

RISK ASSESSMENT

of Vitamins and Minerals

ERNA

Introduction

Risk assessment - the key to consumer safety

Developments in food science over the past few decades, have led to a greater understanding of the importance of vitamins and minerals to human health. This in turn has stimulated a new range of food products. Widespread fortification in, for example, cereals and fruit juices, growing interest in a large range of food supplements and, more recently, the appearance of functional foods, e.g. probiotic foods, fermented milk products, have transformed the European marketplace. Alongside the potential health benefits that such products offer are often concerns that consumer intake of vitamins and minerals will increase to an extent where there is a risk of experiencing unwanted adverse effects.

As regulators work to develop new legislative frameworks that reflect developments in the food market, the safety of the products on sale remains a central issue. Careful analysis is required to ensure that the particular characteristics of vitamins and minerals and their implications for safety are fully

understood. This analysis is known as risk assessment. While risk assessment often appears complex, it is a process that forms the cornerstone of all decisions relating to vitamin and mineral products. Indeed, expert groups both at European level (the Scientific Committee on Food) and at national level (UK MAFF Expert Group on Safety) are currently in the process of discussing appropriate upper safe levels of intake for vitamins and minerals. An understanding of risk assessment is therefore crucial to all those consumers, regulators and companies with an interest in this growing area of the food market. With this booklet, ERNA aims to provide an insight into the issues and considerations involved in risk assessment with clear step-by-step diagrams explaining the process.

Executive Summary

A framework for assessing micronutrients

Risk assessment forms a scientific platform for those charged with ensuring safe food for consumers (risk management) and informing consumers about potential dangers (risk communication). In the context of vitamins and minerals, risk assessment aims to establish the likelihood that the population will be exposed to excessive nutrient intake.

The risk assessment of vitamins and minerals is a complex process, not least because the amount of relevant data available varies according to the nutrient concerned. A starting point for the assessment of micronutrients has been the risk assessment work that has been carried out on chemicals, including acceptable levels of food additives or contaminants in food. The data used in this process are primarily derived from the study of animals and are then made applicable for humans by including an appropriate safety factor. This approach must be questioned for micronutrients for two reasons. Firstly, the data used in the assessment of micronutrients are

mainly derived from the study of humans so that the same uncertainties do not necessarily apply as for animal studies. Secondly, it is likely that applying the traditional risk assessment approach to micronutrients could result in final intakes for some nutrients below the established recommended daily allowances (RDA). Scientists have therefore aimed to adapt this approach to micronutrients.

The micronutrient risk assessment model consists of four steps: hazard identification, dose-response assessment, exposure assessment and risk characterisation.

Hazard identification establishes the potential health problems (adverse effects) that may arise through excessive intake of micronutrients.

The second stage, **dose-response assessment**, establishes at what levels of intake any adverse effect may occur. A level of intake that will be safe for the general population can then be

ascertained. These levels are often, somewhat confusingly, referred to as 'upper safe levels'. This wrongly implies that levels above that level are 'not safe' or 'dangerous'. The upper level is the point above which the risk of adverse effects gradually increases. This upper level includes an 'uncertainty factor' that reflects the quality and quantity of the scientific data available and the severity of the adverse effect concerned.

Through **intake assessment**, the risk assessor evaluates the actual intake of every micronutrient in order to ascertain whether there is a real risk that any population group would exceed the tolerable upper intake level.

The final conclusion of this assessment, **risk characterisation** is the basis on which the risk manager will act.

Risk Analysis

A structure for food safety

While food safety has always been a key consideration for regulatory authorities, the recent attention given to food scares has focussed public attention more keenly on the way food is assessed. Discussions at national and international level have led to the development of a basic structure for the assessment and management of risk related to food. The whole process is known as risk analysis and is generally judged to comprise three stages: risk assessment, risk management and risk communication.

RISK ASSESSMENT

This first step in the risk analysis process represents a purely scientific task. Using all the scientific data available, experts are charged with providing an assessment of risk. The exact process will depend on the area of food safety being dealt with and the data available. There are essentially four steps to this process:

Hazard identification - identifying any adverse effect or potential adverse effect of an ingested substance.

Hazard characterisation - establishing the exact relationship between that substance and the adverse effect.

Exposure assessment - analysing which population groups are exposed to the substance and at what levels.

Risk characterisation - summarising the risk assessment process, where possible defining the nature and extent of the risk including an evaluation of the uncertainties (e.g. through lack of data) of assessing risk.

