Australian Government
Department of Health

MINISTRY OF HEALTH
MANATŪ HAUORA

General principles for establishing safe upper levels of intake for micronutrients – Issues for consideration

A supporting reference document to the methodological framework for the review of Nutrient Reference Values

Contents

Preface

Nutrient Reference Values (NRVs) are a set of recommendations for nutritional intake for individuals and/or population groups based on current available scientific knowledge. Recommendations are used to assess the health status of populations and individuals, advise individuals, and provide a fundamental evidence base for development of health policy.

In 2002, the Department of Health and Ageing (DoHA), in conjunction with the New Zealand Ministry of Health (NZ MoH), commissioned the National Health and Medical Research Council (NHMRC) to review the existing Recommended Dietary Intakes (the only type of nutrient reference values that had been produced at the time). The review resulted in a new set of recommendations known as the *Nutrient Reference Values for Australia and New Zealand (2006)*. To ensure values remain relevant, appropriate and useful, NHMRC recommended that NRVs be reviewed every five years.

As a result, in 2011 DoHA, in consultation with the NZ MoH, commissioned a scoping study to determine the validity of, and scope for, undertaking a review of NRVs. Stakeholders consulted during the study argued that a consistent methodology and approach is needed to increase confidence in the recommendations of subsequent reviews. A key finding from the study was that a future review provides the opportunity to improve the rigour of the nutrient review process through:

- greater transparency in the decision making process including clear justification for inclusion of experts and determination of nutrient values
- clear documentation of all underlying decisions, evidence, assumptions and rounding processes
- development of robust methodologies to construct recommendations, particularly for nutrients with gaps in the data for specific population groups.

To realise these objectives, the scoping study recommended the development of a methodological framework to guide future reviews of nutrient values.

In January 2013 the Department of Health (formally DoHA), in consultation with the NZ MoH, engaged Nous and a consortium of experts (led by Professor Peter Clifton, and including Dr Andrew Bartholomaeus, Professor Caryl Nowson, Associate Professor Jennifer Keogh, and Kylie Lange) to develop the methodological framework. The framework aims to ensure broad stakeholder support and confidence in the recommendations of subsequent nutrient reviews through inclusion of methodologies and approaches that support the objectives of consistency, transparency and efficiency.

This document was developed by Dr Andrew Bartholomaeus as a supporting reference document to the methodological framework. It aims to provide guidance to Nutrient Expert Working Groups (EWGs) appointed to review NRVs on the general principles used to develop Upper Levels of Intake (ULs) for micronutrients. It discusses the key issues for consideration in the development of ULs and different approaches to the risk assessment process.

1 Background

The risk assessment process for setting Upper Levels of Intake (ULs) for micronutrients presents a number of unique challenges which necessitate substantial modifications to the human health risk assessment (HHRA) paradigms applicable to other chemicals in food. In many respects the assessment process for micronutrients is more closely aligned to that of the risk benefit analysis applied to pharmaceuticals, which employs substance specific mechanistic data to guide the analysis and the level of precaution appropriate to the specific therapeutic context.

The traditional precautionary approach used for chemical risk assessment applies uncertainty factors (UFs) to the highest demonstrated levels not producing toxicity in experimental animals or human subjects to derive a "safe" level of exposure. If applied to pharmaceuticals or micronutrients, this approach has the potential to yield outcomes that would preclude or prevent the beneficial pharmacological or nutritional outcomes of those substances. [(1) (2)]

The impact of the establishment of ULs on food fortification efforts (3) and the lack of scientific rigour behind current ULs [(4)] has been raised in the literature. To a large extent these issues arise due to a lack of robust data from which to derive these values [(5)] and the inappropriate use of chemical risk assessment processes without adequate adaptation to the context of the HHRA.

As a result, a key consideration for Nutrient Expert Working Groups (EWGs) tasked with setting ULs for micronutrients is whether: (i) the data are sufficient to provide a basis for a scientifically credible UL; or (ii) some alternative form of guidance (e.g. a provisional UL (pUL), guidance level (GL), highest observed safe level (OSL) or observation that insufficient data exists to support a UL) is more appropriate to ensure greater transparency and recognition of the weakness of the data supporting the value. [(6)]

Where the data are considered sufficient to demonstrate a need for (and to support the establishment of) a UL, the process needs to be sufficiently robust to withstand regulatory and scientific challenge:

- For classical chemical HHRA, the endpoint of the process is a single point estimate of the maximum daily intake for which there is full confidence of safety. The implicit or explicit lower bound is zero.
- In nutritional HHRA, consideration of both an upper and a lower bound is required to ensure excessive precaution does not unnecessarily preclude public health measures such as fortification, achievement of optimal intakes across all sub-populations or legitimate development of specialist food products.
- The upper bound is the intake above which toxicity has been convincingly demonstrated in at least some individuals
- The lower bound is the intake at which no clinically significant effect, toxicity, in any healthy individual is likely
- The point estimate for a population UL, inclusive of any uncertainty factors applied, will then be within this range.

Although the regulatory issues are not directly the concern of Nutrient EWGs, the credibility of the Nutrient Reference Value (NRV) review process is undermined if regulatory and appeals bodies reject established ULs as unreliable or scientifically unsupportable[1].

The complexity of issues affecting establishment of ULs for specific nutrients means it is not possible to develop a rigid process that is suitable for every nutrient as part of the methodological framework. The

[1] [1] An excellent case study in this regard is the FSANZ assessment of the UL for fluoride as a component of Application A588 "Voluntary addition of fluoride to packaged water". [(7)] The fluoride UL was adopted by the NRV/ANZ/WG [(8)] from the FNB:IOM [(9)]

approach needs to be tailored and adjusted for each nutrient to suit: (i) the quality and quantity of available data; (ii) the nature and mechanisms of any adverse effects identified; (iii) the spread between beneficial intakes and potential adverse effects; and (iv) relevant characteristics of each sub-population for which a UL is being considered.

