

ADDITION OF NUTRIENTS TO FOOD: NUTRITIONAL AND SAFETY CONSIDERATIONS

Moving towards a scientific consensus



SUMMARY OF A WORKSHOP HELD IN DECEMBER 1997

Organised by the ILSI Europe
Addition of Nutrients to Food Task Force

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Summary Report of a Workshop on Addition of Nutrients to Food: Nutritional and Safety Considerations – moving towards a scientific consensus

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***ADDITION OF NUTRIENTS TO FOOD:
NUTRITIONAL AND SAFETY CONSIDERATIONS***

Moving towards a scientific consensus

SUMMARY OF A WORKSHOP HELD IN DECEMBER 1997

ORGANISED BY THE ILSI EUROPE ADDITION OF NUTRIENTS TO FOOD TASK FORCE

NOVEMBER 1998

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INTRODUCTION AND BACKGROUND

In a workshop held by ILSI Europe in Lisbon (4–5 December 1997), experts from academia, regulatory agencies, industry and consumer groups from key countries in Europe reviewed the nutritional and safety considerations associated with the addition of nutrients to foods. The discussions were triggered by the plans of the European authorities to harmonise the regulatory framework in this area: current rules differ significantly between countries and could lead to barriers to trade which could be avoided and to possible disadvantages to the consumer. In addition to the perspective of the European Union, current considerations by Codex Alimentarius were reviewed, because harmonisation at all levels will benefit from a solid science base.

ILSI Europe was seen as a competent group to bring together scientific experts in the relevant fields to determine how, and to what extent, the addition of nutrients to foods can affect the nutritional and health status of consumers in Europe and where potential safety concerns would necessitate restrictions. It was recognised that the results of this scientific workshop would be of relevance to the regulatory processes and, therefore, may affect future public health in Europe.

In preparation for this workshop three expert groups developed “theme papers”, which are summarised below. They will be submitted for publication in their full length in a peer-reviewed journal. These papers collected and reviewed the relevant information and were distributed to all participants before the meeting to provide a basis for discussion. The papers addressed the following questions:

- What is the actual level of intake and status for relevant micronutrients? Is there a need to discuss the addition of micronutrients, i.e., does suboptimal micronutrient status exist among Europeans?
- Are there benefits, beyond preventing deficiency diseases, of increasing dietary intakes of some micronutrients beyond current recommended daily allowances (RDAs)?
- What safety concerns arise when micronutrients are added to food?

The conclusion was that there is a need to discuss the addition of micronutrients because some subgroups of the population have insufficient intakes of certain micronutrients. Moreover, data suggest benefits with intakes beyond current RDAs. The addition of nutrients to foods, however, can be considered only if we are convinced that it can be done safely. In practice, it is known that for most of the nutrients considered in this context, no negative health aspects are to be expected, but in some cases a careful approach is necessary.

For practical reasons, and in line with the current regulatory debate, discussions at the workshop focused on a limited number of micronutrients, i.e. those which are most commonly considered in the context of their addition to food. It is, however, recognised that other substances – trace elements, essential amino acids, fatty acids and some “non-nutrients”, e.g., phytochemicals – are of potential interest. The conclusions from the examples used – vitamins and some minerals – are expected to help address the principles to judge the safety and efficacy of most other substances being considered for addition to foods.

When discussing the addition of micronutrients to foods, we not only include fortification, i.e., the addition of micronutrients which are not normally present at relevant levels in a given food, but also address restoration of micronutrients lost during storage and processing. The latter include the addition of nutrients to “substitution products”, which replace typical sources of key nutrients, e.g., margarine as a replacement for butter.

In these discussions it was recognised that most foods naturally contain appreciable levels of micronutrients in desirable combinations and that adding micronutrients to foods extends this natural range to allow consumers a broader choice of foods with high nutrient density to help them meet dietary needs.

Nine statements, given below, were presented early in the workshop and were discussed in the final session, where they received support by most participants. This led to the following overall conclusion:

- 1. The addition of nutrients to foods can provide an effective and safe tool to improve actual micronutrient intake and status by restoring amounts lost, by providing key nutrients in foods that replace traditional products, and by extending the range of foods rich in relevant micronutrients.*

The workshop aimed at moving towards a scientific consensus. There appeared to be broad agreement on the following overall conclusions:

2. Nutrition surveys across Europe indicate that several population subgroups do not reach national RDAs for several important nutrients. In many cases, the gap between actual and recommended intakes is significant and the prevalence of suboptimal intakes is high, so that improvements are desirable. However, in many other cases, no supporting data on nutrient status are available.
3. Reaching current intake recommendations is usually possible via a balanced diet, but it is becoming more difficult as recommendations to reduce food energy intake following sedentary lifestyles are implemented. Without adjustments – and changing dietary habits is a slow process – lower food energy intakes from diets as currently constituted are directly correlated with reduced intakes of micronutrients.
4. Current RDAs are intended as population reference values to cover the nutritional needs of the vast majority of individuals. However, individuals do not know their actual nutrient needs and status. Therefore, intakes by individuals at the high end of need can be a prudent way of ensuring an optimal micronutrient situation.
5. For a number of micronutrients, recent research suggests that intakes at and above current RDAs may provide additional benefits, e.g. by reducing the risk of certain degenerative diseases. If additional research confirms these benefits, the gap would widen between actual and desirable nutrient intakes.
6. For the majority of micronutrients, comfortable safety margins have been shown between safe upper intake levels and intakes likely to be achieved from food products with natural and added micronutrient contents; some micronutrients, however, have a narrow safety margin which requires special care in the overall dietary context.

