Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin

Federal Institute for Health Protection of Consumers and Veterinary Medicine

Berlin, 18 January 2002

Toxicological and Nutritional Aspects of the Use of Minerals and Vitamins in Foods

Part I: Minerals (including trace elements)

Proposals on regulations and upper limits (maximum levels) to protect the consumer from overdose when consuming food supplements and fortified foods

Contents

1 Problem description

The Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV) is highly concerned about the development on the market for food supplements or dietary supplements[1] as well as to the trend towards the uncontrolled fortification of processed foods for general consumption[2] with micronutrients and non-nutrients. This means that the consumer is increasingly losing control of his daily intake of vitamins and minerals from these sources and the risk to overdose is growing. We believe that the health-conscious consumer is particularly at risk when he starts the day with a multivitamin tablet and fortified muesli, enjoys a corresponding dairy product as a snack and in the afternoon ingests fortified beverages and "performance-enhancing" snacks in the form of bars and the like. We are particularly concerned about the fortification of sweets since this gives them unjustified status in nutrition and children could run the risk of consuming minerals on a by no means safe level.

For that reason we believe there is an urgent need to influence this development in such a way that effective consumer protection can be guaranteed.

For this, however, we need a concept which so far has not been consistently developed and a scientific basis for tolerable daily intake which at present is only available for a few vitamins and minerals. The EC Scientific Committee on Food has taken up this task and started to derive tolerable upper intake levels for vitamins and minerals.

[1] "Food supplement" or "Dietary supplement" means a product wich is usually a concentrated source of nutrients and other ingredients, alone or in combination and marketed in dose form.

[2] Fortification of processed foods means the addition of nutrients to common foods for a number of reasons such as enriching foods with nutrients they usually do not contain or contain at lower levels, restoration of the nutrient levels lost during processing foods, or ensuring nutritional equivalence of products replacing common foods in the diet. Another reason can be to increase the image of a less valuable product in order to get a better placement on the market.

1.1 Food supplements

The **proposal for a directive** of the European Parliament and the Council on the approximation of the laws of the Member States **relating to food supplements**, which was submitted on 8 May 2000 for the first time (EU 2000 a) and on 19 March 2001 as an amended proposal (EU, 2000b), is an attempt on Community level to protect the consumer against potential health hazards from these foods.

In paragraph 13 of the amended proposal it is stated,

> that *"...for vitamins and minerals excessive intakes may result in adverse effects and, therefore, necessitate the setting of maximum safe levels for them in food supplements, as appropriate. Those levels must ensure that the normal use of the products are in line with the instructions of use provided by the manufacturer will be safe for the consumer"*

In paragraph 4 and 5 it is further stated:

> *(4) Consumers, because of their particular lifestyles or for other reasons, may choose to supplement their intake of some nutrients through food supplements.*
>
> *(5) In order to ensure a high level of protection for consumers and facilitate their choice, the products that will be put onto the market must be safe and bear adequate and appropriate labelling.*

For many of the nutrients used in food supplements, scientific studies on the correct dosage efficacy, safety and interaction with other nutrients are only available in a limited manner or not at all.

In its earlier assessment of individual products in the group of food supplements, the BgVV assumed that the additional intake of vitamins and minerals occur as a rule from the consumption of only one product per day. In the meantime the market has changed to such an extent that it must be assumed that there is parallel consumption of several such products which may contain the same nutrient despite different presentation, orientation and composition. Hence, maximum levels of minerals must be specified which reflect the daily intake of individual products but also the overall situation.

In 1997 in Germany alone vitamin products worth more than DM 1.1 billion were manufactured, almost 14% more than in 1996 (German Institute for Nutrition Research Potsdam-Rehbrücke, 1998). The overall sector of food supplements accounts for around DM 2 billion. In 1997 just under one-third of Germans stated that they spent up to DM 50 per month for freely available food supplements containing vitamins and minerals (DAK, 1999).