The following sections discuss some of the issues that need to be addressed in the development of ULs, and provides alternative approaches that might be included with (and used to modify) the classical HHRA approach[2].

[2] For discussions of the classical approach used internationally to date see reference (10) and chapter 3 of reference (9), and for some discussions on alternative approaches see reference (11) and reference (12)

2 Nature of the Dose/Intake Benefit Risk Relationship

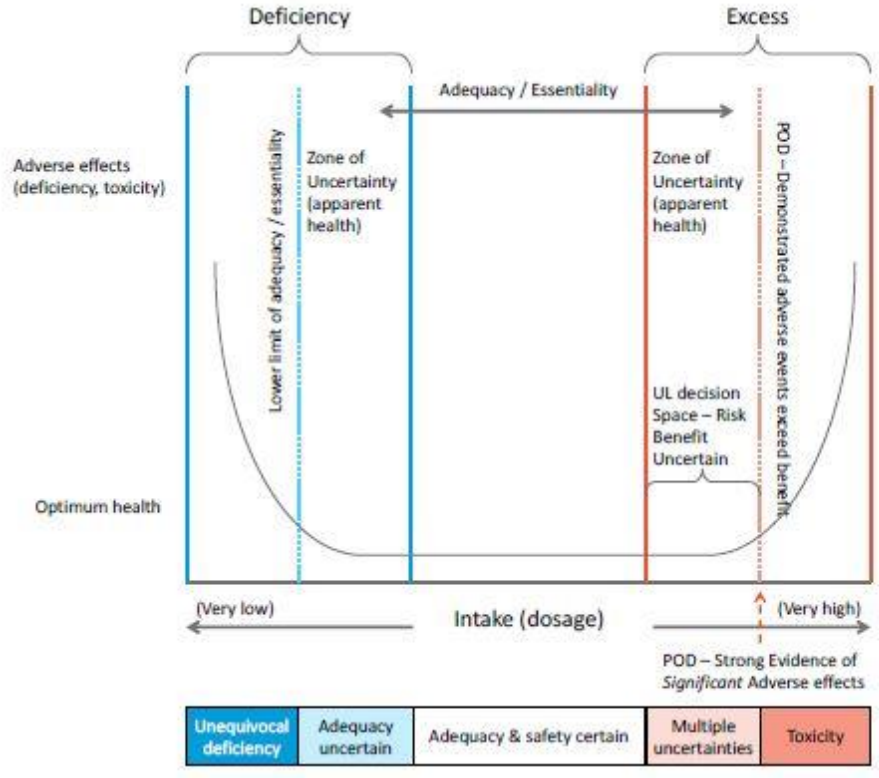
The traditional (although somewhat simplistic) view of the micronutrient benefit risk profile is a U shaped curve where dietary deficiency related disease: (i) decreases as dosage rises from inadequate levels; (ii) plateaus at levels of adequacy; and (ii) increases as intake becomes excessive (toxicity) (see Figure 1). This is an accurate conceptualisation for some specific micronutrients such as fluoride, where the beneficial and dose limiting adverse effect is the same (mild fluorosis of the tooth enamel). However the broader reality is that toxicological and nutritional mechanisms:

- are not necessarily related (termed off target effects in pharmaceutical risk assessment)
- may be different in different sub populations (e.g. pregnant women compared to the remaining population).

Additionally, the dose response curves are likely to be discontinuous with a separate dose response curve for each toxicological end point, potentially overlapping the benefit dose response curve(s) (see Figure 2).[14]

Figure 1 illustrates some important concepts in UL establishment. Since virtually all micronutrients are available as supplements which will be taken in high dosage by at least a proportion of the population, a micronutrient with potential toxicity (as opposed to more subtle sub optimal health outcomes) at realistically achievable intakes will generally have some evidence of that toxicity available in the literature (at the least as case reports). That evidence, despite various levels of uncertainty, will likely establish a level above which overt toxicity in at least some individuals is certain or at least highly probable.

Figure 1: Classical conceptual U shaped dose responsive curve for micronutrients (modified from [13])

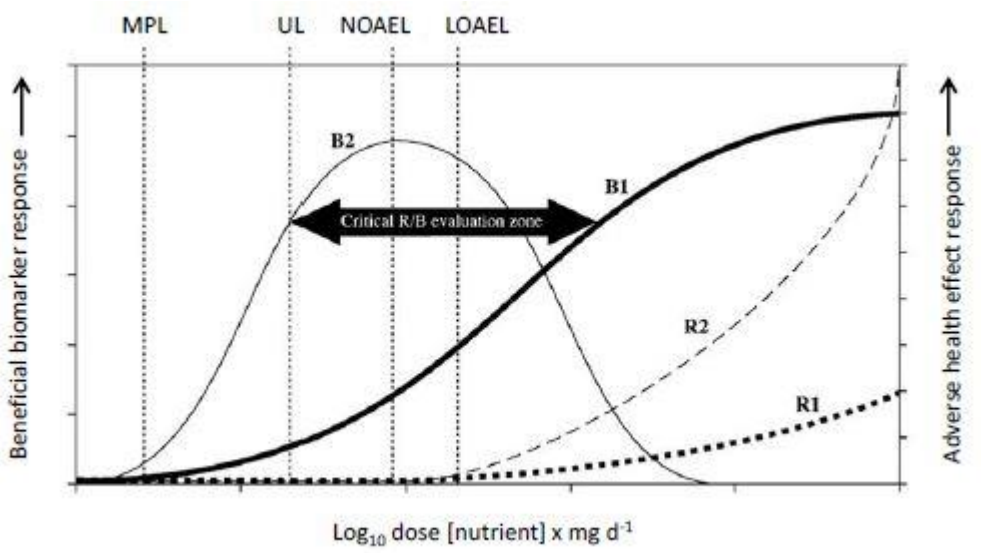


In the absence of Human studies exploring the dose response curve for that adverse effect, the slope of the curve (and in particular the threshold at which adverse effects become manifest) will be unknown.