RISK MANAGEMENT

This is the responsibility of those decision-makers involved with food safety. They must ensure the safety of the population with measures that reflect the risk characterisation resulting from risk assessment.

RISK COMMUNICATION

This final element of risk analysis is again primarily a task for the authorities and requires interaction with the population to effectively explain the risks associated with a particular food or substance. Consumer confidence is largely dependent on clear, consistent and accurate risk communication. A visible and open risk assessment process is generally considered to be an important element in reassuring the public about food safety and this has been reflected in an increased transparency in the work of Europe's scientific groups.

What makes Risk Assessment of Vitamins and Minerals so complex?

For some vitamins and minerals, access to available databases makes it possible to evaluate the occurrence of adverse effects from which safe intake levels can be determined. For others, however, sufficient evidence may not be available. This sometimes arises when the lack of any indication of adverse effect has not encouraged research or simply because deliberately feeding excessive amounts of nutrients to subjects is not acceptable. In other cases, risk assessors will consider that there are insufficient data, for example, about the interaction between different nutrients and the variation in how different human beings react to nutrients. Where gaps remain in their understanding, risk assessors need to take these uncertainties into consideration. The following summarises some of the complexities associated with assessing nutrient risk:

NUTRIENTS

- Data on humans are limited for several nutrients.
- Nutrients have different effects depending on their chemical form, the timing of intake and the other constituents of the diet.
- Excessive intake of one nutrient may have an effect on other nutrients, for example, by inhibiting their absorption or excretion.

HUMANS

- The ability to absorb nutrients could be influenced by the individual's nutritional status and health.
- Risk assessors have to consider variation in the population due to age, gender and lifestyle. Sub-groups of the population e.g. children may possibly be particularly sensitive to the effects of certain substances.
- Extensive data on population nutrient intake are not available for all micronutrients.

Risk Assessment

Key terminology

One of the central elements of risk assessment is the establishment of the upper level of intake (during hazard characterisation). The terminology used sometimes detracts from what is, theoretically, a relatively simple process.

The intake levels established during risk assessment are often referred to as 'safety levels'. This terminology is not always favoured, as it may give the impression that levels above the 'upper level' are 'not safe' or 'dangerous'. This is not necessarily the case.

Short-term intake or even longer-term intake above the upper level of intake may have no adverse consequences. The upper level is the point above which the risk of adverse effects gradually increases. In this way, the 'upper level of intake' can be compared to the 'best before date' on many food products: the longer one goes beyond the 'best before date' (or upper level), the greater chance of adverse health effects. In order to avoid confusion over the term 'safety', some expert groups have developed alternative terminology. The US Food and Nutrition Board, for example, in its extensive evaluation of nutritional needs and tolerance has adopted the term 'tolerable upper intake level.'

Tolerable Upper Intake Level (UL)

'The highest level of daily nutrient intake that is likely to pose no risk of adverse effects to almost all individuals in the general population.'¹

In order to ascertain the UL, the risk assessor first needs to establish the level, if any, of vitamin and mineral intake that may cause an adverse effect based on data in healthy persons. Two markers can be identified that may assist the risk assessor in this process:

No Observed Adverse Effect Level (NOAEL)

The highest level of intake at which no adverse effect has occurred.