The German market and the products available there are presented in a detailed manner in a study report on Food Supplements published by the German Consumer Centers and consumer federations on the basis of a market check conducted in Germany in 1999. Altogether 170 purchases were made, mainly in consumer-markets, drug stores and supermarkets, in health food stores, by mail order and on the Internet. 139 foods were recorded, 12 dietary foods and 19 medicinal products, of which 14 had neither a marketing authorisation number nor a registration number for homeopathic agents. Hence, 81.8% of the purchases were deemed to be foods for general consumption and almost exclusively to be classified as food supplements because of their appearance and consumption recommendations. The study report of the Consumer Centres points out that products which contain vitamins and minerals trigger high expectations. They "stand for health, energy, activity and vigour. They are supposed to make the consumer feel good and increase his ability to concentrate". Some even promise help "for instance in the fight against cancer, heart attacks or rheumatism" (Verbraucherzentralen, 2000). Large-scale advertising campaigns suggest to the consumer that he should supplement his daily food with these products (DGE, 1998).

The purpose of the food supplement was only stated on the packaging of 42% of the products, i.e. as a supplement to daily food. For most products one or more purposes or goals were mentioned which, according to the distributor, could be achieved through the intake of the product. Overall up to five different purposes were found on the packaging. The study also focused on the question of how many nutrient groups are combined with one another and which combination is given priority in distribution. Of the 139 products 124 contained vitamins, 99 products contained minerals and trace elements, 46 products so-called "special substances" and 19 products plant components. In most cases products contained substances from two groups and in 39 cases only one substance group (Verbraucherzentralen, 2000).

Focussing on this subject the BgVV published in 2001 several articles by different authors (Bundesgesundheitsblatt (Viell, 2001; Verschuren et al., 2001; Ringel Heller and Silverglade, 2001; Sjölin, 2001; Streinz, 2001).

1.2 Fortification of conventional foods for general consumption

A particularly problematic situation would arise if it were generally permitted for vitamins and minerals to be added to conventional foods for general consumption in the same way as to food supplements. The consumption volume of conventional foods for general consumption is oriented first and foremost towards the amounts of vitamins and minerals contained therein and is determined mainly by factors like hunger, thirst, appetite and availability. In that case consumption recommendations are not possible or would not be followed in contrast to food supplements.

In Germany the Vitamin Regulations dating back to 1942 permit the addition and corresponding declaration of vitamins C, B_1, B_2, B_6, pantothenate, vitamin E and niacin to foods without any restriction on volume. In contrast, minerals and trace elements are equated with additives and their addition is only permitted to certain foods.

Based on the goal of Europe-wide uniform regulations for the addition of nutrients to foods, a **proposal for a Directive of the European Parliament and the Council for the approximation of the laws of the Member States relating to food supplements** (Doc. SANCO/1478/00; SANCO.02-BM/cv) (EU, 2000 d) was published and discussed. This proposal contains, amongst other things, rules for the addition of nutrients to foods for the following reasons:

1. proven undersupply of the population or groups in the population;
2. possible undersupply because of change in eating habits;
3. new findings about nutrient functions.

Earlier[3], we suggested that the first two reasons of this proposal should be linked to the goals of Codex Alimentarius (prevention of undersupply) and that the third reason should be deleted.

[3] BgVV report FB1-2440-121819 of 25 September 2000 to the German Ministry of Health

Back in 1971 the World Health Organisation stressed the opinion that the fortification of foods must be linked to a proven need for such a fortification within the target group (WHO, 1971). Representatives of the BgVV have also made extensive comments on this in the past. For instance, it was stated that fortified foods under certain conditions could make a major contribution to ensuring the supply of essential nutrients. To achieve this, from today's perspective, the following conditions must be met:

1. There must be a provable endemic supply deficit which cannot be remedied by changing diet habits.
2. The fortified food is regularly consumed by the target group in an adequate quantity.
3. The nutrient concerned is added as a dose to the food.

One example of targeted fortification is the iodisation of table salt which aims to overcome the iodine deficiency of the German population. However, up to now, the common practice of nutrient fortification in Germany has not been oriented towards proven gaps in supply. It mainly concerns foods which are often not recommended as part of a balanced diet and whose consumption is not foreseeable (Przyrembel, 1998).

2 Result

- For nutritional reasons, the use of minerals in food supplements should only be admissible in future for the following nine minerals, molybdenum, selenium, chromium, copper, zinc, iron, iodine, calcium and magnesium. Insofar we do not agree with Annex I of the EC Draft Directive for Food Supplements (EU, 2000 b), which also mentions manganese, sodium, potassium, fluorine, chlorine and phosphorus (cf. chapter 3.6.1).