This situation results in a grey area or "zone of uncertainty" bounded on one side by clear evidence of hazard and on the other by the upper level of known health benefit. Within this space there may be no reliable evidence of adverse outcomes despite a not insubstantial proportion of the population consuming the micronutrient at these levels (e.g. through supplements). There may also be suggestive evidence of additional health benefit and that evidence may be stronger than the evidence for adverse effects within this zone. This situation is the decision space to consider establishment of a UL.

In practice it may be more complicated as there is a potential that the dosage which gives rise to increasing benefits in some individuals may overlap with those presenting potential adverse effects in others. This is shown in Figure 2 below.

Figure 2: Conceptual model of possible dose benefit response relationship (B1 & B2) and dose toxicity response relationships (R1 & R2)[3]



A relevant example in this regard is niacin which has a maximum UL of 35 mg/person/day (based on skin flushing), with RDIs up to 16 mg/person/day. Leaving aside for the purposes of this discussion the outcomes of the AIM-HIGH study, [15] the "beneficial" effects of niacin on HDL and LDL cholesterol continue and increase as doses approach 3g /day. Other claimed benefits at intakes above the RDI include improved glucose control and anxiety management.

The mechanisms for these effects are quite separate to the electron carrier function applicable to dietary adequacy. [16] Effects of niacin on circulating cholesterol include inhibition of a key liver enzyme for TG synthesis, diacylglycerol acyltransferase–2, resulting in accelerated intracellular hepatic apo B degradation and the decreased secretion of VLDL and LDL for example. Conversely niacin flushing of the skin is caused by the stimulation of production of prostaglandins D2 and E2 by subcutaneous Langerhans cells through a specific G protein–coupled niacin receptor.

As discussed by Verkerk [14]) niacin flushing (the most sensitive "adverse" health effect) is: (i) a reversible pharmacological effect to which tolerance develops with continued use; (ii) may be exacerbated more by the rate of increase of circulating nicotinic acid than the absolute level; and (iii) is largely a self-limiting endpoint where high intake is likely to be intentional and discretionary. The suitability of the end point for the establishment of a UL is therefore open to discussion and further consideration. The key observation here however is that there may be multiple, quite separate, mechanisms for multiple benefits and hazards with the dose response curves overlapping and having quite different slopes.

[3] *LOAL = Lowest observable adverse effect level; NOAEL = No observable adverse effect level; MPL = Maximum permitted level (in food supplements). Reproduced from (14)*

To evaluate a proposed UL, critical considerations include: (i) the relative strengths and uncertainties supporting benefit and risk at higher intakes; and (ii) the number needed to treat (NNT) for each beneficial outcome versus the number needed to harm (NNH) for each adverse outcome. This consideration has been addressed by Renwick et al [(12)] and outlined in Table 1 below.

Table 1: Comparing risk and benefit for a micronutrient across potential intake ranges[4]

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 5,000	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	< than 1 in 1,000,000	1 in 100	
119		1 in 1,000	< 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 1,000
290			1 in 500
370			1 in 100
490			1 in 20

Whether less reliable data with higher uncertainty should result in a UL that constrains intakes (which are supported as beneficial by higher quality data with less uncertainty) might reasonably depend on a risk benefit consideration (i.e. consideration of the nature and consequence of the pivotal adverse effect and the importance of the apparent beneficial effect). Similarly, where a postulated risk occurs in one sub- population, the setting of an overly precautionary UL may unnecessarily preclude food

[4] The format of advice to risk managers for a nutrient that shows a deficiency syndrome (with an estimated ED50 of 50mg/day), a marginal benefit (with an estimated ED50 of 75mg/day) and clear toxicity (with an estimated ED50 of 1000mg/day). Reproduced from reference (12).

fortification or other risk management approaches to improve health outcomes in another sub-population.

A key consequence of the discontinuous benefit and risk relationships to dose is that risk (in terms of exceedance of a UL) might arise for individuals at levels that are essential or beneficial to other individuals. As a result, absolute protection of an entire population through establishment of a UL may not be possible.