7. Storage and processing, both industrial and in the home, can affect the levels and utilisation of some critical nutrients in foods. These effects need to be considered when deciding the extent to which the addition of nutrients should be considered.

These factual observations also led to the following key considerations:

8. The science base for a regulatory framework allowing the responsible addition of nutrients to foods is needed to enable the food industry to provide products which help optimise the intake and status of critical micronutrients.
9. The appropriate addition of nutrients is one tool to achieve this goal. This needs to be combined with other steps, such as improved nutrition education and information, i.e., overall increased public awareness of the importance of the diet in optimising health.

The discussions and the agreement reached on the above points are important steps in moving towards a scientific consensus on the nutritional and safety considerations concerning adding nutrients to foods.

EXECUTIVE SUMMARY OF THE PRESENTATIONS AT THE WORKSHOP

The objective of the workshop was to move towards a scientific consensus on the nutritional and safety aspects of adding micronutrients to food. It brought together representatives from academia, consumer organisations, the food industry, government, regulatory agencies and research institutes. The workshop was based mainly on three review papers prepared by expert groups and circulated to participants in advance and being presented at the meeting. These papers reviewed “Nutrient intakes and status in Europe”; “Micronutrient benefits up to and beyond current recommended daily allowances (RDA)” and “Safety aspects of addition of nutrients to food”.

Introductory session

Dr. Basil Mathioudakis, EC-DGIII, Brussels, Belgium, and Professor Arpad Somogyi, BgVV, Berlin, Germany

No harmonised regulatory framework on the addition of vitamins and minerals to foods exists yet in the European Union. A discussion paper on the most important issues which need to be considered for the regulation of the addition of vitamins and minerals was prepared by Directorate General III of the European Commission (EC). General comments on the EC paper addressed the separate measures for the addition of vitamins and minerals to foods and for food supplements. There was concern about the addition of nutrients other than vitamins and minerals. It was also noted that mandatory additions should be left to national authorities and that harmonisation should be limited. Discussions focused on the maximum limits and how they should be determined. Should they be based on nutritional recommendations or solely on safety considerations? Other issues of concern included which nutrients should be added, lower limits of addition, the quantity of food to which limits should be related, and labelling and notification procedures. The debate is ongoing and the EC will gather further information and clarify certain points.

The approach of the joint FAO/WHO Codex Alimentarius programme to make recommendations on the addition of vitamins and minerals was explained. Codex standards, guidelines and recommendations have increased in importance since the signing of the General Agreement on Tariffs and Trade (GATT), especially the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS), the Agreement on Technical Barriers to Trade (TBT) and the establishment of the World Trade Organisation (Uruguay Round, 1995). SPS measures must be based on an assessment of the risks to human life based on scientifically sound evidence.

Micronutrient intakes and status in Europe

Dr. Jantine H. Brussaard, TNO, Zeist, The Netherlands, “Evidence of marginal intakes in Europe”

- Marginal intakes of one or more micronutrients appear to exist within Europe for several population subgroups.
- Data are incomplete for all micronutrients and for all population subgroups within Europe, making international comparison difficult.
- Standardisation of methods to measure and to evaluate food consumption are needed before internationally meaningful comparisons can be made.

- Ideally, more direct measures of micronutrient status would provide conclusive evidence of marginal micronutrient status in population subgroups.

Dr. Henk van den Berg, TNO, Zeist, The Netherlands, "Micronutrient status surveys in Europe"

- Most representative surveys use easily accessible static indicators, such as vitamin and mineral concentrations in blood or urine.
- These indicators are difficult to interpret in terms of nutritional deficiency or risk to health, and at best merely reflect adequacy of body stores.
- There is a great need to improve and to validate markers of biochemical function, which are better indicators of nutritional requirements.
- From data available, nutrients (and populations at risk) include vitamin B₆ (particularly elderly people), iron (women), vitamin D (elderly people) and iodine (general population).
- For folate and vitamin B₁₂, putative functional markers such as homocysteine already exist. These show widespread suboptimal status in adults and suggest increased risk of birth defects and possibly coronary heart disease.
- The development of reliable functional indicators should provide more definitive RDAs and give indicative evidence of marginal nutritional status in population subgroups.

Professor Olga Moreiras, University of Madrid, Spain, "How changing lifestyles may affect dietary habits"

- Lifestyle changes in the West have resulted in reduced food and energy intakes owing to reduced physical activity, dieting and demographic ageing.
- National intake data (United Kingdom, Spain) show that these changes have resulted in reduced intakes of iron, calcium, zinc, vitamin A and vitamin C.
- Changes in meal patterns and food choices can also result in reduced nutrient density in the overall diet.
- Medication can adversely affect nutrition, particularly in elderly people.
- Antioxidant status is compromised by smoking.

Dr. David Buss, Independent Nutrition Consultant, United Kingdom, "Conclusions, with particular regard to the impact of fortification"

- The nutritional value of foods can be increased in many ways, including better preservation, storage and processing, as well as fortification.
- Micronutrients are added to foods in many European countries by statute, including vitamins A and D to margarines and infant formulae.
- These nutrients are voluntarily added, as in the case of iodine to salt or folic acid to breakfast cereals, or for technological reasons, e.g., vitamins C and E.
- The risk of excessive intakes from fortification is likely to be much less than from widely taken dietary supplements.
- Such additions can beneficially increase population or subgroup intakes of specific nutrients, which often may not be achieved by other means.