- The use of substances like sodium, potassium, chlorine and phosphorus, which form corresponding salts with the nine above-mentioned minerals and which are also used for technological purposes (e.g. to guarantee sufficient solubility and bioavailability) should be regulated in Annex II of the Directive (cf. chapter 3.6.1).

- Manganese and fluorine definitely should not be used in food supplements (cf. chapters 3.6.2.8 and 3.6.2.5).

- The following principle is proposed for the derivation of maximum levels[4] for minerals in food supplements (cf. chapter 3.5.2):

  The mineral intake resulting from a normal (conventional) diet **(DINF)** is deducted from the Tolerable Upper Intake Level for the daily intake of that mineral from all sources **(UL)**. The remaining quantity may not be exceeded through additional intake from other sources like food supplements, fortified conventional foods and other sources. Given the large number of possible additional intake sources for minerals, this remaining quantity must be divided by a corresponding multi-exposure factor **(MEF)**. This leads to the amount **(TL)**, which a single product in a daily ration may contain if it should be guaranteed that the UL is not exceeded.

$$\mathbf{TL} = \frac{\mathbf{UL - DINF}}{\mathbf{MEF}}$$

- Given the inadequate database, presently, this principle can only be applied to the addition of magnesium. For chromium, iron, iodine, copper, molybdenum, selenium and zinc the previous upper limits of the BgVV should be maintained. For calcium individual evaluations are still necessary[5] until an assessment has been undertaken by SCF. (cf. chapter 3.6.2).

[4] In this context "maximum level" means also "upper limit"

[5] In case of handling an application on a certificate of exemption under the terms of the German Food Law.

Maximum levels for minerals in a daily ration of individual products (as per January 2002)

Minerals	Maximum level per daily ration food supplement	Restrictions
Calcium	Individual evaluations are necessary as in the past until the final assessment by SCF	
Magnesium	**62.5** mg	Not for children under 4
Chromium	60 µg	
Iron	5 mg	
Iodine	100 µg	
Copper	1 mg	
Molybdenum	80 µg	Not for children under 7
Selenium	30 µg	Not for children under 7
Zinc	5 mg	

- Labelling rules are proposed whereby food supplements must be indicated on the label with the statement that a supplement of this kind only makes sense in the case of undersupply and that mineral intake beyond the daily requirement may result in adverse effects (cf. chapter 3.6.3.2).

- To protect consumers against deceit a minimum amount regulation for minerals is proposed for food supplements whereby the content of a mineral in a food supplement should be dosed in such a way that with the daily consumption amount of the food supplement to be stated by the manufacturer must account for at least 15% of the respective maximum level (cf. chapter 3.6.3.1).

- Conventional foods for general consumption should, in the opinion of the BgVV, only be fortified with minerals in specifically substantiated exceptional cases when firstly an endemic deficiency has been proven for the mineral and secondly it has been guaranteed that the fortified food is regularly consumed only by the target group on an envisagable scale and that a limited amount of the mineral concerned is added as a dose to the food. Fortification of this kind must be undertaken as a general health policy measure and not as an individual action by the manufacturer (cf. chapter 3.7).

- In order to derive maximum levels for the use of minerals in the production of foods, there is a need for considerable research to collect the consumption data whereby a distinction must be made between mineral intake from conventional foods for general consumption, food supplements, fortified foods and other intake sources (cf. chapter 3.8).

3 Substantiation

3.1 Minerals

According to DGE [6] the elements in question could be broken down into

- **Quantitative elements**, like sodium (Na), chlorine (CI), potassium (K), calcium (Ca), phosphorus (P) and magnesium (Mg)
- **Trace elements**, like iron (Fe), zinc (Zn), manganese (Mn), cobalt (Co), iodine (J), selenium (Se), chromium (Cr), nickel (Ni), fluoride (F), copper (Cu), and molybdenum (Mo) and
- **Ultra-trace elements,** for which up to now no physiological function could be detected in man like aluminium (Al), boron (B), lithium (Li), strontium (Sr), antimony (Sb), bromine (Br), mercury (Hg), thallium (TI), arsenic (As), cadmium (Cd), rubidium (Rb), titanium (Ti), barium (Ba), caesium (Cs), samarium (Sm), bismuth (Bi), lead (Pb), germanium (Ge), silicon (Si) and tungsten (W) (DGE-DACH, 2000) as well as vanadium (V) and tin (Sn).

