

Risk Assessment and Risk Management of Vitamins and Minerals

Report of a workshop organized by the European Academy of Nutritional Sciences (EANS) and by the European Responsible Nutrition Alliance (ERNA), April 30, 2003, Brussels, Belgium

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Objective of workshop: The EANS workshop held in 1998 examined the various approaches to determine requirements and safety of vitamins and minerals. The methodology used and approaches taken on both sides of the Atlantic provided the focus of the event. Over three years later, and with risk assessment much advanced, the progress made was reviewed and inadequacies as well as limitations were defined.

In addition, this workshop looked beyond assessment to the broader context in which nutrition science operates. What are the particular problems facing risk managers in the light of risk assessment conclusions? To what extent can nutrition research provide the answers that risk managers require and should the nutrition research agenda be shaped by the needs of the policymaker?

Introduction

Some of the objectives of the European Academy of Nutritional Sciences (EANS) are to initiate meetings, offer a platform for scientific discussion, and provide a scientific umbrella for investigating the application of nutrition science. In 1998, EANS, in cooperation with the TNO Nutrition and Food Research Institute (Netherlands), sponsored a workshop for experts from academia and regulatory bodies to discuss the approach of the US Institute of Medicine's Food Nutrition Board (FNB) and Health Canada to daily nutrient requirements and their relevance for Europe [1]. This workshop focused on the general concept and approach for defining and establishing requirement values, the so-called Dietary Reference Intakes

(DRI). The workshop considered in particular the FNB model for the development of tolerable upper intake levels (UL), and whether such an approach could also be applied for the risk assessment of nutrients in Europe. The development of a benchmark for safety in the form of the UL for vitamins and minerals was considered necessary due to the increased interest in fortified foods and the broad availability of dietary supplements. The UL as defined by the US FNB is the highest level of daily chronic total nutrient intake that is likely to pose no risks of adverse health effects in almost all individuals in particular life stages and gender groups. As intake increases above the UL, the risk of adverse effects increases [2].

The translation of the result of the risk assessment process by risk managers into guidance for regulatory ac-

tion was not addressed at the 1998 workshop. At that time, the FNB had applied the risk assessment model to a set of minerals (calcium, phosphorus, magnesium, vitamin D, and fluoride) [2], whereas a sub-committee of the Scientific Committee on Food (SCF) of the European Community (EU) had just started its own process for risk assessment with the objective of elaborating an opinion on upper tolerable levels of intake for vitamins and minerals. There had previously been a number of activities in various countries in Europe to establish safety levels for vitamins and minerals; e.g., by the UK COMA [3], the Dutch National Food and Nutrition Council [4], the EU Scientific Committee on Food SCF [5], the French Conseil Supérieure d'Hygiène Publique [6], the Nordic Council of Ministers [7], the WHO/FAO/IAEA [8], and the European Federation of Health Product Manufacturers [9]. However, different risk assessment procedures were utilized in these activities with focus on safety aspects, but in most cases ULs were not defined.

Since the 1998 workshop substantial progress has been made in Europe in building the necessary scientific foundations for the EU's regulatory framework. The Scientific Committee on Food (SCF) of the European Community (EU) on Upper Levels of Vitamins and Minerals has published guidelines for the development of tolerable upper intake levels [10], and has already developed opinions on the majority of vitamins and minerals [11]. The European Commission has drafted a proposal for a harmonized regulatory framework on the voluntary addition of vitamins and minerals to foods [12]. This follows the adoption of a Directive by the European Community governing the use of vitamins and minerals in food supplements in 2002 [13].

The US FNB/Health Canada has finalized the DRI process for vitamins and minerals and evaluated the setting of tolerable ULs for all vitamins and minerals using the risk assessment model [14]. No ULs were established for vitamins B₁, B₂, pantothenic acid, biotin, vitamin B₁₂, vitamin K, beta-carotene, chromium, arsenic, and silicon, because either available human data were not sufficient to develop a UL, or no evidence of adverse effects in animals were observed, or due to lack of evidence on adverse effects in humans [2, 15–17]. Several national committees (Germany/Austria/Switzerland; Japan; China) have issued within their re-evaluation of the dietary recommendations, safety values, or tolerable upper levels of intake for vitamins and minerals [18–20], however, without applying the comprehensive approach of risk assessment used in the USA/Canada or now by the SCF in Europe. In the UK, an Expert Group on Vitamins and Minerals (EVM) undertook a review on the intake levels of individual vitamins and minerals associated with adverse effects applying the risk assessment process in order to provide guidance to the Food Standards Agency on safe upper levels

of intake from supplements. A provisional report was published for comments last year [21] and shortly after the workshop the final report was published [22].