Micronutrient benefits up to and beyond current RDAs

Professor Klaus Pietrzik, University of Bonn, Germany, "Micronutrient benefits up to and beyond the RDA"

- RDAs were set to prevent deficiency diseases.
- There is growing evidence that a number of micronutrients provide benefits beyond simply the prevention of deficiency states, including optimal development and maintenance of physiological functions, the prevention of certain degenerative diseases, or both.
- Folic acid provides the best such evidence, where an intake of 400 µg (ca. twice the reference value of the nutrition labelling directive) results in a 70% reduction in neural tube defects in newborn infants.
- Folic acid also reduces elevated blood levels of the amino acid homocysteine, which is observationally linked to a reduced risk of cardiovascular disease.
- Vitamins E and C and β-carotene may lower the risks of coronary heart disease and cancer.
- Intakes of calcium at the upper end of current RDAs may optimise bone development in children and adolescents and reduce bone loss in women, thereby reducing the risk of osteoporosis.
- Although further clinical intervention trials are desirable, the evidence is sufficiently strong to advocate practical implementation of these findings. Adverse health effects are unlikely.

Dr. Detlef J.G. Müller, Procter & Gamble, Germany, "Health effects of nutrients beyond suggested physiological amounts"

- Although all of the mechanisms of beneficial effects are not yet fully understood, the evidence supporting health effects continues to build.
- Provided that safety can be properly addressed, waiting for definitive evidence before putting these findings into dietary practice may not be prudent.
- Lower energy intakes and resistance to dietary change make it highly unlikely that consumers can obtain the potential benefits of increased intake above the RDA of some nutrients from a balanced diet only.
- The appropriate addition of micronutrients to food is one way of achieving the desirable micronutrient density in the diet of Western Europeans.

Professor Antti Aro, National Public Health Institute, Helsinki, Finland, "What provides the benefits? Individual nutrients versus total diet"

- Observational epidemiological studies suggest that high fruit and vegetable consumption confers health benefits to the consumer in terms of reduced risk of coronary heart disease and cancer, possibly owing to high levels of certain nutrients such as antioxidant vitamins.
- However, other components of such diets, e.g. high levels of dietary fibre, flavonoids and phytoestrogens, low levels of saturated fat and lifestyle factors such as physical activity and smoking make the true role of nutrients in observational studies difficult to assess.
- Clinical trials with individual nutrients given as galenic preparations with high bioavailability have failed, to date, to decrease the incidence of chronic diseases.
- Few data are available from interventions at physiological amounts in natural or supplemented foods.
- In the context of the whole diet, the roles of all components, including macro- and micronutrients, fibre and non-nutrients, should be considered.

Safety aspects of the addition of micronutrients to food

Professor Ron Walker, University of Surrey, United Kingdom, "Safety aspects of the addition of micronutrients to food: safety evaluation"

- Unlike other food components, the evaluation of micronutrient safety must take into account potential adverse effects of low intakes (clinical deficiency) as well as effects from intakes that are too high (clinical toxicity).
- The comparative safety of nutrients has previously been expressed in terms of the safety index (SI), defined as the lowest dose associated with minimal adverse effects (LOAEL or lowest observed adverse effect level) divided by the RDA (or equivalent).
- Additional complications arise from nutrient interactions, which preclude the determination of a unique RDA or LOAEL.
- The safety limit (SL), i.e., the arithmetic or geometric means of the LOAEL and RDA, is a more appropriate approach for "problematic" nutrients, where RDAs for some population subgroups may overlap the LOAEL for others.
- Some further weighting of the mean is suggested to take into account the nature, severity and reversibility of adverse effects owing to deficiency versus excess.

Dr. Manfred Lützw, Hoffmann-La Roche, Switzerland, "Safety evaluation of micronutrients: single cases"

- This section applied the above concepts to individual micronutrients and compared SLs for selected micronutrients, in particular vitamin C, folate and vitamin A.
- The adverse effects of vitamin C deficiency are well documented, whereas the side effects of intakes even above 1000 mg are only anecdotal and not valid for safety evaluation.
- In recommendations to increase intakes of folic acid by the general population to reduce the risk of neural tube defects (NTD), the small risk of masked B₁₂ deficiency in certain individuals needs to be considered.
- Although foods naturally rich in vitamin A are a potential teratogenic risk, recommended safe levels for pregnant and pre-pregnant women are set at levels close to those for the general population. This is because active avoidance of such products increases the risk of marginal deficiency in this population subgroup.

Dr. Jürgen König and Professor Ibrahim Elmadfa, University of Vienna, Austria, "Dietary exposure of fortified foods"

- Low intakes of several nutrients exist in all European countries, and most European countries are considering food fortification as one means of addressing this.
- Several studies show clear dietary intake improvement by both voluntary and compulsory fortification of foods, including 40% of vitamin D intake from the voluntary fortification of spreads (United Kingdom) and significantly increased intakes of vitamins B₁, B₂, B₆, and D and iron from voluntarily fortified breakfast cereals (France, United Kingdom, the Netherlands and Ireland).
- In Austria iodisation of salt, providing 40-45% of the intake, now ensures that children and adolescents typically meet the RDA. No other adequate dietary source exists.
- However, few good data exist in most European countries to analyse the effects of food fortification on diet. More detailed information is needed to adequately assess food fortification, particularly for single nutrients with narrow safety margins.

