management decision

Defining only the optimum is not practical advice

Advice to risk managers should describe the calculated risks at different intakes

Advice to risk managers should describe the nature of the “risks”

Advice to risk managers can be based on a generic tabulation if the generic default CVs are used for benefit and toxicity

Specific modelling and a specific tabulation would be needed if nutrient-specific CVs are used

### Simplified Table of Incidence of Deficiency and Toxicity

<table>
<thead>
<tr>
<th>Incidence of deficiency or absence of benefit</th>
<th>1:10</th>
<th>1:100</th>
<th>1:10³</th>
<th>1:10⁵</th>
<th>1:10⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - is the ED50 for the benefit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B - is the ED50 for the toxicity</td>
<td>1.21A - 0.58B</td>
<td>1.21A - 0.37B</td>
<td>1.21A - 0.27B</td>
<td>1.21A - 0.16B</td>
<td>1.21A - 0.13B</td>
</tr>
<tr>
<td></td>
<td>1.41A - 0.58B</td>
<td>1.41A - 0.37B</td>
<td>1.41A - 0.27B</td>
<td>1.41A - 0.16B</td>
<td>1.41A - 0.13B</td>
</tr>
<tr>
<td></td>
<td>1.59A - 0.58B</td>
<td>1.59A - 0.37B</td>
<td>1.59A - 0.27B</td>
<td>1.59A - 0.16B</td>
<td>1.59A - 0.13B</td>
</tr>
<tr>
<td></td>
<td>1.89A - 0.58B</td>
<td>1.89A - 0.37B</td>
<td>1.89A - 0.27B</td>
<td>1.89A - 0.16B</td>
<td>1.89A - 0.13B</td>
</tr>
<tr>
<td></td>
<td>2.03A - 0.58B</td>
<td>2.03A - 0.37B</td>
<td>2.03A - 0.27B</td>
<td>2.03A - 0.16B</td>
<td>2.03A - 0.13B</td>
</tr>
</tbody>
</table>

Notes
A – is the ED50 for the benefit
B – is the ED50 for the toxicity
CVs of 15% and 45% are used to define the slopes for benefit and toxicity
Application of the approach

The approach does NOT solve issues of database inadequacies but rather adds to the problem by requiring incidence data from which to derive the ED50 in order to apply the model.

The approach does NOT compare benefits and risks using a common currency.

CONCLUSIONS

There is no a priori reason to expect that high intakes of micronutrients will be any more safe than high intakes of other food chemicals

The database available on micronutrients often contains extensive data from human studies but these rarely address the potential for toxicity; the animal and human studies usually do not meet the quality standards for risk assessment

The human database may identify adverse effects but rarely defines the incidence at a given intake

The risk benefit model does not take into account the severity of the adverse health effects due to a lack of benefit or toxicity

The risk benefit model is a practical method but does not resolve risk assessment issues that require expert judgement
Uncertainties, such as species differences, can be allowed for by adjusting the ED50 – equivalent to an uncertainty factor.

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Extrapolation

1. Select GSD
2. Determine NORMSINV for %ile
3. Multiply log GSD*NORMSINV
4. Antilog product for dose ratio to ED50

**In example** - 61mg gives 10% incidence

1. CV = 40% : GSD = 1.47
2. NORMSINV for 10% = -1.286
3. Log GSD*1.286 = -0.2144
4. Antilog = 0.610
5. ED50 = 61mg/0.61 = 100mg