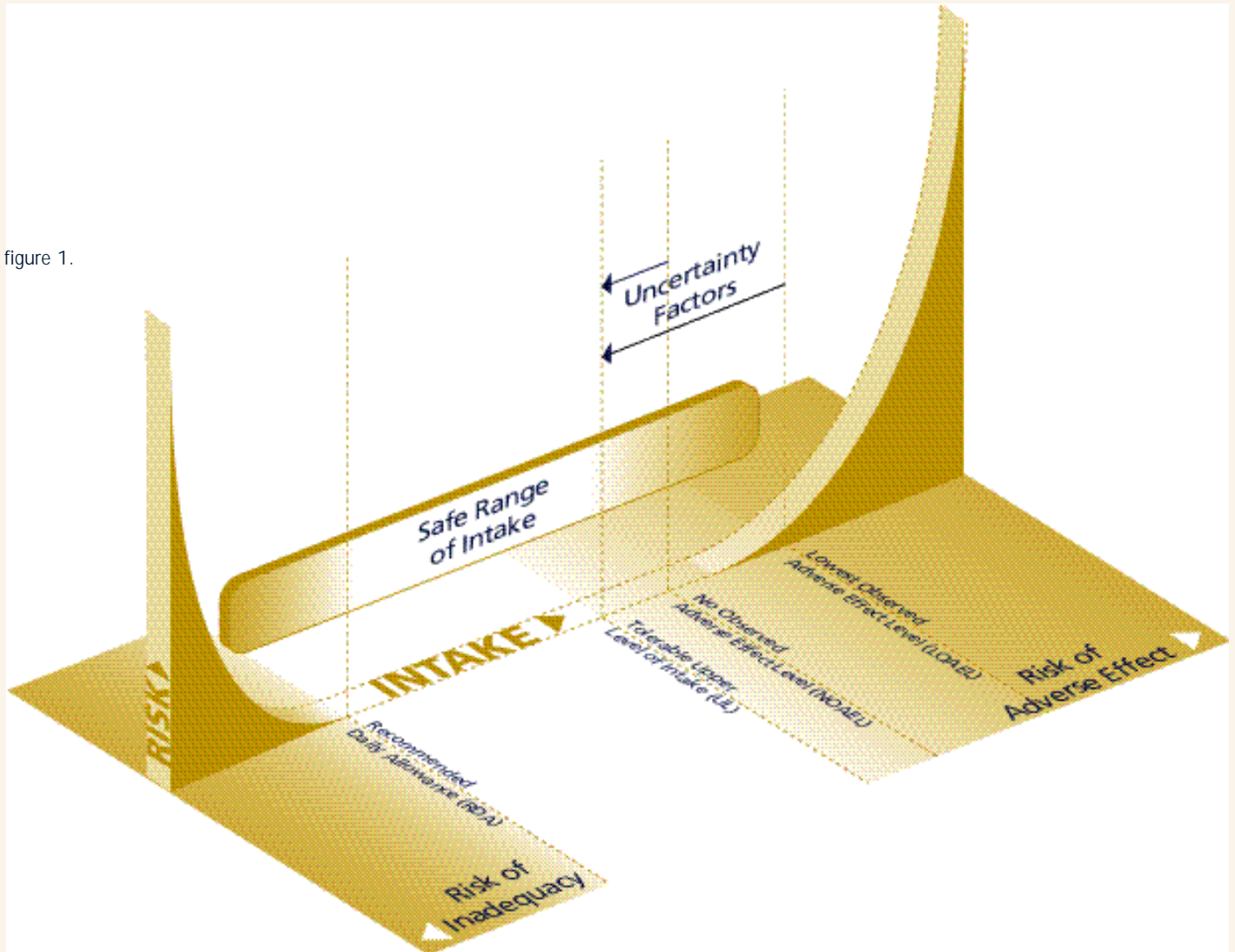
Lowest Observed Adverse Effect Level (LOAEL)

The lowest level of intake at which an adverse effect has occurred.

The UL will be lower than the NOAEL or LOAEL in order to allow for a margin of uncertainty (uncertainty factor) (see figure 1).

¹ Food and Nutrition Board, Institute of Medicine, National Academy of Sciences (1999), 'Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients.'

figure 1.



Building the Right Model for Micronutrients

Given the complexities involved in risk assessment as outlined above, risk assessors build a 'safety margin' into the risk assessment process. This element of caution is known as an 'uncertainty factor'. Exactly what size of factor should be used has been the subject of some debate. The starting point for this discussion has been the approach used for developing Acceptable Daily Intakes (ADI) for chemicals in foods (e.g. food additives). These ADI are primarily based on toxicity data established through animal studies. Having used the data to establish the NOAEL, (the highest level of intake at which no

adverse effect is observed), the toxicologist would then divide this by a safety factor of 10 to take into account the differences between animals and man, and then by a further factor of 10 to take account of variation between individual humans.

This traditional 'toxicological' type of model is not, however, the most suitable one for dealing with nutrients. Firstly, the traditional model relies primarily on animal data whereas the evidence used to assess micronutrients, by contrast, is primarily derived from human data. Secondly, unlike many substances,

nutrients are essential to human life. If the 'toxicological' model were to be applied to nutrients, the final intake level would in some cases end up lower than the current recommended intakes (RDA). The tendency when assessing micronutrients is therefore to apply a different 'uncertainty factor' (generally between 1-10) for each nutrient. This 'uncertainty factor' takes into account the quality and extent of the human data available and the severity of the potential adverse effect. This model is designed to reflect more accurately both the individual characteristics and evidence base of each micronutrient.