Viewpoints on addition from the European Consumer's Organisation

Mr. Kees de Winter, Bureau of European Consumers, Brussels, Belgium

- In the Member States of the EU, the popularity and the sale of food supplements have increased rapidly over the last few years. The EC intends to propose legislation for food supplements and for food products to which vitamins and/or minerals have been added. Consumer groups believe that there is also a need to draft legislation to cover supplements which contain components other than vitamins and/or minerals. Food supplements should be considered foodstuffs and medical claims should therefore be prohibited. Important issues with regard to fortified food products and supplements are safety, effectiveness and the use of claims. A grey area between food products and medicines is undesirable.
- For a long time, little was known about the possibility of adverse effects of increased intakes of micronutrients and restrictive policies were followed. In addition, some defined foodstuffs were compulsorily fortified with specific micronutrients to prevent deficiencies. Policies are gradually becoming more liberal. Scientists increasingly acknowledge that intakes above the official RDAs may have beneficial effects and do not constitute a danger to human health. Such increased intakes can be obtained through a balanced diet. However, because the average intake of energy is diminishing and empty calories are increasingly consumed, intakes of some micronutrients may be marginal.
- Positive effects from added nutrients will be especially significant if those categories of the population can be reached which are most vulnerable. However, there are indications that food supplements are often bought by people who have healthy food habits and who are therefore the least likely to benefit from their use. Additions of micronutrients alone cannot constitute a healthy diet, because nutritional well-being depends on the overall composition of the diet. The health-protective effects of high intakes of fruits and vegetables also depend on the presence of many other naturally present components, such as flavonoids and carotenoids.
- The expectations for antioxidants, especially β -carotene, vitamin E, vitamin C and selenium, and the prevention of chronic diseases were high. However, in Finland, a randomised intervention trial which lasted 7 years showed that supplements with vitamin E and β -carotene either alone or in combination did not reduce the risk of lung cancer in heavy smokers. This result has been confirmed by the results of the CARET-trial and the Physicians Health Study in the United States. For these reasons, the US National Cancer Institute (NCI) does not advise people to take food supplements. Rather, they advise people to consume ample fruits, vegetables and cereals.
- Apart from the above randomised intervention trials (the only type of epidemiological studies which, if generalizable, demonstrate causal relations), few others have provided information on the health effects of high doses of micronutrients. There is a lack of scientific evidence on specific health benefits resulting from very high vitamin intakes. Consumers who buy supplements or fortified products expect to receive value for their money. Therefore, minimum amounts of the relevant micronutrients must be laid down legally.
- Food claims are often made to promote the sale of fortified products and food supplements. EC legislation for nutritional and health claims has not yet been adopted. Therefore, Member States may apply their own rules. These rules are likely to affect the functioning of the internal market.

Commentary on the scientific principles discussion

Professor Helmut F. Erbersdobler, Institut für Humanernährung und Lebensmittelkunde der Christian-Albrechts-Universität, Kiel, Germany

- There is no doubt that fortification of food can be helpful, as is best demonstrated by long experience with iodine fortification of common salt and recently in the case of folate. The overall conclusion of the workshop (see page 5) is therefore widely accepted.
- No unanimous opinion exists about the handling of nutrients with moderate and narrow safety margins. Both the time limitations of the meeting and the authority of the meeting do not make it possible to create lists of permitted or prohibited nutrients or to provide the science base to regulate fortification horizontally (restriction to several foods) or vertically (limiting the amounts added). Consumers organisations want to have compulsory regulation. This possibly will solve some problems, but probably, will not work effectively and rapidly enough and will be in most cases too strict.
- There is apparently no decision or agreement about which foods should be fortified. It is generally accepted that fortification should make a good food better and should not be used to polish the image of certain foods with low nutrient density. To do otherwise would mislead and confuse consumers. However, there appears to be no way to regulate this. One can hope that self-regulatory effects will prevent the main excesses.
- Many problems can be reduced by informative labelling and claims. If it is true that we are heading towards a “service society”, then nutritional information will be one of the most important tools. In this way, resistant groups of the population such as adolescents, poor people etc., can be reached.
- All these considerations should be based on sound scientific knowledge. All groups represented here are responsible to change the way and practice of fortification immediately if new results are valid enough to make it necessary.
- Recommended daily allowances may not be a suitable basis for fortification. However, the spirit of RDAs – whether we like it or not – will always be present.
- Food fortification combined with functional food ingredients could solve some of the above mentioned problems. However, functionality is focused mostly in special goals such as cancer prevention or probiotic changes of gut flora, whereas fortification has to lead towards an optimal nutritive supply.

SUMMARIES OF THE EXPERT GROUP PAPERS

I. Micronutrient intakes and status in Europe

The first step in determining whether there is micronutrient deficiency in Europe and, if so, in what risk groups is to estimate the prevalence of intakes below the minimum requirement. Before drawing conclusions about intakes, it is important to acknowledge that there are inherent problems with food consumption surveys owing to difficulties in collecting reliable data and variations in methodology which make comparisons between groups with apparently high and low intakes difficult. In addition, intakes are usually compared with RDAs and the philosophical approach to these can differ between countries. Many of the values are based on limited evidence, so that estimates of recommended and/or minimum requirements may differ widely from one country to another. This can lead to difficulties in a proper comparative evaluation of European food consumption surveys, where a certain level of intake may be considered adequate in one country but inadequate in another.