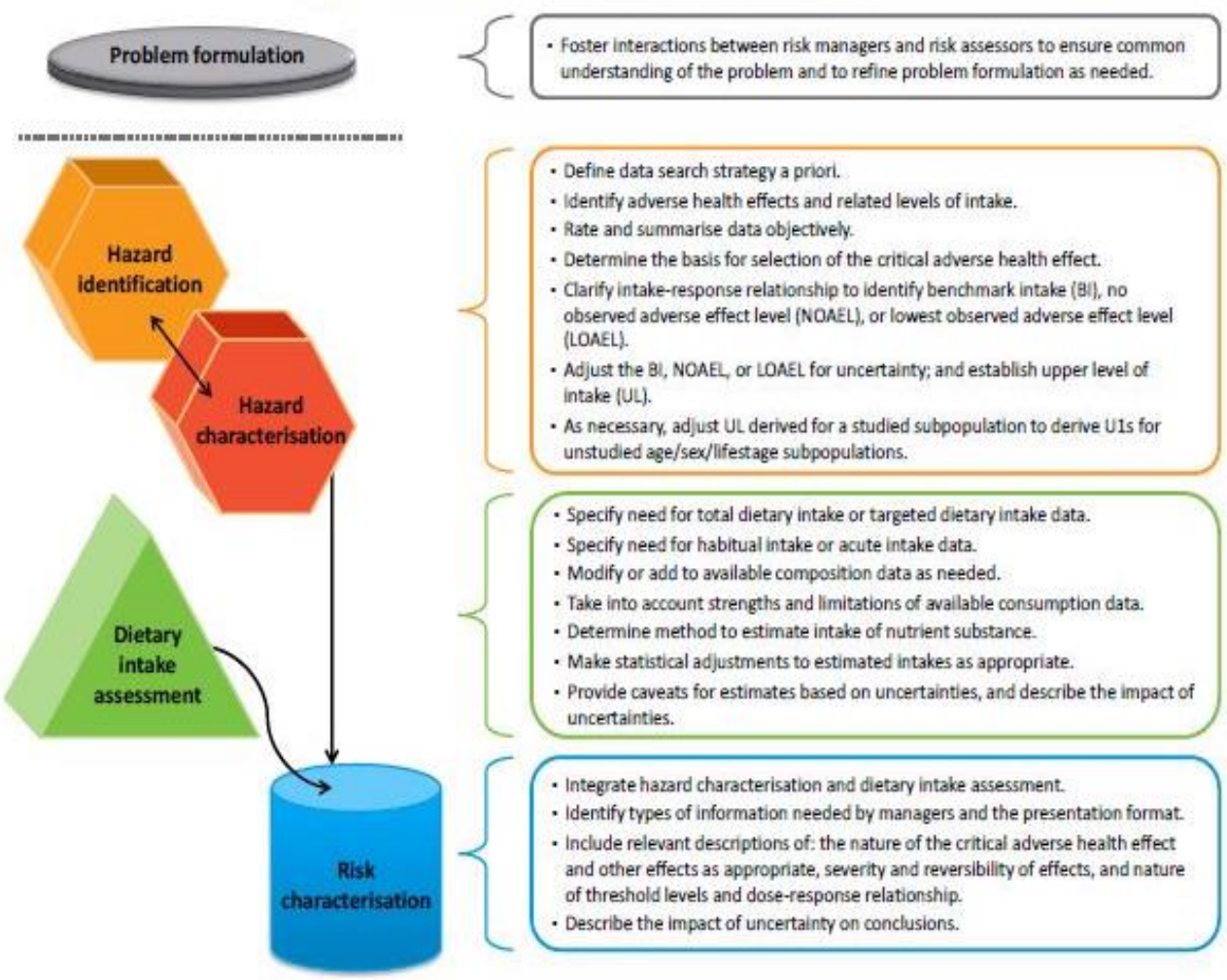
3 Outline of the process

The HHRA essentially utilises the following three common sequential processes (regardless of the substance being assessed or the nature/ circumstances of potential exposure):

1. Hazard Identification (HI) and Hazard Characterisation
2. Exposures Characterisation (EC)
3. Risk Characterisation and establishment of health reference values (RC)

The first two steps of the process are independent and their outcomes inform the third step of the process. Figure 3 below outlines the classical process used by the Food and Agricultural Organization (FAO)/World Health Organization (WHO) model for establishing ULs. [10]

Figure 3: The FAO / WHO model for establishment [10]



Action subsequent to hazard and exposure characterization diverges depending on the nature of the exposure scenario and the applicable regulatory paradigms. At one end of the spectrum, human pharmaceuticals undergo a risk benefit analysis where potential health benefits to the exposed population are weighed against the potential risks. Even for quite severe potential adverse effects (e.g. the long term potential to produce cancer) the benefits may still outweigh the risks. For example, the treatment of childhood leukaemia where prevention of death at an early age from untreated disease clearly outweighs a possible increase in cancer incidence 30 or more years later.

When considering the potential for adverse effects to become present at therapeutic exposures, the HHRA for pharmaceuticals employs a Margin of Exposure (MOE) approach rather than the establishment of a health reference value through the use of multiple arbitrary uncertainty factors. The MOE approach compares actual achieved human systemic exposures at therapeutic (i.e.

beneficial) doses against the No Observable Adverse Effect Level (NOAEL) and the Lowest Observable Adverse Effect Level (LOAEL) dosages for specific toxicological endpoints of concern in the context of the therapeutic indication of the pharmaceutical substance. At the other end of the spectrum, an industrial chemical is largely assessed and controlled on hazard alone, without a specific risk characterisation. This is conducted on the basis that no benefit accrues to the exposed individual and a wide range of control options exist to minimise exposure to As Low As Reasonably Achievable (ALARA).

The assessment of substances added to food (either through agricultural use or as a direct food additive) falls somewhere between these extremes. In all cases a risk characterisation is conducted and an acceptable daily intake (ADI) is established. Although distinct benefits from the use of these chemicals can be identified to society (e.g. food security and food safety), the risk characterisation does not generally involve a formal consideration of benefit and conservative assumptions are applied to provide a very high degree of protection of public health and safety. This conservatism primarily involves: (i) the approach taken to differentiation between adverse and adaptive or physiological responses to the substance; and(ii) the application of uncertainty factors to compensate for defined and characterised sources of uncertainty in the HHRA.

For micronutrients, both benefits and potential risks are associated with: (i) levels of intake; (ii) frank deficiency states or suboptimal health status at lower levels; and (iii) potentially, overt toxicity at excessive levels of intake. Adequacy values may be less variable across the population than toxicity estimates which are potentially more susceptible to variability due to genetic variability in xenobiotic toxicokinetics (the pharmacokinetics of high doses) at high intakes, life stages such as pregnancy or infirmary or critical periods of growth or development.

Note however this might not always be true, because: (i) homeostatic mechanisms exist to achieve and maintain adequacy of systemic micronutrient levels where the diet is adequate to achieve this; and (ii) pharmacokinetic parameters tend to be less variable at low levels of intake. As a result, uncertainty in the estimates of ULs is unavoidable.

Current / Classical UL approach

The current approach for many bodies setting ULs is derived primarily from classical chemical HHRA, without apparent significant influence from pharmaceutical or nutrition specific toxicology considerations (10). Once the hazard occurring at the lowest dosage is identified from the available studies: (i) the highest dosage below that level not producing that effect is determined (known as the point of departure or POD); and (ii) a series of (generally arbitrary) uncertainty factors (UFs) is applied to establish a UL.