The risk assessment that has been generated worldwide has been considerable. Once completed, risk managers must then critically elaborate on problems they are facing and translate these opinions into coherent policy and, where necessary, regulatory measures. EANS therefore invited both risk assessors and risk managers to the 2003 workshop to provide a platform for exchange of experience between actors involved with these two stages of risk analysis. This workshop did not deal with what is traditionally considered to be the third element of risk analysis, namely risk communication to the consumer.

The Risk Assessment Process

Risk is defined as the probability of an adverse effect occurring at some specific level of long-term exposure. The model for the assessment of risk has been discussed in the earlier workshop by EANS [1] and has been described in detail elsewhere [2, 10, 23]. A. Flynn, the chairperson of the SCF Working Group on Upper Levels for Vitamins and Minerals, summarized the main principles of the risk assessment process for the workshop participants. For nutrients, there is a long history of safe consumption at intakes with the normal diet. For some of the nutrients there is also a long-term consumption at levels above dietary intake (e.g., dietary supplements) without reported adverse effects. However, there is concern that for some sensitive individuals the total exposure to some of the vitamins and minerals from all sources including supplements and fortified food could reach intake levels that might cause adverse effects. Therefore, risk assessment for some of the nutrients is considered to be essential for setting the scientific basis for decisions related to safety and is intended to avoid harm from excessive intakes. Risk assessment is the first step in risk analysis, followed by risk management and risk communication. It is considered to be a purely scientific exercise that in principle should not be influenced by value judgments, but should be a neutral evaluation of the hazard-harm relationship.

Risk assessment consists of the following steps:

- **Hazard identification:** collection, organization, and evaluation of all available information, preferably human data, regarding adverse effects of a given nutrient. It determines the potential health problem that may occur through excessive intake.
- **Dose-response assessment:** determination of the relationship between nutrient intake and adverse effect in

terms of incidence and severity. This step identifies a NOAEL (no-observed-adverse-effect-level) or a LOAEL (lowest-observed-adverse-effect-level). The tolerable upper intake level (UL) is generally based on a NOAEL (the highest intake at which no adverse effect has been observed), or if a NOAEL cannot be identified, on the LOAEL (the lowest intake at which an adverse effect has been observed). The derivation of a UL from a NOAEL (or a LOAEL) involves a series of choices about what uncertainty factor (UF) should be used to deal with uncertainties such as gaps in data (lack of human data, uncertainties in methodology and study design, severity of an adverse effect, variation of effects between individuals, differences between animal and human data).

- **Exposure assessment:** evaluation of the distribution of total nutrient intake within the general population.
- **Risk characterization:** this final step expresses a possible risk as the fraction of the exposed population, if any, that exceeds the UL and characterizes the magnitude of any such risk and the scientific uncertainties.

The participants were in agreement that risk assessment does not take into account any possible benefits of a nutrient and is not dealing with strategies and recommendations for reducing risk, since this is the focus of risk management.

Table I gives an overview on upper levels for vitamins and minerals published by different organizations and committees. The table was presented by J. Hathcock.

This table indicates three groups of nutrients:

- Nutrients for which, on the available scientific evidence, no UL was set, or are considered safe also at high intakes (vitamins B₁, B₂, B₁₂, pantothenic acid, biotin, folate from diet, vitamin K, potassium, chromium, calcium). No special concern by risk management is required.
- Nutrients for which the values set by the various organizations and committees are quite similar (vitamins D, C, E, magnesium from supplements, folic acid). These nutrients should be monitored by risk management.
- Nutrients for which the values differ substantially (vitamin A, vitamin B₆, iron, selenium, zinc, beta-carotene). These nutrients require special attention by risk management on a case-by-case basis and a close follow-up on newly emerging scientific evidence. Several of these nutrients will be discussed in the next chapter.

Difficulties in Risk Assessment

1. Interpretation of Available Data

Three case reports that illustrated some of the limitations of the risk assessment approach were presented by risk assessors attending this workshop. In his introductory remarks, I. Munro underlined that, besides the uncertainty in the overall database, the major difficulty for an expert group dealing with risk assessment is considered to be avoiding “judgment”. Since risk assessment is a scientific exercise it should in principle not be influenced by value judgment. However, the selection of parameters or biological markers to be used in order to define an adverse effect is one that requires a considerable amount of judgment on the part of the risk assessor. The question, for example, of whether an effect on a marker leads to long-term clinical effects or whether it is simply a homeostatic response most often cannot be answered.