For many population groups, and for nutrients such as selenium, the risk may not be known because no studies have been undertaken. However, the comparisons which have been made suggest that for almost all vitamins, minerals and trace elements, one or more population subgroups have intakes below national recommended levels, especially for iron, iodine, vitamins B₂, B₆ and D.

Biochemical methods are generally considered objective measures for identifying “at risk” individuals or groups at an early stage, when body reserves become depleted but clinical deficiency cannot yet be demonstrated. A number of studies on nutritional status from national surveys or smaller-scale studies in EU countries use a wide range of biochemical methods. These include static tests, which are convenient, reproducible and robust, but are mainly descriptive, and functional tests which have advantages but are not available for all nutrients. Major studies in Germany, France and the Netherlands, as well as the SENECA study, show substantial numbers of adults with inadequate status in most age and sex categories, but especially elderly subjects; depleted iron stores in adult menstruating women; low vitamin D status in elderly subjects; low iodine excretion in the Netherlands, Germany and Eastern Europe; and low folate status, especially in women of childbearing age but also possibly in most adults. These findings compare well with dietary intake assessments.

Lifestyles and some food habits are changing in many sectors of the European population as a result of higher standards of living, an increased proportion of women in the workforce, urbanisation, hedonism, tourism and an increased number of meals eaten outside the home. People are also more sedentary, and this is related to a reduction of food and energy intakes and, consequently, micronutrient intakes.

Slimmers deliberately choose low-energy diets, and those with anorexias carry this to extremes. Many such young women have been found to be at risk of vitamin deficiencies. Vegetarians may have low intakes of iron, vitamin B₁₂, iodine, copper and calcium, although intakes of vitamin C, carotenoids and fibre are higher than average. The bioavailability of micronutrients may also be altered because of the special characteristics of vegetarian diets, with iron better absorbed from meat than from vegetables and inhibited by some types of phytates.

Smoking is increasing in several countries, particularly among the young, and smokers, antioxidant nutrient status is particularly jeopardised. Drugs prescribed by doctors or taken voluntarily for health or recreational reasons can have adverse nutritional consequences which may be particularly important for elderly people.

The consumption of industrially processed foods is increasing. Processing can increase the bioavailability of some nutrients such as vitamin B₆, folate and certain carotenoids, and can inactivate anti-nutritional factors, but there may be losses of vitamins during the longer storage life that results. There can, however, be much greater losses during subsequent domestic or catering preparation and cooking.

Optimisation of nutrient intakes in at-risk populations can be achieved in a number of ways, including modifying dietary habits, increasing intakes of fortified foods and using dietary supplements. Fortification may be the safest and most effective of these.

Early examples of successful fortification to improve health were the addition of niacin to flour and vitamin D to partially skimmed milk in the United States and the addition of iodine to salt in several European countries. Compulsory additions, such as vitamin D to margarine in the United Kingdom and voluntary additions such as B vitamins to fortified breakfast cereals, make increasingly major contributions to nutrient intakes and status in Europe. Nutrients can also be added indirectly to foods, for example, by the use of iodine in cattle feed in the United Kingdom and selenium in fertilisers for cereal crops in Finland. For determining future public health policy, the effects of potential fortification can be modelled for different population groups using the results of dietary surveys.

Discussion points

The consequences of marginal intake depend on the nutrient, but we are far from having the defined endpoints and the biomarkers to understand the consequences for all nutrients. Dietary intake data alone are not sufficient. Some indicators are known; for example, depletion of iron stores can be demonstrated and homocysteine can be measured as an indicator for folate status. Some participants believe there is a need for further research to demonstrate clear-cut benefits for the addition of vitamins and minerals to foods.

Fortification of food may be compulsory or voluntary and it is important to distinguish between the two. To deal with a specific nutritional problem, the foods that the population in question eat must be targeted. Suitable foods will vary from country to country. For example, in the United States and United Kingdom breakfast cereals are fortified with folic acid and other B vitamins and are eaten by young women, but in Sweden young women do not eat breakfast cereals but do eat bread. However, bread is also eaten by men, but in much greater quantities, so there is concern that men might be exposed to very high levels of folate. To find one suitable food may be difficult, since people eat such a large variety of foods. Voluntary fortification, therefore, of a number of different foods may be more effective. Supplements are less effective, as demonstrated by public health campaigns to increase folate intake in young women, because they do not regularly take them. For some nutrients the aim may be to raise the average intake slightly, in which case fortifying a range of foods is probably the answer. Supplements are usually taken by those who already have larger intakes from food. Some workshop delegates believed that only foods that already contain some of the nutrients in question should be fortified; to do otherwise would lead to public confusion. A more realistic approach would be simply to choose foods that the target population eat.

Research needs

Improvements need to be made to the methodologies of dietary surveys, for both whole populations and some subsections of the population. New and more effective markers need to be developed for assessing the status of nutrients such as calcium and zinc. The relevance, reliability and sensitivity of direct and functional methods for all nutrients need to be improved and the methods harmonised between laboratories. New and more representative data on dietary intakes and nutrient status are needed for some populations in Europe. For many population groups the relationship between nutrient intakes and status needs clarification so that the scientific basis of some RDAs can be improved. A greater understanding of the relationship among energy intakes, micronutrient intakes and status is required. More research is needed on the role of fortification in reducing chronic diseases and birth defects. Greater use should be made of predictive modelling to help achieve the most effective fortification practices.