If the derived UL is below a key NRV for adequacy, the UFs are revised (again largely on an arbitrary basis) to achieve a UL above the relevant NRV. The principle deficiency of this approach is that the essentially arbitrary (or policy/values based UFs) used to derive ULs are not sufficiently robust to withstand regulatory or scientific challenge.

Currently, every uncertainty is assumed to operate in a direction which would make the subpopulation of interest more sensitive to the adverse end point than the test population. This is not invariably valid. To some extent this deficiency can be addressed: (i) by a specific analysis of the nature and likely direction of each uncertainty; and (ii) by applying a reality check of any derived UL against the actual high end exposures of the population not associated with observed adverse outcomes.

4 Intake assessment

There are two observations or key points for consideration in dietary modelling for NRVs:

- In Australia and New Zealand, the consumption of nutritional supplements is common (occasionally at quite high levels)
- Validation of proposed ULs against actual population intakes requires consideration of supplement use.

In Australia, the NHMRC drinking water guidelines include health based reference values for a range of minerals including iodine, fluoride, molybdenum and selenium. The intake assessment for these minerals requires consideration of the intake from water. Consideration should also be given to guidance provided in the Ministry of Health's Drinking-water Standards for New Zealand.

The classical HHRA process is essentially linear from hazard identification through to exposure assessment and risk characterisation. For consideration of a UL for a micronutrient, it may be more appropriate to conceptually approach the issues through three parallel (but inter-related and iterative) processes. These are outlined below.

1. Intake assessment

For each defined sub population of interest, determine the upper bound of intakes from all sources (inclusive of supplements and drinking water where applicable) that has not been associated with adverse outcomes in reliable studies. Key points for consideration include:

- The percentile selected to establish the upper bound is a policy decision but would reasonably be influenced by the number of subjects in the survey at that level of intake and therefore the robustness of both:
    - the estimate of intake and
    - the likelihood that adverse effects relevant to the specific micronutrient would pass unnoticed if they occurred
- This value provides a reality check for comparison with any proposed UL.
- The further the proposed UL is below this bound, the stronger the evidence in support of the UL needs to be in order to be sustainable in any regulatory or scientific challenge
- If the proposed UL is below this bound primarily because of the magnitude and number of UFs applied to derive the UL, then the scientific basis of the UFs should be reviewed.

2. Hazard identification (HI)

The primary objective of the Hazard Identification (HI) is to identify the specific toxicological or pathological endpoint(s) of concern and to characterise the dose response curve(s) for each of these.

3. Disposition characterisation

For most micronutrients, reliable evidence of the hazard dose response will not be available for all sub populations potentially at risk and may not be available for any group. Disposition characterisation provides the basis for identifying the scaling approach applicable between the population from which the evidence was obtained and the population being extrapolated to. This process involves:

- the determination of the nature of any variability in pharmacokinetic parameters across age groups or other life stages for the specific micronutrient (i.e. systemic exposure from dietary intake at high levels)
- the influence of metabolic rate on dietary requirements and disposition processes for the micronutrient

- potential variations within and across sub populations in pharmacokinetics at high versus lower intakes (such as transition from carrier mediated or active transport at low intakes to passive diffusion at high intakes)
- the magnitude of any increased micronutrient demand related to the life stage of the subpopulation (e.g. growth related in children, demands of pregnancy) which might increase the tolerable intake.

The approaches described above are essentially bottom up approaches which: (i) focus on the lower doses and work up the dosage range until reaching the lowest dose at which effects are observed (the LOAEL); and (ii) then identify the highest dose below this at which no adverse effects are observed (the NOAEL). This approach is effective, relatively straight forward and provides sufficient overlap across the data set to assess reproducibility of many endpoints for toxicology data sets which are:

- conducted under highly standardised conditions
- conform to standardised test protocols
- include a comprehensive range of study designs to cover the broadest possible range of toxicological endpoints.

For the determination of micronutrient ULs where data are likely to be of highly variable and limited quality, quantity and reliability, inclusion of a top down approach as described by Hathock & Shao (17) may be more informative. This approach is discussed in section 6.

In practice, the HHRA underpinning the UL will need to use the most robust approach or a combination of approaches consistent with the nature, quantity and quality of the available data. Using more than one approach to derive a UL may assist in identifying weaknesses or limitations in the underlying assumptions of each.

5 Hazard identification

Hazard identification broadly involves the six steps outlined below. Whilst many of these steps may be self-evident, they may prove challenging in situations where neither the quality nor breadth of evidence base is high.

The six steps for hazard identification are:

1. **Gather all data** potentially relevant to the toxicology assessment of the substance of interest using standard literature search techniques.
    - For micronutrients this will primarily be human studies, although it may be valuable to explore toxicological mechanisms in animal models to: (i) support physiologically based threshold estimates; and (ii) inform considerations of the nature and potential direction of uncertainties.
    - The data will include studies that have monitored adverse effects but found none.
2. **Screen and score data** for quality and reliability in the normal manner, but with a specific focus on the approach of the study to the estimation of adverse effects at high doses.
3. **Identify potential treatment related** effects in each study, including consideration of:
    - Dose response in terms of both incidence and severity of each effect.
        - Dose Metrics includes the amount of substance administered/consumed but also the frequency, route, duration and form of administration.
        - Response pattern may vary between bolus doses (tablet or capsule for example) versus dietary administration, 7 days per week versus 5 days per week administration.
    - Magnitude of the apparent effect compared to background variation.
    - Concordance of the observation with correlating parameters.
    - Consistency with known mechanisms of toxicity.
    - Statistical significance as normal.
4. **Assess the toxicological significance** of the observed effects to the specific test population (or to the model if not a human study) in terms of:
    - The biology of the sub population, with consideration of the Pharmacokinetics (PK) of the compound (or any potential genetic or life stage PK differences in the test population)
    - Toxicology, differentiating between adaptive responses and adverse effects, considering
        - Reversibility of the effect
        - Pathological significance of the endpoint in terms of normal biological and physiological function (i.e. differentiate between adaptive physiological effects and adverse pathological effects)
        - Time of onset (i.e. how long does it take the effect to manifest)
        - Progression of the severity and/or incidence of the effect over time
        - Species specificity or cross species concordance of effect where animal studies are involved
        - Primary or Secondary nature of the effect (e.g. differentiate between the unmasking of pre- existing sub clinical disease due to high micronutrient intake from de novo initiation of pathology)
        - Mode of action leading to the effect.