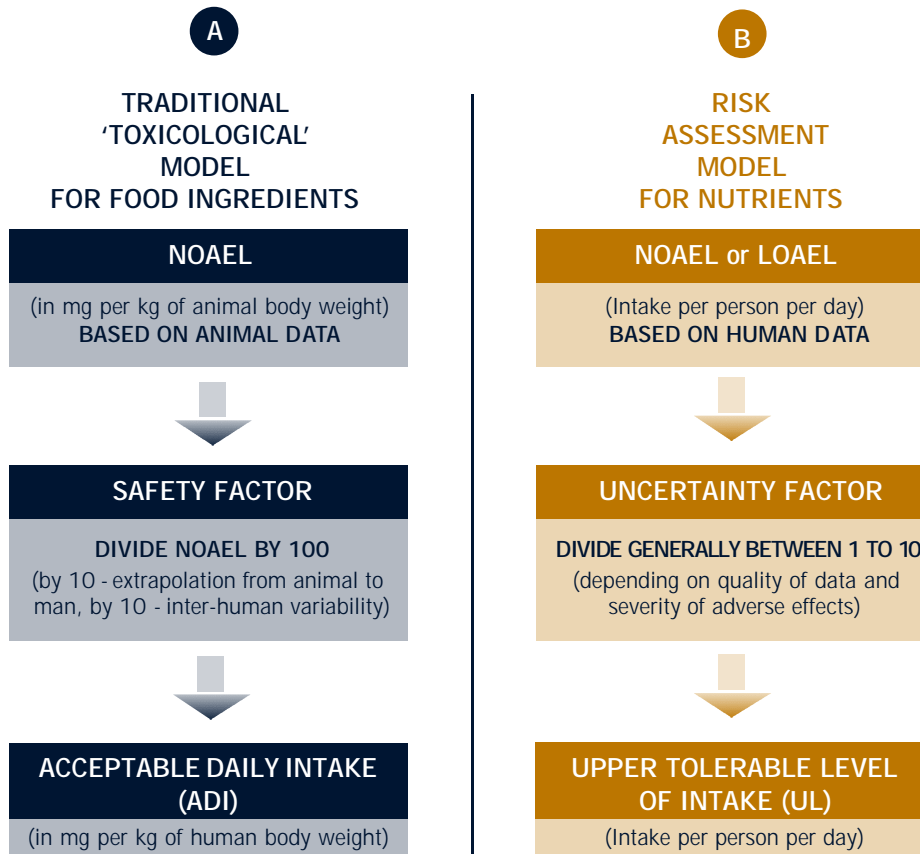


Figure 2.

Carrying Out Risk Assessment

As has been suggested above, there are a number of inherent difficulties facing risk assessors. The different groups that have in the past undertaken the task of evaluating vitamin and mineral safety have adopted slightly different approaches. The French Ministry of Hygiene, Section of Nutrition, for example, devised levels based upon the division of the NOAEL by a safety factor of 10.²

A different method was adopted by Shrimpton, in a review of existing literature in 1997, establishing 'upper safe levels' that are considerably lower than reported levels of adverse effect.³

Hathcock, by contrast, supported an approach based on 'observed safety', namely establishing a safety limit that corresponds to the highest levels that have been widely consumed by humans without adverse effect.⁴

Whatever the exact approach used, risk assessors of vitamins and minerals will work to the following key principles:

- Risk assessors should make use of all the scientific evidence available, in particular human data, when setting upper intake levels.
- Upper intake levels should include a reasonable margin to allow for the occurrence of adverse effects.
- Given the different characteristics of individual nutrients, a specific uncertainty factor should be developed for each nutrient.
- Upper intake levels should not be below the recommended intake for the particular nutrient.

² Conseil supérieur d'hygiène publique de France, Section de l'Alimentation et de la Nutrition (1996). 'Les limites de sécurité dans les consommations alimentaires des vitamines et des minéraux.'

³ Shrimpton, D.H. (1997) 'Vitamins and Minerals. A Scientific Evaluation of the Range of Safe Intakes' European Federation of Associations of Health Products Manufacturers. (EHPM)

⁴ Hathcock, J.N. (1996) 'Safety Limits for Nutrients' J Nutr. 126: 2386S - 2398S.