II. Micronutrient benefits up to and beyond current RDAs

There is growing evidence that a number of micronutrients provide benefits beyond those traditionally considered when setting recommended daily allowances (RDAs) based on the prevention of deficiency diseases. These additional benefits relate to the optimal development and maintenance of physiological functions and/or the prevention of certain degenerative diseases. Commonly, these benefits are found at and above current RDAs (which are frequently not achieved) and include micronutrients for which no traditional RDAs have been defined. The theme paper focuses on a limited number of examples of traditional micronutrients – vitamin C, vitamin E, β -carotene, folic acid and calcium – where there are strengths and weaknesses in the supporting data. The paper also looked at the combined effects of some dietary nutrients.

Prospective studies suggest a protective effect of vitamin C in the development of cancer, but results are not conclusive. There appears to be a clear benefit for vitamin C in reducing the risk of coronary heart disease, although the significance of this has yet to be evaluated. Requirements for vitamin C are increased in physiologically stressful situations such as injury and may also be increased in pregnancy. Vitamin E also appears to be effective in reducing the risk of coronary heart disease, probably by preventing the formation of oxidised low-density lipoprotein (LDL), and cancer. It is clear that vitamins C and E have a synergistic effect in antioxidation. Smokers have higher requirements for vitamin C and possibly also for vitamin E. For vitamin C, levels above the RDAs – about 100 to 200 mg per day – as long as they are physiologically utilised and retained in the body, can provide additional benefits. For vitamin E, higher intakes may be desirable, but knowledge is insufficient to recommend a specific amount.

The traditional health effects of β -carotene are mediated by conversion to vitamin A. Recently it has been suggested that β -carotene has additional beneficial “antioxidant” activity, but this has not been convincingly demonstrated *in vivo*. There is, however, ample evidence of protection by a diet high in fruit and vegetables against cancer, particularly of the lung and upper gastrointestinal tract, and cardiovascular disease. Results from studies with high supplemental doses of β -carotene have raised concern over their possible adverse interaction with smoking and alcohol, but even these studies have demonstrated a benefit from a high dietary intake. Current evidence suggests that there may be benefits from increasing β -carotene intake within the range that is possible to achieve by the consumption of a diet abundant in fruits and vegetables (up to 4–6 mg per day), but this does not exclude the possibility that β -carotene is primarily a marker for such a diet.

There is now proof that the risk of neural tube defects can be markedly reduced by supplementation with folic acid before and in the early stages of pregnancy, so it is now recommended that women wishing to bear children should have an intake of 400 µg per day. It is clear that if this measure were universally adopted, about 70% of all neural tube defects could be prevented. The authorities in the United States have already acted on this knowledge and introduced a food fortification programme. More recently a role for folic acid in the prevention of cardiovascular disease has been suggested through its ability to reduce plasma homocysteine levels, and this effect may be enhanced in combination with vitamins B₆ and B₁₂.

Dietary intakes of calcium at the upper end of current RDAs (1000–1200 mg per day) and above have been shown to optimise bone development in children and adolescents and to reduce bone degradation in postmenopausal women. Optimal calcium intakes throughout life are associated with reaching an individual's peak bone mass and delayed loss of calcium, thus reducing the risk of developing osteoporosis in later life. There are also indications that high calcium intakes may help reduce the risks of developing kidney stones and colon cancer and may have a favourable effect on blood pressure, although the data are less consistent.

Most foods contain a mixture of macro- and micronutrients, and diets contain a mixture of foods. Therefore, it seems likely that nutrients may act in combination with one another. For example, it is known that vitamin C improves the absorption of nonhaem iron and the regeneration of vitamin E. The beneficial effects of a diet rich in fruits, vegetables and grains cannot be ascribed to any one nutrient or group of nutrients, so individual nutrients should not always be studied in isolation.

Even though for many of the postulated benefits no definitive scientific proof is available, in several cases the available evidence is sufficiently strong to encourage the practical application of these findings to consumers and their diets. This seems a sensible approach, since for the relevant nutrients no adverse health effects are to be expected at the levels believed to be effective.

Discussion points

RDAs are universally used as standards against which to measure intakes. It is important, therefore, to be sure that they are securely based. Although they are meant for use with population groups, in the absence of any other guide they are also used by individuals for assessing the adequacy of their intakes.

The need for biomarkers is particularly important for assessing the benefits of intakes above the RDA. Some biomarkers have been used in the studies reported in the accompanying paper and all new studies will use them. However, they are complicated to use and we still have to learn how effective they are.

Studies to assess the benefits of nutrient intakes above the RDA should ideally be done on a nutrient by-nutrient-basis, although some specific nutrient mixtures should also be included. However, it would be an impossible task to study all nutrients, so some indicator nutrients should be chosen. To be scientifically correct, primary prevention studies should be done first, but when people have some knowledge of benefits they generally do not want to wait. Do we need to wait for evidence of benefit in order to permit voluntary fortification, or do we just need the absence of risk?

In an ideal world we would be able to get all the vitamins and minerals/trace elements we need from food without fortification. This would require some major changes in our dietary habits; however, people do not change their diets that easily (in a recent European survey 70% of people said they thought their diet was adequate). If they did change their dietary habits and complied with nutrition guidelines, there would be insufficient food for us all to meet these guidelines. And as a result of, e.g., the United States' recommendations to eat five to seven servings of fruit and vegetables every day, the RDAs for vitamin C and A (as β -carotene) would be exceeded by diet. If the population cannot presently obtain optimal nutrient intakes from food alone, we need to continue to look for the best alternative.