5. Consider the **relevance of the test system**, study design, animal model or other data generation technique, to the Australian and New Zealand population potentially at risk of exposure to the substance. This requires consideration of:
    - Mode of action
    - Comparative biology, anatomy and behaviour between test subjects/species and the Australian and New Zealand population
    - Relevance of the test population (i.e. is the test population a realistic model for the dietary, health status and genetic characteristics of Australia and New Zealand).
6. Identify the **population potentially at risk** from those effects (gender, age group, life stages such as pregnancy, lactation).

6 Determination of the point of departure

There are three key approaches to determining the point of departure – the classical bottom up procedure, the alternative top down procedure, and benchmark dose modelling. Each approach is outlined in more detail below.

Classical bottom up procedure

Under the classical bottom up procedure, the point of departure (POD) used as the basis for establishing the UL is the highest dose that does not produce the adverse effect that occurs at the lowest dose in the most sensitive sub population (or species for animal studies).

If a risk benefit component is added to the assessment, the nature of the adverse event may also be considered in terms of consequences. For example, whether a mild transient flushing or transient nausea (resolving with continued administration/intake) provides sufficient basis for establishing a UL is an issue of policy, values and objectives.

Alternative top down procedure

In the top down approach, studies are ordered from highest to lowest dosage. Studies are then sequentially assessed for quantity and quality of data (starting with studies at the highest dose) until a study is identified where: (i) no adverse effects are observed; and (ii) the study is of sufficient quality that no UF is warranted. In effect, this should identify a study which demonstrates a clear threshold for the pivotal toxicological end point.

In reality, a study of sufficient quality is unlikely to be available that covers all relevant life stages and sub- populations. A study however may be available for a specific sub population (e.g. males between 18 and 60 years) that provides a sound basis for setting a POD. The POD can then be adjusted by substance specific, physiologically based UFs, relevant to the specific subpopulations being addressed. If permitted by the available data, this approach has the advantage of providing a robust starting point for subsequent extrapolations and limits the use of UFs to those applicable to the extrapolation across specific subpopulations.

In practice, this approach also needs to consider the studies at lower dosages to the same extent as the bottom up approach. This is to ensure: (i) a more credible, robust, study did not provide equally or more convincing evidence of effects at lower doses; and (ii) other aspects of the dose metrics beyond daily intake over the period of the study (e.g. duration of exposure) were adequately accounted for. The difference between the approaches is more conceptual than practical. However, once a study of sufficient quality has been identified, other lesser studies showing effects at lower doses might be given less weight and attention, or be rejected, in the HHRA.

Benchmark dose modelling

The NOAEL and LOAEL are essentially artefacts of the dose selection used in the pivotal study. Their use as the basis for determining a POD has been criticised both for their partially arbitrary nature and because the approach fails to utilise all the (potentially) available data on the dose response curve.

If more than one effect dose is available, a Bench Mark Dose (BMD) model can be used to mathematically model the slope of the dose response curve and estimate a POD based on a predetermined level of increased risk (usually 5 or 10%). If supported by the data, the BMD approach can provide a more complete and descriptive characterisation of the shape of the dose response and may improve the estimate of a threshold for a specific adverse effect. Although BMD software can fit curves to data with only one effect level, these are no less arbitrary and no more informative than the NOAEL/LOAEL approach.

7 Dose metrics consideration

Dose is the amount of a substance administered. The dosage however is the amount administered (or consumed) for the following parameters: (i) per person or per kg of body weight; (ii) per period of time (e.g. hourly, daily, weekly) for a specified period; (iii) by a specific route; and (iv) in a specific form. Collectively these parameters form the dose metrics.

Definition of dose metrics may be critical to the interpretation of the safety data for a micronutrient. For example, even reasonably extreme iodide intakes as a single isolated event (or repeated weekly or monthly) may be without apparent harm. Conversely, much lower intakes every day for a period of several months have been associated with a number of outbreaks of thyroid disease in Australia and New Zealand. (Note this also depends on the presence (or absence) of pre-existing thyroid disease and whether the population have had inadequate or deficient intakes for long periods of time prior to exposure).

The dose metrics within the definition of the UL must be consistent with the dose metrics of the pivotal study or studies used to define the UL and/or the adverse effect on which the UL is based. In some cases, more than one UL may need to be defined to accommodate variation in hazard manifestation due to different dose metrics/consumption patterns (for example iodine).

8 Uncertainty factors

The nature, magnitude and number of UFs used in the derivation of a UL is arguably the most challenging, arbitrary, contentious, and (as commonly practiced) the least scientific aspect of the process. The magnitude of commonly used UFs (generally up to ten for each defined uncertainty) is simply derived from one order of magnitude and would be equally valid or invalid if they were based on eight or twelve (e.g. if the number system used base 8 or base 12).

The extent to which the experimental evidence supports these factors is variable and arguable. In general however, the resulting UFs tend to be conservative to very conservative and tend to achieve the desired protection of public health and safety for non-nutrient chemicals. They are not however scientifically robust for risk benefit type analysis and, as discussed earlier, are not generally used for HHRA of pharmaceuticals.

As a result, provision of a more scientifically sound basis for UFs (if or where required) is a critical aspect for the establishment of robust, defensible ULs. Where substantial UFs are considered necessary for a nutrient, the suitability and reliability of the supporting data is questionable and should be closely examined.