1.1 B-Vitamins: Vitamin B₆, nicotinic acid/nicotinamide, folic acid

The judgment of the risk assessor is even more important when the scientific quality of data is the subject of discussion as in case of vitamin B₆. K. Pietrzik summarized in his presentation the scientific database on high doses of vitamin B₆, duration of treatment, and the occurrence of sensory neuropathy. Within the same database, in particular the studies by Dalton and Dalton [25, 26] were differently evaluated by the US FNB and the EU SCF Working Group during the risk assessment process. The FNB concluded that the weaknesses (e.g., no placebo control) and inconsistency of the results in the Dalton and Dalton studies ruled out the use of these results to determine a UL for vitamin B₆. The FNB decided on the basis of other studies a NOAEL of 200 mg/day and an uncertainty factor of 2 to establish a UL of 100 mg/day for adults [15]. In contrast, the EU SCF Working Group judged the scientific merit of the Dalton and Dalton data differently and included these in its evaluation and established a UL of 25 mg/day for vitamin B₆ using a more stringent UF than the FNB. The average intake in these studies of 117 mg/day was divided by a factor of 2, because this intake corresponds to a possible effect level for long-term intake, and by an additional factor of 2 to allow for deficiencies in the database [11]. The discussion showed that no agreement can be reached on the Dalton and Dalton data [25, 26]. It was therefore questioned whether such studies would correspond to the criteria of “scientific risk assessment based on *generally accepted* scientific data” as provided for by the EU Directive on Food Supplements (Article 5) [13]. Critical reviews on the weaknesses of Dalton and Dalton study results have been published elsewhere [27, 28].

Table I: FNB, SCF, EVM and CRN Safety Values

NUTRIENT	FNB	SCF 2003	EVM 2003	CRN 1997	CRN 2003
Vit A, µg	3,000	3,000	3,000 bone mineral density, 1,500 bone fragility	3,000	1,500 suppl (all adults)
Beta -carotene, mg	25	none	7	25 non -smokers	25 non -smokers
Vit D, µg	50	50	25	20	60
Vit E, mg	1,000	300	800 IU = 540 mg	1,200 IU = 800 mg	1,600 IU = 1,070 mg
Vit K	none	none	1,000 µg	30 mg	10 mg
Vit C, mg	2,000	open	1,000	1,000	2,000
Vit B-1, mg	none	none	100	50	100
Vit B-2, mg	none	none	100	200	200
Vit B-6, mg	100	25	10	200 suppl	100 suppl
Folic acid, µg	1,000	1,000	1,000	1,000	1,000
Vit B-12, µg	none	none	1,000	3,000	1,000
Nicotinic acid, mg	35	10	17 suppl	500 (250 slow release)	500 (250 slow release)
Nicotinamide mg	(w/NA)	900	500 suppl	1,500	1,500
Pantothenic acid, mg	none	none	200 suppl	1,000	1,000
Biotin, µg	none	none	900	2,500	2,500
Calcium, mg	2,500	2,500	1,500 suppl	1,500	1,500
Phosphorus, mg	4,000	open	250 suppl	1,500	1,500
Potassium, mg	none	open	3,700	--	1,500 (3x500)
Magnesium, mg	350 free	250 free	400 suppl	700 total	400 suppl
Boron, mg	20	open	9.6	--	6.2
Chromium, µg	none	none	10 mg (not picolinate)	1,000 (any salt)	1,000 (any salt)
Copper, mg	10	5	10	9	9
Fluoride, mg	10	open	--	--	6
Iodide, µg	1,100	600	940 total, 500 suppl	1,000	500 suppl
Iron, mg	45 empty	open	17	65 full stomach	65 full stomach
Manganese, mg	11	none	1.2 total, 4 suppl	10	10
Molybdenum, µg	2,000	600	230 diet, 0 suppl	350	350 suppl
Selenium, µg	400	300	300 total, 200 suppl	200 suppl	200 suppl (direct data)
Zinc, mg	40	25	25 suppl	30 suppl	30 suppl

Footnote to Table I: The table has been updated with the recent SCF values [11].