Research needs

Future research should focus on individual nutrients and for this the development of a better range of biomarkers is essential. Specific topics which were highlighted were: developing a greater understanding of the significance of vitamin C in prevention studies which will enable recommendations for vitamin E intake to be made, studies on the relationship between plasma homocysteine and cardiovascular disease and benefits of higher calcium intakes other than those related to bone health. More studies need to be based on physiological intake levels, that is, interventions where the intake from food plus supplements approximates that which could, given availability, be obtained from food alone.

III. Safety aspects of the addition of micronutrients to food

The mandatory and voluntary addition of nutrients to food requires as a prerequisite for risk assessment and risk management an understanding of various safety aspects.

Toxicological concepts and nutrients

The safety assurance process for compounds present in food traditionally involves three stages: hazard characterisation (determining risk through toxicology studies), safety evaluation (establishing exposure limits without appreciable risk), and risk management (implementing measures which ensure that expected exposure levels do not carry unacceptable risk).

The characterisation of chemical hazards is based on animal or human studies which describe consistently observed adverse effects in a dose-response relationship. Such symptoms may be observed only in particular circumstances such as pregnancy and may be dependent on acute or chronic exposure.

Based on selected pivotal studies, a lowest observed adverse effect level (LOAEL) and a no observed adverse effect level (NOAEL) are established, the latter being without appreciable risk. In the case of essential nutrients a major complication is that the dose-response relation may be markedly non-linear with negative effects occurring in both deficiency and excess. Differences in absorption, metabolism and distribution will also be essential features of a safety profile of nutrients (water-soluble versus fat-soluble vitamins, vitamins versus minerals).

The safety evaluation of, e.g., food additives usually involves the application of a safety factor to the LOAEL, which then leads to a safe level of exposure which is traditionally defined as the acceptable daily intake (ADI). In the case of nutrients, such a schematic algorithm may be considered simplistic because there are cases where such "safe levels" would be significantly lower than the nutritional requirements (e.g., vitamins A and D,

fluoride, iodine, selenium). For others there is a large gap between the RDA and the intake at which adverse effects become manifest (e.g., vitamins B₁, B₂, B₆, E and K, manganese and trivalent chromium). For a third group, possible side effects depend on the insufficient presence of a second nutrient (e.g., iron, vitamin C, folic acid or vitamin B₁₂). An example of a specific approach for nutrients which considers both safety aspects (risk of deficiency and risk of toxicity) is the safety index (SI), which is calculated according to the formula $SI=LOAEL/RI$ (where RI is an appropriate standard recommended intake).

Establishing safe exposure levels for nutrients requires a “minimal risk approach” which takes into account the risk of deficiencies and possible benefits of intakes beyond the RDA. As conventional safety factors cannot be applied, a case-by-case consideration for each nutrient is required.

Influencing factors for modulating toxicity

The safety assessment of a nutrient is usually based on data derived from human clinical studies using galenic preparations. Such studies are very often performed at therapeutic levels in populations with increased sensitivity which makes it difficult to use these data to assess safety for the general population. In contrast to toxicological studies in animals, safety is usually not an endpoint in the design of such studies, which creates additional questions in selecting them as pivotal. Such factors, which have to be described in a sufficient number of reports, include such issues as evidence of toxicity, severity and specificity of effects, description of source, level and duration of exposure, health characteristics of study participants and number of studies reporting no effects at high exposure levels (to determine the LOAEL).

The interaction of nutrients with other components of the food (micro- and macronutrients) and the dilution in a matrix of different food components ingested over the whole day will probably lead to different pharmacokinetic behaviour and significantly different exposure levels of target tissues compared with the administration of nutrients as a bolus.

A diet containing a broad variety of different food items constitutes the best supply of recognised nutrients and other biologically active constituents. Current and potential future fortification policies may affect nutrient intake patterns.

Whether the exposure of subjects to a wider variety of fortified foodstuffs and to foods which contain nutrients for technological purposes would lead to intakes of concern to public health is uncertain. For essential nutrients, intake scenarios add up maximum food intakes and maximum fortification levels leading to unhealthy and unrealistic dietary patterns seems to be inappropriate. Reliable and standardised methods to predict the exposure of consumers to changes in fortification need to be developed. In the meantime, specific attention should be given to those nutrients where a narrow gap between requirements and levels of adverse effects have been reported.

Considerations for selected nutrients

Various authors (individual toxicologists, committees) have assessed the safety of nutrients, identified possible adverse effects and defined levels associated with them. Three groups of nutrients have been identified, which are illustrated by the following three vitamins:

Vitamin C displays a large gap between mild, reversible side effects like increased oxalate excretion or gastrointestinal stress at gram intake levels and the dietary requirements of between 45 and 80 mg for healthy individuals.

In the case of folic acid adverse effects at a level of 5 mg per day have been observed in patients with untreated vitamin B₁₂ deficiency, a condition which may lead, if not diagnosed and treated properly, to the development of peripheral neuropathy. The latter may be irreversible after extended exposure. The possible adverse effect on people with undiagnosed pernicious anaemia led to a NOAEL of 1 mg per day. The benefits of elevated folic acid intakes from the food supply for certain segments of the population (women of childbearing age, individuals with high homocysteine plasma levels) need to be carefully balanced against possible side effects to individuals with undiagnosed pernicious anaemia.

Vitamin A is a fat-soluble vitamin which has been linked to two side effects, hypervitaminosis A and teratogenicity. Owing to the lack of appropriate data, it has been difficult to determine a LOAEL for humans for teratogenicity. Recommended daily allowances for pregnant women (1000 µg) are, therefore, currently close to levels considered safe (2400–3000 µg).