The classical application of uncertainty factors in toxicology is founded on the basis that from a public health perspective, there can never be too little of a particular chemical in food. For chemicals that are used in specific food technology or agricultural purposes where a functional minimum exists, extensive toxicology databases are produced that reduce the uncertainty and therefore the range of applicable UFs. Substances for these purposes are also generally developed specifically to have low mammalian toxicity. This ensures that application of standard UFs do not preclude the intended use of the substance. As a result, a high degree of conservatism in this context generally has limited practical significance. If this is not the case, the standard procedure is to revisit each specific aspect of the risk assessment leading to the level of conservatism and refine the assumptions forming the basis of that conservatism (based on the best available relevant science).

For standard chemical HHRA, uncertainty factors are applied for a range of identified uncertainties. In each case, the uncertainty is assumed to operate in a direction which makes: (i) the human population more sensitive than the animal model; and (ii) the broader population or sub-populations within it more sensitive than the test population (or the true value for the LOAEL obtainable from adequate quality and quantity of studies lower than that from the available study(s)). For micronutrient risk assessment, these assumptions may be testable through consideration of mechanism and the broader evidence base.

Table 2 outlines commonly applied uncertainty factors for a range of identified uncertainties.

Table 2: Commonly applied uncertainty factors

Source of Uncertainty	Nature of Uncertainty	Range of the UF	Potential basis for reduction of UF
Interspecies extrapolation	Although the animal models that are chosen for toxicity studies are known to generally reflect human responses quite closely, species specific variation is common and the accuracy with which the model predicts the human dose response is variable.	0-10	Validation of the quantitative relationship between the animal model and humans
Intraspecies extrapolation	The Human test subjects may be a less sensitive sub- population than are other identifiable groups.	0-10	A consideration of the nature of the potential variation between sub- populations and the relevance of that variation to the sensitivity of the groups to the specific mechanism of toxicity for the pivotal adverse effect
Extrapolation from subchronic studies to chronic effects	Where only shorter term studies are available, some adverse effects that require prolonged exposure may not be manifested or may occur in the short term study at higher doses than would be found in longer term studies	0-10	A consideration of the mechanism of toxicity, the nature of the adverse event, and the range of intakes in the community not associated with adverse outcomes
Incomplete data package	Key toxicological end points may not have been investigated	0-10	
Steep Dose response curve	Where the dose-response curve is steep, a small error in extrapolation may have a substantial impact on the protection provided by a UL	0-10	
No NOAEL	Where the pivotal study does not demonstrate a NOAEL and an estimate of this needs to be made based on the LOAEL	0-10	If more than one effect dose is available in the pivotal or other available studies, it may be possible to model a dose-response curve using the BMD approach which may provide a sufficiently robust estimate of the threshold dose that the UF can be reduced or removed.

For classical HHRA based on animal studies, the default is a UF of 100. Based on this model, a UF of 1,000 to 100,000 might be applicable (in theory) for ULs based on a limited number of sub optimal human studies of relatively short duration. The resulting UL would in many cases be incompatible

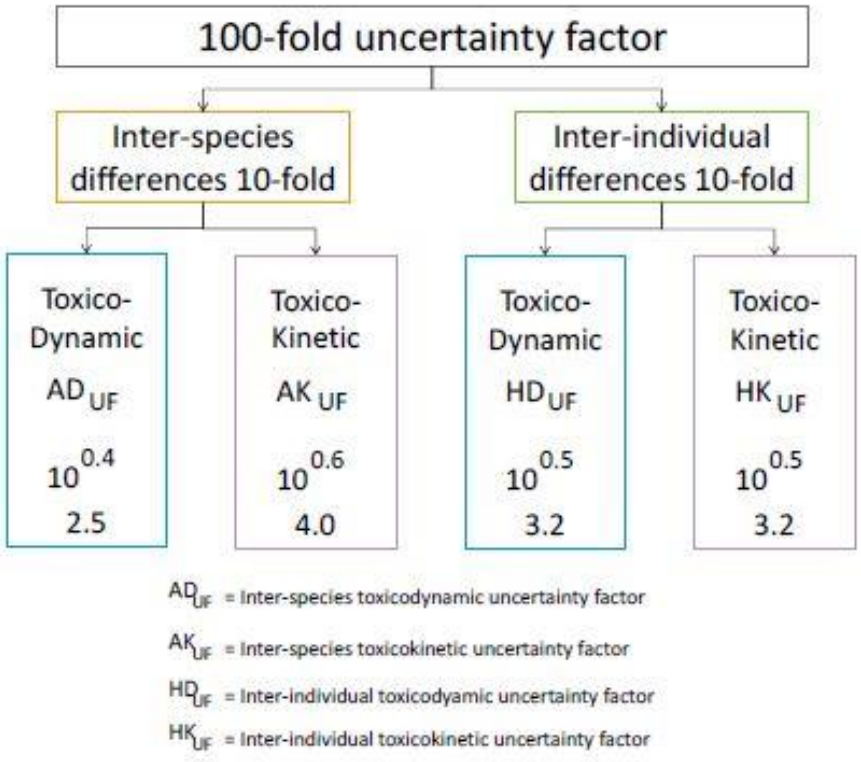
with other NRVs and therefore impractical. This situation has been discussed by Renwick et al. [12] [11]

Consequently, the identification of specific uncertainties relevant to each micronutrient and a careful and considered exploration of the nature, direction and magnitude of the uncertainties is essential.

The subdivision of the default 100 fold UF has been discussed in the literature both in the context of classical chemical toxicology and in the context of micronutrient risk assessment. [18]

Figure 4 illustrates one conceptual model for this subdivision (note however the subdivision of the arbitrary 10 fold uncertainty factors is also essentially arbitrary).