FNB: SCF: opinion on *tolerable upper levels of intake (UL)* set by FNB/Health Canada [2,15-17] and by the SCF subcommittee of the EU resulting from risk assessment [11]; (*open*: to be established, not yet evaluated; *none*: evaluated and no UL set)

EVM: UK Expert Group on Vitamins and Minerals: values represent *safe upper levels of intake* to be used as guidance for maximum levels of vitamins and minerals in supplements taken from the provisional report issued 2002 [21].

CRN 1997: *safe intake levels* for vitamin and mineral supplements given in a report [9] commissioned by the European Federation of Health Product Manufacturers Association EHPM

CRN US 2003: *safe intake values* for vitamin and mineral supplements as guidance for the food supplement industry [24]

The EVM and CRN approach includes what are traditionally understood as risk management aspects as guidance for the respective supplement manufactures.

Similarly, using the same scientific data, the EU SCF Subcommittee used the observation of occasional flushing at 30 mg/day intake of nicotinic acid and a higher UF of 3 for nicotinic acid led to the setting of a UL of 10 mg/day, whereas the US FNB used the LOAEL of 50 mg/day (consistent flushing) and a UF of 1.5 to derive a UL of 35 mg/day for adults [11, 15]. There were no differences in the evaluation of a UL for folic acid and both experts' groups decided on a UL of 1000 µg folic acid/day and on no UL for folate from food [11,15].

1.2 Vitamin A

Diane Bedford, a member of the Food Standard Agency (FSA), presented a case study on vitamin A. The task of the FSA is to protect public health from risks that may arise in connection with the consumption of food and food supplements sold under food law in the UK. FSA had undertaken to evaluate the opinion generated by the risk assessment process that was carried out by the EVM (draft report published August 2002 [21]) to establish principles on which controls for ensuring safety of vitamin and mineral supplements could be based on. In addition, the opinion of the EU SCF on vitamin A [11] was used in the deliberations of the FSA. The EVM and the EU SCF expressed with regard to the potential teratogenicity of vitamin A the same opinion:

- "it is prudent to take 3000 µg RE/day as the threshold for teratogenicity (EVM)" (guidance for women in reproductive age).
- "a cautious approach would be to use the low value from the study of Rothman *et al* [29]" and a upper tolerable level of intake was set at 3000 µg RE/day (EU SCF).

Likewise, the US FNB based their opinion on teratogenicity as critical adverse effect and set a tolerable upper level of intake UL of 3000 µg /day for women in the child-bearing age based on the results of the Rothman *et al* data [29].

The EVM also took into account, however, recent epidemiological data on changes in bone mineral density and hip fracture risk associated with vitamin A intakes from food of 1500 and 3000 µg RE/day, respectively [30, 31] and decided on the basis of these data that "it is not possible to establish a safe upper level of intake for vitamin A and suggested as a guidance that total intakes greater than 1500 µg RE/day may be inappropriate". On the contrary, the EU SCF committee considered that the currently available data on potential adverse effects of vitamin A regarding reduction of bone mineral density and increase in hip fractures did not provide sufficient evidence of causality, and were not appropriate for establishing a tolerable upper level for women. Similarly, the US FNB [17]

concluded that "the findings from these studies are provocative but conflicting, and therefore, they are not useful to set a UL for vitamin A", and "that more research is needed, primarily among pre- and post-menopausal women" to demonstrate a possible link between bone density, risk of fracture, and vitamin A intake.

1.3 Iron

Sue Fairweather-Tait reviewed the scientific basis on which requirement values and tolerable upper levels of intake UL were set. The iron content in the body is highly conserved and iron balance is maintained by the regulation of iron absorption in the small intestine, which is subject to homeostatic control. Whereas heme iron is highly bioavailable, non-heme iron absorption depends on the iron source and the presence of dietary modifiers either enhancing or inhibiting non-heme iron absorption. For iron overload in adults there are a number of biochemical markers available, but it seems difficult to define cut-off points due to inter-individual variation.

Most cases of acute iron overload occur in young children from overdose of supplemental iron. In women the response to iron supplementation depends on total iron absorption, which is inversely related to the respective iron stores. Most patients with the iron overload disease hereditary hemochromatosis are homozygous for the C282Y mutation of the *HFE* gene, but clinical penetration of the gene seems not to be high (< 1%). Since the prevalence of this group is rather low, regarding the UL this group was considered as a special group and not included in the setting of a UL by the US FNB. Heterozygous carriers of the C282Y mutation of the *HFE* gene could be at increased risk for accumulation of iron from dietary sources, but currently there is no evidence to support this possibility. Therefore, the US FNB has included this group in the general population in setting a UL for iron.