Considerations for the safe addition of nutrients to foods at physiological levels

Five steps are proposed for a safety evaluation if nutrients are added to food. These steps follow the recently established approach of the Food and Nutrition Board (FNB) of the US Institute of Medicine:

- Hazard identification (inherent toxicity)
- Dose-response evaluation at the beneficial and the toxic range
- Exposure assessment: likelihood that intakes may exceed the safe range
- Interaction risks: addition of one nutrient may lead to disturbances in the utilisation of others
- Risk management: steps to reduce risk for nutrients with narrow safety indices

Based on this stepwise procedure, a policy framework for the addition of nutrients to food has to consider the basic requirements of populations to avoid deficiencies, has to take into account growing knowledge that certain micronutrients provide benefits beyond such levels and must consider micronutrients with particular risks.

Food fortification and risk management

For the majority of micronutrients likely to be added to foods, the safety index (SI), makes it practically impossible to exceed the recognised safe intake range from the combination of conventional foods and foods with a micronutrient added. For those with a much lower SI, specific risk management steps will be required. Such measures may be advisory (e.g., labelling) or legislative (maximum levels). Possible adverse effects in specifically defined subpopulations with a defined risk factor (e.g., hyperoxaluria) may not be a suitable endpoint for managing the exposure risk and quantitative limits of the total population. However, if the condition is not known to the individual at risk (e.g., subclinical pernicious anaemia), there may be reasons to deviate from this principle.

The dose range of “too little” and “too much” has to be positioned against expected intake scenarios, which should consider levels present in unprocessed foods, nutrients added and the technological use of nutrients as food additives. A refined methodology for realistic exposure assessment has to be developed for those nutrients with a low SI.

Discussion points

We can differentiate between micronutrients with and without potential adverse health effects from overdosing by taking the following steps and answering the following questions:

- (i) Define micronutrients for which the SI is sufficiently large so that even their uncontrolled addition to foods will not lead to risks of overdose.
- (ii) Define those micronutrients for which a small SI makes restrictions necessary.
- (iii) Ensure a reasonable approach for nutrients with a moderate SI.
- (iv) For nutrients where restrictions are needed, how can we define acceptable upper intake levels?
- (v) Can they be related to the RDA (which ones)?
- (vi) What would be an appropriate RDA multiple to apply in specific cases?
- (vii) Should added micronutrients refer to specific amounts of food consumed, e.g., percentage of the RDA in 100 g, in a portion or in a reasonable daily consumption?
- (viii) How can “overages” or overfortification be taken into account to cover processing and storage losses (mainly vitamins)?
- (ix) How do the bioavailability and pharmacokinetics of different chemical forms or routes of dietary administration of nutrients influence the LOAEL and the NOAEL?
- (x) How should potential synergistic effects, imbalances and interactions among nutrients be taken into account and the potential deleterious effects prioritised?
- (xi) How should the potentially simultaneous consumption of enriched food and food supplements containing high amounts of problematic nutrients be assessed and, if necessary, controlled?
- (xii) How should the presence of an added nutrient be declared in order to be understandable for consumers (e.g., absolute amounts, fractions of the RDA)?
- (xiii) In what circumstances should the addition of nutrients be restricted to certain food groups? Should certain groups be excluded?

IV. Evaluation of risks and benefits

Discussion points

At the current level of scientific knowledge, it is difficult to weigh objectively the benefits of increased nutrient intakes for those who need them against the risk of excessive intakes for those whose intakes are already satisfactory. For example, how can the decreased risk of cold or neural tube defects be weighed against the risk of excessive intake? It was also generally agreed that, at present, it is not possible to define specific RDA multiples for fortification likely to optimise benefits versus risks.

Although for trade reasons it would be desirable to harmonise fortification regulations, in terms of the overall benefit/risk for the consumer, they should not be contrary to national food and nutrition principles. This concerns mostly food fortification per se, however, rather than restoration, standardisation and substitution.

Concerning folate and vitamin B₁₂, there is a need to weigh the protective effect of folic acid in the prevention of neural tube defects against that of undiagnosed pernicious anaemia, due to vitamin B₁₂ deficiency, although it was recognised that this analysis will be very difficult. There were, however, differences of opinion concerning folic acid and vitamin B₁₂. Some argued that at "normal" folate fortification levels the risk of undiagnosed pernicious anaemia is probably insignificant. Conversely, it was stated that dietary folate intake should not exceed a certain level in order to avoid any possibility of masking vitamin B₁₂ deficiency (pernicious anaemia) and that such a level could easily be exceeded through fortified foods. However, evidence for the possible masking of vitamin B₁₂ deficiency by supplemental folic acid is mainly taken from case-control studies dating back to the 1940s. At that time, pernicious anaemia was sometimes incorrectly treated with folic acid, which had the effect of curing the anaemia of vitamin B₁₂ deficiency but not the associated neuropathy. The Centres for Disease Control and Prevention (CDC, Atlanta) have stated that intakes of less than 1 mg per day are safe, but this is unsubstantiated. Intakes of 400 µg per day may be safe; such levels are widely consumed in the United States without apparent effect on the incidence of pernicious anaemia. There are no data for intakes in the range of 400–1000 µg per day. The newly emerging and convincing evidence of the role of folic acid in lowering homocysteine, a risk factor for CHD, supports the need for the risk-benefit evaluation.

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