Figure 4: The subdivision of the usual 100-fold default uncertainty factor into separate factors for species differences (10-fold) and human variability (10-fold) [18]



The option of increasing or decreasing the magnitude of uncertainty factors in proportion to the severity or seriousness of the specific toxicological endpoint has been proposed. This approach however confuses legitimate scientific uncertainty analysis with risk management concepts. The data are not more or less uncertain because the effect caused is more or less severe. Depending on the seriousness of the adverse effect, risk managers may however legitimately choose to apply a higher or lower level of precaution to manage the risks of exposure scenarios likely to result in an exceedance of a UL.

Ultimately there are no easy options for establishing UFs. If UFs are to be used in the derivation of ULs, the magnitude and direction of each factor should be based on a careful analysis of the underlying physiology and biochemistry giving rise to the uncertainty. Actual variation observed amongst test subjects may provide a guide to the likely magnitude of the uncertainty and to the direction for specific extrapolations.

If a UF over 10 is considered necessary, the validity of the data supporting the UL and the requirement for a UL should be closely scrutinised and explicitly justified.

9 Reality checks

If the available data supports derivation of a UL and a tentative value has been determined, a series of "reality checks" should be conducted to gauge the plausibility and defensibility of the value. This should be conducted prior to finalisation of the value.

The derived UL for each sub-population should be compared to:

- all relevant human studies with a safety component to their design (to assess how many studies (and of what quality) included doses above the UL with no evidence of the proposed pivotal adverse effect).
- the proportion of each subpopulation likely to be exceeding the postulated UL at current intakes.
- the mean intake of the nutrient in the top 10% (or other selected appropriate high intake segment of the population), inclusive of supplements and drinking water where applicable, with no evidence of the occurrence of the postulated pivotal adverse event. Note:
    - This approach is somewhat analogous to the establishment of an AI based on the mean intake of a nutrient in a population without appreciable deficiency (except that the population of interest is the high consumer group and the end point is safety rather than dietary adequacy).
    - If the postulate pivotal adverse effect is mild and largely self-limiting (e.g. flushing), any error here is of limited public health significance.
    - If the pivotal postulated effect is substantial and would result in significant morbidity or mortality, a failure to observe the effect in high consumers is less likely and an absence of such observations provides some reassurance that the effect is not manifested at realistic intakes.
- the upper range of the intake benefit curve. Note:
    - If the UL is close to or below the upper intake range for a benefit, a comparison of the nature and likely incidence of the adverse effect with the nature and likely incidence of the benefit may be warranted. This comparison should include consideration of the relative strengths and weaknesses of the data supporting the benefit and the adverse effect.
- the postulated mechanism underlying the adverse effect and the plausibility of the dose response for that effect extending down to the proposed UL.

Appendix A Bibliography

1. Renwick A. Toxicology of Micronutrients: Adverse Effects and Uncertainty. The Journal of Nutrition. 2006; 136: p. 193S-501S.
2. Vertek R, Hickey S. A critique of prevailing approaches to nutrient risk analysis pertaining to food supplements with specific reference to the European Union. Toxicology. 2010;(278): p. 17-26.
3. Klaus Kraemer K, Waelti M, de Pee S, Moench-Pfanner R, Hathcock J, Bloem M, et al. Are low tolerable upper intake levels for vitamin A undermining effective food fortification efforts? Nutrition Reviews. 2008; 66(9): p. 517-525.
4. Zlotkin S. A critical assessment of the upper intake levels for infants and children. American Society for Nutrition. 2006;(136): p. 502S506S.
5. Munro I. Setting tolerable upper intake levels for micronutrients. The Journal of Nutrition. 2006; 136: p. 490S-492S.
6. Rasmussen S, Andersen N, Dragsted L, Larsen J. A safe strategy for the addition of vitamins and minerals to food. European Journal of Nutrition. 2006;(45): p. 123-145.
7. FSANZ. Assessment of Application A588 - Voluntary addition of fluoride to packaged water - Supporting document 4 - Derivation of the upper level of fluoride intake. Canberra: Food Standards Australia New Zealand; 2009.
8. NH&MRC; NZ MoH. Nutrient reference values for Australia and New Zealand. Including Dietary Intakes. Fluoride. 2006;: p. 175-180.
9. Food and Nutrition Board Institute of Medicine. Dietary Reference intakes for calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. In. Washington: USA National Academy press; 1997.
10. FAO/WHO. A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances. Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment WHO Headquarters, Geneva, Switzerland 2-6 May 2005. 2006.
11. Renwick A, Barlow S, Hertz-Picciotto I, Boobis A, Dybing E, Edler L, et al. Risk characterisation of chemicals in food and diet. Food and Chemical Toxicology. 2003; 41(9): p. 1211-1271.
12. Renwick A, Flynn A, Fletcher R, Müller D, Tuijtelaars S, Verhagen S. Risk–benefit analysis of micronutrients. Food and Chemical Toxicology. 2004; 42(12): p. 1903-1922.
13. Hanekamp J, Bast A. Why RDAs and ULs are incompatible standards in the U-shape micronutrient model: A philosophically oriented analysis of micronutrients standardization. Risk Analysis. 2008; 28(6): p. 1639-1652.
14. Verkerk R. The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. Toxicology. 2010;(278): p. 27-38.
15. Investigators TAH. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. The New England Journal of Medicine. 2011 December 15;(365): p. 2255-2267.
16. Kamanna V, Kashyap M. Mechanism of action of niacin. The American Journal of Cardiology. 2008; 101(8 Supplement): p. S20-S26.
17. Hathcock J, Shao A. Expanded approach to tolerable upper intake guidelines for nutrients and bioactive substances. The Journal of Nutrition. 2008;(Supplement): p. 1992S-1995S.
18. FAO/WHO. Principles for the safety assessment of food additives and contaminants in food. Environmental Health Criteria. Geneva: WHO; 1987. Report No.: 70.