Furthermore, the relationship between the level of dietary intake of iron and the risk of coronary heart disease and whether a moderately elevated iron status causes disease was discussed. A recent meta-analysis of 12 prospective epidemiological studies concluded that there is no strong association between iron status and coronary heart disease [32]. Other data from prospective studies suggesting an increased risk of colorectal cancer with increased iron stores was considered inconclusive at this time.

Bioavailability has a major impact on iron status. Therefore, Sue Fairweather-Tait questioned the setting of a single value for the UL of iron, especially with regard to the individual genotype that may affect absorption of dietary iron. This may necessitate ULs directed towards individuals rather than population groups

The case studies presented demonstrated that opinions resulting from risk assessment using one and the same sci-

entific database may be different due to the judgment of the experts involved in the evaluation, leading to different UL values or different opinions. Risk managers should be aware of these differences when translating the results from risk assessment into proposals for action by the authorities.

2. Setting Uncertainty Factors

Another element that necessitates judgment on the part of risk assessors is the setting of the uncertainty factors for the various nutrients. The UF takes account of scientific uncertainties associated with the extrapolation of observed data in a selected group to the general population, with the inadequacies of available data, the selection of the parameters to determine a NOAEL or LOAEL, and the consideration of the severity of an adverse effect (mild reversible change, e.g., choline; irreversible adverse effect, e.g., vitamin B₆). Given the number of factors involved, it is perhaps unsurprising that the selection of different UFs is the primary cause of major divergences in the setting of a UL. Vitamin B₆, nicotinic acid, iron, magnesium, zinc, selenium, and molybdenum were mentioned as examples. Two reasons for the necessity of judgment were stressed by A. Flynn: the issue of the variability in population groups and the lack of sufficient scientific data for the risk assessment process leading to the introduction of uncertainty factors. Nevertheless, A. Flynn stressed that the risk assessment process is dealing with all uncertainties and that additional “safety factors” no longer need to be introduced by risk managers when translating the results of risk assessment into guidelines and proposals for regulatory action by the authorities.

3. Setting ULs for Children

A. Flynn pointed out that appropriate data on adverse effects for most of the vitamins and minerals in infants and children are lacking and, therefore, the ULs for these age groups were determined by extrapolation from the UL for adults based on body weight differences using reference weights ($UL_{\text{child}} = (UL_{\text{adult}}) (\text{weight}_{\text{child}}/\text{weight}_{\text{adult}})^{0.75}$). The use of these reference weights yields a conservative UL to protect the sensitive individuals in each age group. However, J. Hathcock informed the participants in the discussion that by using the NHANES III survey data from the US (Third National Health and Nutrition Examination Survey, 1988-1994) the current intake of several of these nutrients exceeds the set UL values by 30–50%, indicating that more basic research data in these age groups are urgently needed [33].

4. Summary

The discussion demonstrated that risk assessment is not so much a precise measurement, but rather an approximation depending on the availability and quality of data, despite thorough and independent scientific evaluation. The presentations and the discussion identified the following inadequacies:

- lack of well-designed human studies of significant duration at multi-dose levels of intake.
- insufficient data for dose-response assessment.
- lack of exposure and intake data in epidemiological studies.
- overinterpretation and usefulness of epidemiological data with regard to safety, since these studies were mostly designed for other purposes than for the detection of adverse effects and were not collected systematically according to safety measurements.
- the lack of data in children.
- limitation in data regarding causality of adverse effects (e.g., vitamin A).
- insufficient data on the variability of the sensitivity of individuals to adverse effects and its dependency on various factors such as age, gender, body weight, lean body mass, genetics, etc.

The achievements made with subjecting nutrients to the process of risk assessment and identifying respective upper levels of intakes were considered a great step forward and of much importance for guaranteeing consumer safety. Nevertheless, due to gaps in the scientific database, certain questions remain unanswered. The group expressed confidence that the pending cases will be solved in the future by emerging science and possibly by more harmonized approaches.

Risk Management: Interpreting Risk Assessment

The afternoon session of the workshop addressed the issue of risk management. Many of the risk managers attending the workshop presented their views on the process of converting risk assessment into risk management and the potential problems that arise.