An Example of Risk Assessment

In the following pages, an example of risk assessment is set out in more detail. It is taken from the ongoing work of The US Institute of Medicine's Food and Nutrition Board and it provides a clear example of the various stages to risk assessment of vitamins and minerals.⁵ The work has received much attention worldwide. Great importance has been placed on the transparency of the scientific process and the involvement of leading experts in the field. Each review of individual nutrients has involved a series of workshops and meetings and considerable correspondence. To demonstrate how results are derived, an example nutrient, vitamin B6, is included in this review at each stage.

⁵ Food and Nutrition Board, Institute of Medicine, National Academy of Sciences (1999), 'Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients.'

Micronutrient Risk Assessment Model

An overview

The risk assessment model used by the FNB is based upon the four steps outlined at the beginning of this booklet. Its basic structure is as follows:

STEP 1 Hazard identification

Review of existing scientific literature to identify the potential health problems that may arise from excessive nutrient intake.

STEP 2 Dose-response assessment

Identification, where possible, of the level at which a nutrient causes adverse effects and the setting of an 'upper tolerable level of intake' (UL), the highest levels of nutrient intake which poses no risk to almost all individuals.

STEP 3 Intake assessment

Evaluation of the average nutrient intake of various population groups and the distribution of intake across the population.

STEP 4 Risk characterisation

Analysis of the risk to certain population groups taking into account the upper tolerable level of intake. Calculation of the risk of excessive intake of nutrient bringing together the data of Steps 1-3.

STEP 1 Hazard identification

MODEL

REVIEWERS CONSIDER THE FOLLOWING QUESTIONS:

- Is there an adverse effect in humans?
- Is there a causal nutrient adverse effect relationship?
- How relevant are the data?
- How complete are the data?
- Are certain population groups particularly sensitive?

IDENTIFICATION OF ADVERSE HEALTH EFFECTS

EXAMPLE NUTRIENT

VITAMIN B6⁶

KEY CONSIDERATIONS

- No adverse effects associated with intake from food sources
- Large doses of pyridoxine used to treat various conditions e.g. carpal tunnel syndrome and premenstrual syndrome
- Well documented causal association between high-dose pyridoxine and sensory neuropathy
- Limited data involving lower pyridoxine intake
- Some evidence of dermatological lesions at long-term daily intake of 2-4g.
- Isolated report of vitamin B6-dependency in newborn