1. Understanding Risk Assessment

I. Munro reviewed the definition of risk and the meaning of the UL for the purposes of risk management. Risk is defined as the probability of an adverse effect at some specified level of exposure to a substance, such as a nu-

trient. The Tolerable Upper Level of Intake (UL) is the highest level of total daily nutrient intake from all sources (food, enriched food, food supplements) and is to be understood as an upper benchmark for long-term, safe daily intake. The risk of adverse effects increases when intake routinely rises above the UL. There are no data available on the variability of the UL within population groups and also the shape of the risk curve beyond the UL is generally not known. However, the application of uncertainty factors for each of the nutrients to derive a UL from either NOAEL or LOAEL covers all uncertainties. Therefore, there is no necessity to have additional uncertainty or *safety* factors introduced during risk management when building on the opinion of risk assessment. Risk assessment is subject to review should additional relevant scientific data become available. That also implies that risk managers have to re-evaluate their view on possibly revised opinions resulting from risk assessment.

2. Variations between Risk Assessment Bodies

Several of the risk managers present expressed surprise at the considerable divergence between the UL set by the EU SCF Working Group and those of the US FNB, with respect to the same scientific database. The SCF UL of 300 mg and US FNB UL of 1000 mg for vitamin E, and the differing values for vitamin B₆ were repeatedly used as examples. It was suggested that from the perspective of the risk manager, divergent results from the scientific risk assessment process were disconcerting. This may leave the risk managers uncertain as to which figure to use for their task of translation of the risk assessment work into risk management measures and may undermine their confidence in the accuracy and value of risk assessment. However, other participants countered that the problem needed to be seen in perspective. In some cases, there were indeed differences in independent evaluations of the database leading to selection of different parameters for evaluating adverse effects and to different uncertainty factors according to the judgment of those expert groups. Nevertheless, most of the UL values are more or less comparable (see Table I) [2, 11, 15–17]. A number of both risk assessors and risk managers suggested that international bodies should come together to address the differences in their risk assessment work and try to reach a consensus. This was felt to be important to the risk managers' confidence in the risk assessment and to avoid potential international trade problems in the future.

3. Different Terminology resulting from Risk Assessment

During the afternoon session, the discussion was complicated somewhat by the different terminology used by participants. The EVM introduced a new terminology besides the tolerable upper levels of intake used by the FNB and by the SCF Subcommittee, namely the safe upper levels to be used as *guidance* for maximum levels of vitamins and minerals in supplements. The scientific basis was considered to be adequate for establishing *safe* upper levels for vitamin B₆, vitamin E, boron, copper, nickel, selenium, zinc, and silicon whereas for the other vitamins and minerals only a certain guidance was possible, since the scientific database for the other vitamins was considered to be insufficient by the EVM. Data were considered inadequate for germanium, sodium chloride, and vanadium.

Similarly, J. Hathcock mentioned in his presentation that an expert group established by the Transatlantic Business Dialogue (TABD; refer to www.tabd.com) used a direct method to establish maximum levels of supplemental intake on the basis of the tolerable upper level of intake, but with stronger reliance on clinical data and reliance on NOAEL from human data, avoiding LOAEL values if possible, by considering hazards only and not nuisance effects, and the use of direct evidence of adverse effects wherever possible, and not biochemical indicators. On this basis a conservative selection of "human supplemental NOAEL" was made. It was suggested that harmonizing the somewhat confusing terminology used by different groups would assist the risk manager in his understanding of the meaning and implications of risk assessment.

4. Application of Risk Assessment by Risk Managers

Complementary approaches to ensuring the supply of dietary micronutrients include food-based strategies, fortification strategies, and food supplementation. In order to protect consumers, risk management must make proposals to the regulatory authorities that guarantee intakes that safely avoid both types of risk: excess and inadequacy.

4.1 Food supplements

B. Viell provided an overview of risk management measures taken in Germany with regard to fortified food and food supplements in response to the EU SCF risk characterization of vitamins and minerals. In general, the UL concept was considered by Germany to have certain weaknesses: it is based on bibliographic evidence, retrospective analysis, underreporting of side effects, and extrapolation to long-term application of nutrients. Therefore, it

was considered that the UL defined by the EU SCF risk assessment must be subjected to additional safety factors. In the discussion, this view was generally disputed, including by members of the EU SCF Working Group who clarified that its risk assessment deliberately dealt with all uncertainties, making additional “safety factors” redundant.

On the available limited database, the EU SCF was unable to set a UL for manganese and determined that oral exposure to manganese beyond the level normally present in food and beverages could represent a risk of adverse health effects (neurotoxicity) without evidence of any health benefit [11]. On the basis of this risk assessment, Germany decided to prohibit the addition of manganese to foods.

For magnesium, a UL of 250 mg/day from supplements (daily intake obtained from two or more doses) was set by the EU SCF. Risk managers in Germany decided that levels up to 200 mg/day should be allowed for food supplements, but dosages greater than 125 mg/day must be divided or the consumer has to be informed about the diarrhoeagenic effect of magnesium salts. Dosages less than 125 mg/day can be marketed without any condition.

The EU SCF opinion regarding β -carotene stated that “existing evidence from human trials indicates that supplemental carotene (20 mg/day or more) is contraindicated for use in current, heavy smokers” and “that there is insufficient scientific basis to set a precise figure for an UL of isolated β -carotene”. Since the intake of β -carotene from food sources and as a food additive depending on seasonal and diet variations represents up to 10 mg/day, there may be a small difference between levels that may confer health benefits (up to 10 mg/day) and those that may produce adverse effects in smokers (20 mg/day). It was concluded that the use of β -carotene as a supplement should be regarded cautiously. The risk management decision in Germany is a proposal for a special directive that sets limits of food supplements of ≤ 2 mg/day and for enriched foods of ≤ 2 mg per 100 mL or per 100 g.

M. Langman, chair of the UK EVM Expert Group, introduced the composition and working procedure of that group and presented an overview on the current status. The composition of the Expert Group differs from the *purely scientific* expert groups of the US FNB and EU SCF, by including, in addition to toxicologists, food and pharmaceutical experts, four observers from the food industry, health food industry, consumers, and complementary medicine. The most recent data from observational studies were used with human studies as preference, but animal data, if of good quality, were also used when human data were inadequate. The exposure assessment within the risk assessment process evaluated intakes from any supplement freely available and included fortified foods as

well, but excluded intake by licensed medicines. The intake data were derived from the UK National Food Survey, the Total Diet Study, and from the National Diet and Nutrition Survey Study.

4.2 Addition of nutrients to food

D. Richardson summarized the current status with regard to additions of nutrients to foods (substitution, restoration, fortification). There are two sides for risk of adverse effects: undernutrition with nutrient deficiencies and overconsumption with adverse effects as consequences. Currently, there are inconsistencies in practice and legislation between different countries and trading partners regarding food fortification. The range of options goes from “no addition allowed to any food, addition allowed to certain foods, certain nutrients allowed to be added only, fortification with limits in added amounts, and fortification with no limits in added amounts”. This makes it difficult for the food industry within the trading blocks, but the forthcoming EU Directive on the addition of vitamins and minerals and certain other substances to foods [12] will solve most of these problems. Nevertheless, there will be other issues to be solved by the food manufacturers such as stability during processing, shelf-life stability of nutrients in the foods, retention in the fortified products (flour, cereals, spreads, etc.). The choice on which iron source is being used has impact on its bioavailability, but also may speed up vitamin degradation and lead to loss of nutritional value of a food product. In addition, there are technical limitations restricting addition to some products, and impact on sensory acceptability (calcium, magnesium).

With regard to safety, D. Richardson proposed that risk management for food fortification might have only to deal with those nutrients with a relatively small safety margin where the recommended daily allowance (RDA) and the UL is not widely separated (vitamin A, selenium, iron, zinc, manganese, copper), and suggested a case-by-case risk management approach for these nutrients. Vitamins and minerals having a large safety margin such as the B-vitamins, vitamins C, E, K, and the minerals magnesium, nickel, iodine, calcium, and phosphorus could be grouped together. Case-by-case risk management solutions should consider, however, that risk assessment has already built in appropriate margins of safety. In addition, issues on short-term and long-term exposure, shelf-life requirements, labeling and education, and mode of addition of nutrients with regard to public health benefits (restoration, substitution, fortification) were suggested to be addressed by risk managers. But, to contribute to consumer protection and consumer choice risk management outcome should be proportionate, pragmatic, and enforceable and should stimulate research and innovation.

The Risk Assessment/ Risk Management Interface

In general terms, nutritional science is helping to provide information and answers in the form of risk assessment opinions. Unfortunately the scientific database will never be complete and there will always be uncertainties and gaps of knowledge. As discussed above, some exercising of individual judgment on behalf of members of expert groups is virtually inevitable, although in principle risk assessment as a scientific exercise should not be influenced by value judgment. Given the element of judgment included in risk assessment and the inherent complexities of many of the issues, it was suggested by participants that dialogue between risk assessors and managers needed to go beyond simply issuing scientific opinions.