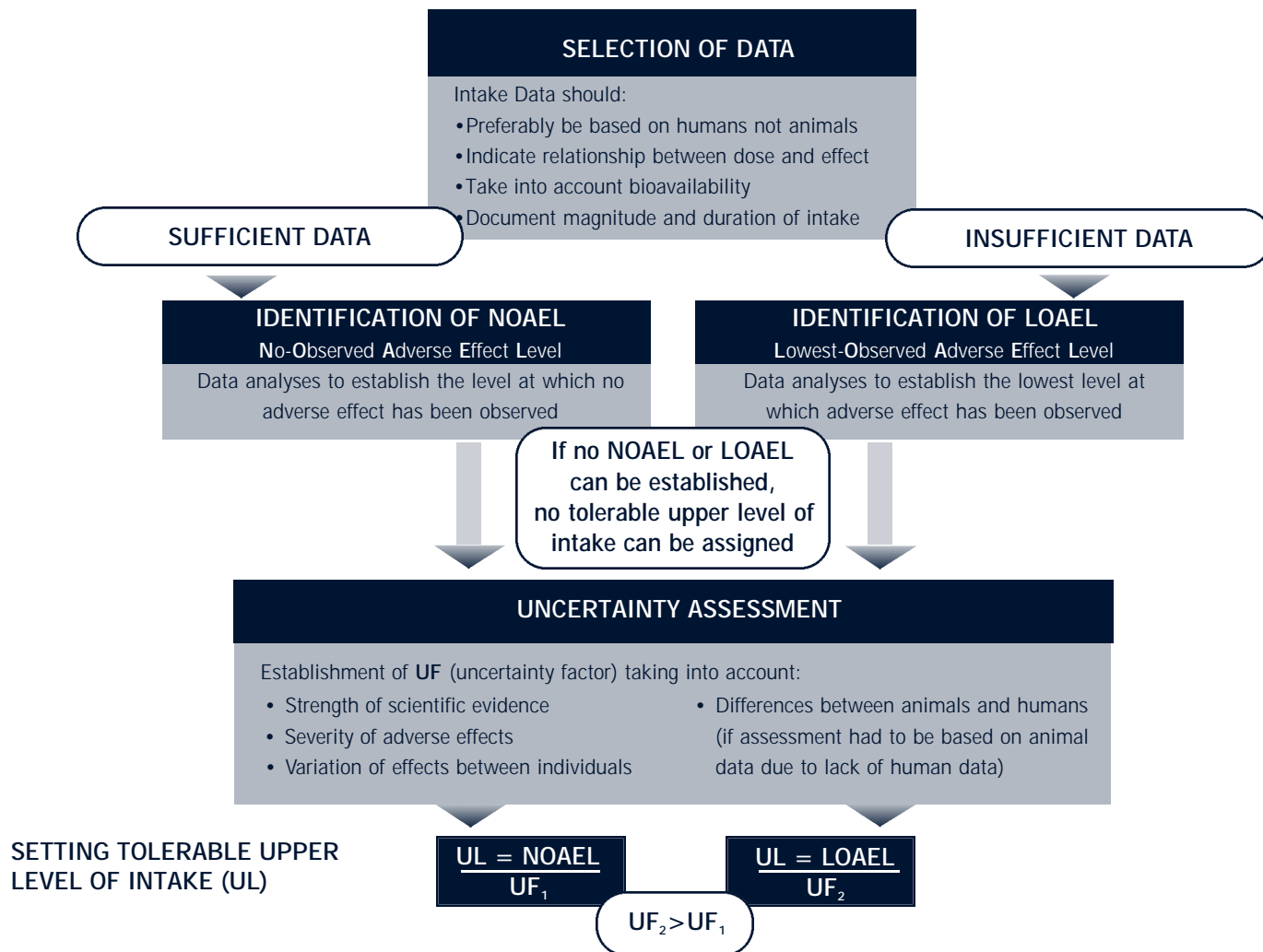
IDENTIFIED ADVERSE EFFECTS

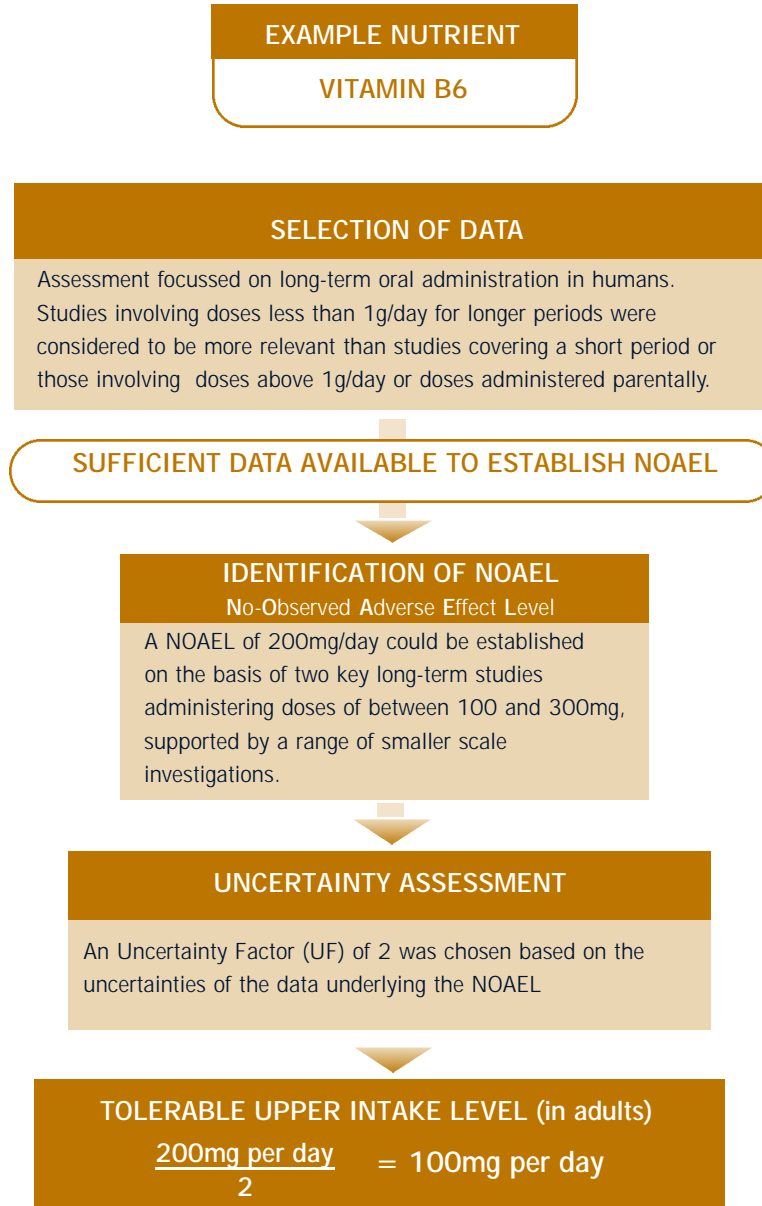
- Sensory neuropathy

No causal association demonstrated between pyridoxine intake and other end points