1. Cooperation between Risk Assessors and Risk Managers

M. Rogers presented on the interface between risk assessment and management within the EU. Risk managers have to know what to regulate, what would be the probability of a given risk, and what risk exposure level might be acceptable in order to evaluate their options. The tendency within the EU has generally been to separate risk assessment and risk management as far as possible [European Food Safety Agency (EFSA)] [34]. However, a more recent regulation stipulates that “*Authority, Commission and Member States shall cooperate to promote the effective coherence between risk assessment, risk management and risk communication functions*” (The regulation EC No 178/2002, article 22.8) [35]. This view would imply a more two-way, interactive, and symbiotic relationship between risk assessors and that risk managers express clearly what they would optimally need to undertake their task.

2. Making Risk Management easier

B. Viell challenged risk assessors attending the workshop to provide risk managers with a framework that includes criteria for a systematic and harmonized assessment (*gold standard*) to be used as if a nutrient would be evaluated for the first time, similar to the process used for Novel Food ingredients. The respective vitamins and minerals were then to be assessed on that basis. This idea was supported by risk managers present at the workshop, along with the availability of such a process to lead to more transparency and less value judgment during the risk assessment process.

3. Need for better Information among Risk Managers

Risk managers present at the workshop considered it important that risk assessors should communicate for what purpose and according to which process risk has been assessed, since the various opinions on safety levels available are not always comparable. By providing the risk manager with transparency regarding purpose, objective, and terminology of the respective safety levels, it will be possible to reduce confusion and misinterpretation. Risk managers argued that this would help them understand different views and interpretations on the same scientific database and the resultant divergence in upper levels. Moreover, participants suggested that regulations or other risk management levels put in place should be subject to review, since the science that forms pre-eminent basis for regulatory action is evolving quickly. Improved communication of the outcome and interpretation of risk assessment by risk assessors would facilitate the risk manager's task of setting maximum dosages for supplements and food fortification and ensure that consumers achieve intakes within safe ranges for all nutrients.

Specifically, it was suggested that better communication would help risk managers to

- understand the nature of risk (reversible versus irreversible)
- judge on the potential magnitude of risk for the general population [what fraction of the population has intakes > UL, > NOAEL, and > LOAEL, and what are the major intake sources (food supplements, enriched food, including mean intake and 95th percentile for various age groups)]
- envisage the degree of uncertainty caused, e.g., by lack of scientific data, underreporting of side effects, extrapolation to long-term intake, and judgment with regard to the introduction of uncertainty factors
- understand how uncertainties had been incorporated into risk assessment
- interpret lack of evidence of adverse effects not necessarily as evidence of absence of adverse effects.
- select the necessary precautionary action for guidance to the regulators
- support the best and most feasible route for regulatory action, including the ability to measure the effectiveness thereof.

Conclusions

In most cases the proposed values for the upper level of intake for the individual vitamins and minerals set by var-

ious organizations and expert committees are quite similar. Exceptions are vitamin B₆, vitamin A, beta-carotene, iron, selenium, and zinc, for which the proposed values differ substantially. Insufficient scientific evidence but also differing opinions on the interpretation of the available scientific database were the main reasons for the divergences in these vitamins and minerals. It was suggested that international bodies meet to address the differences in the risk assessment process and to elaborate a consensus.

There is a considerable lack of sound scientific data on adverse effects for most of these nutrients in infants and children that has made it necessary to extrapolate the upper levels of intake from those of adults. For several of the vitamins and minerals there is also a lack of long-term human studies at multi-dose level of intake and insufficient data for dose-response assessment. However, many of these studies cannot be carried out for ethical reasons. It is nevertheless important that risk assessment is subject to review on the basis of newly emerging scientific data. The role of science as the basis for regulatory action was not disputed.

In their task of translating the outcome of the risk assessment process into risk management measures, it was considered essential that risk managers closely cooperate with the risk assessing bodies. Such a closer co-operation would be further facilitated by the development of a common terminology. This process would reassure risk managers that all the inherent uncertainties of risk assessment have been accounted for and that the risk manager is not obliged to introduce additional risk or safety factors. Case-by-case risk management will be necessary, especially for those nutrients with a relatively small margin between the recommended daily intake (RDA) and the tolerable upper level of intake (UL).

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Appendix

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