⁶ Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences (1999). 'Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin and Choline.'

STEP 2 Dose Response Assessment





STEP 3 Exposure Assessment

MODEL

REVIEW OF NUTRIENT INTAKE DATA

Assessment of the usual total daily nutrient intakes, taking account of:

- Normal food sources
- Fortified foods
- Food supplements

EXAMPLE NUTRIENT

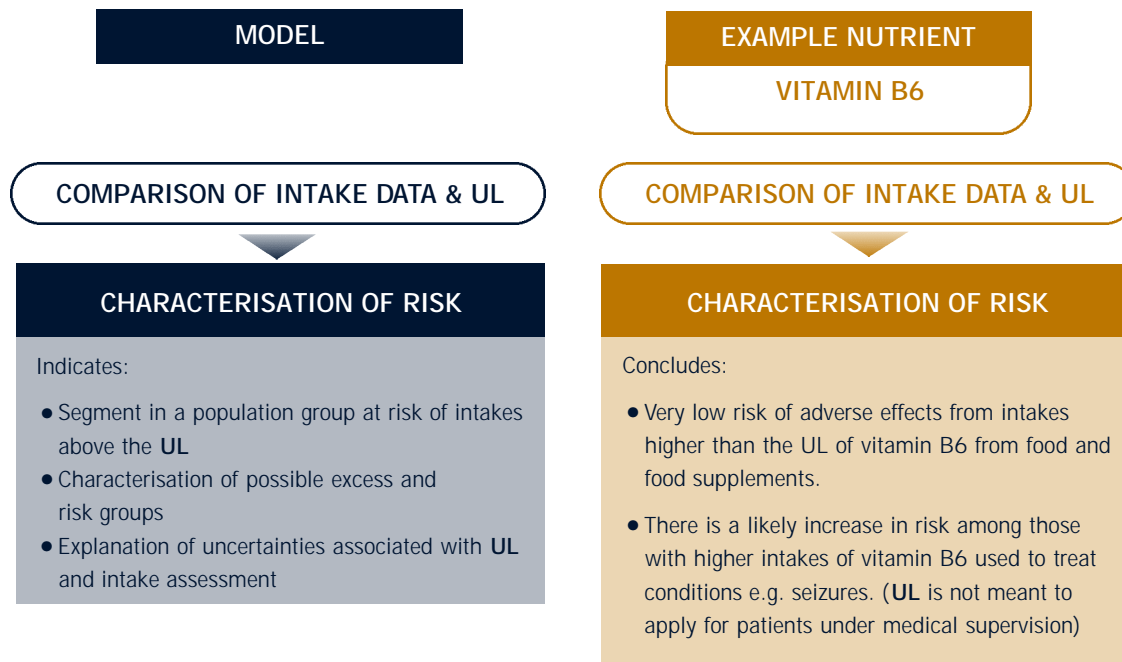
VITAMIN B6

REVIEW OF NUTRIENT INTAKE DATA

Key points for assessment (based on the Third National Health and Nutrition Survey (NHANES III))

- Highest mean intake of vitamin B6 from foods and supplements for any gender and life-stage group was 9mg/day (for pregnant females aged 14 to 55 years)
- Highest reported intake at ninety-fifth percentile was 21mg/day (again for pregnant females aged 14 to 55 years)

STEP 4 Risk Characterisation



Conclusion

The risk assessment of vitamins and minerals is not a simple process. Limitations in the databases both of dose-response relationships and current total nutrient intake (from food sources, fortified foods, food supplements) of European citizens pose problems for risk assessors.

The model outlined in this booklet does, however, provide a valuable framework for risk assessment and one that reflects the specific characteristics of vitamins and minerals. Through the essential information it provides to risk managers, risk assessment will help to characterise and eliminate the risk of adverse effects through excessive nutrient intake.