With this report we only use the generic term "minerals".

3.2 Exposure (mineral intake)

Details about the recommended or actual daily intake of minerals and trace elements can be found in various international and national reviews. Intake data mostly are not representative because focussing on special population groups or on limited regions. For our purposes we used the German consumption data of the National Consumption Study (VERA study, 1995) and for recommended intake we used the new nutrient reference values which are published jointly by the Societies of Nutrition in Germany (DGE), Austria (ÖGE) and Switzerland (SVE, SGE) for the German speaking countries (D-A-CH, 2000). They are the continuation of the earlier "Recommendations on Nutrient Intake" published by the German Nutrition Society

[6] The German Nutrition Society (cf. chapter 4)

(DGE-Empfehlungen, 1991).

In table 1 the consumption data are compared with recommended intake (all consumption data in columns 2 and 3 refer to adult women):

Table 1: Daily intake of minerals without food supplements:

Minerals		**Estimated, normal intake without food supplements**		**Recommended intake (D-A-CH, 2000)**
		Median	*97.5 percentile*	
Sodium	mg	2770 [1]	5070 [1]	550 [5]
Potassium	mg	2740 [1]	4520 [1]	2000 [5]
Chloride	mg	4120 [1]	7450 [1]	830 [5]
Iodine	µg	114 [1]	328 [1]	180 - 200 [2]
Magnesium	mg	285 [1]	489 [1]	300 - 400 [2]
Calcium	mg	632 [1]	1403 [1]	1000 - 1200 [2]
Phosphorus	mg	1165 [1]	1972 [1]	700 - 1250 [2]
Iron	mg	12.6 [1]	21.8 [1]	10 - 15 [2]
Zinc	mg	9.6 [1]	16.1 [1]	7.0 - 10 [2]
Copper	mg	1.77 [1]	3.13 [1]	1.0-1.5 [3]
Fluoride	mg	– [6]	– [6]	2.9 - 3.8 [4]
Manganese	mg	– [6]	– [6]	2.0 - 5.0 [3]
Molybdenum	µg	– [6]	– [6]	50 - 100 [3]
Chromium	µg	– [6]	– [6]	30 - 100 [3]
Selenium	µg	– [6]	– [6]	30 - 70 [3]

[1] Daily intake by women aged between 25 and 50 (according to VERA study, 1995)
[2] Recommended nutrient intake for adolescents and adults from age 13 onwards (D-A-CH, 2000)
[3] Estimates for appropriate daily intake (D-A-CH, 2000)
[4] Guidance value for appropriate total fluoride intake for adolescents and adults aged 13 upwards (D-A-CH, 2000)
[5] Estimate for minimum intake (D-A-CH, 2000)
[6] In Germany there are no representative intake data with medians and percentiles for these minerals. A study by Anke et al. (2000) has analysed the intake of these trace elements (excluding fluoride). However, this was done in a limited regional manner with a very small group which means that it does not make sense to take the mean values established in this study as the decision-making basis for maximum levels in food supplements for the general population in Germany.

Some studies exist in Germany pertaining to the usage of food supplements and their intake (Winkler et al., 1997; Winkler et al., 1998; Schellhorn et al.,1998; Mensink and Ströbel, 1999; Klipstein-Grobusch et al., 1998; Anke et al., 1991a; Anke et al., 1991b; Hahn and Wolters, 2000a; Hahn and Wolters, 2000b). According to this, up to 30% of women and up to 20% of men take these products more or less regularly. Around 50% of the consumers of food supplements use monoproducts which only contain one nutrient. It is difficult to calculate the contribution of food nutrients to total nutrient intake. It is the highest for vitamins C and E,

calcium and magnesium. Here, too, it applies that these studies only describe the situation in a sporadic manner.

Studies conducted prior to the year 2000 are still using the intake recommendations of DGE from 1991, which have since been revised and published in 2000 as reference values for nutrient intake (D-A-CH, 2000). The main changes are briefly summarised below (Table 2).

Table 2:
Comparison of the DGE recommendations from 1991 for the recommended or estimated daily need of minerals with the new nutrient reference values (D-A-CH, 2000) for nutrient intake by adults over the age of 19

Minerals	DGE recommendations (1991) for adults aged 19 upwards	Nutrient reference values for adults (D-A-CH, 2000)	Way of Change
Calcium[1]	800 mg -1000 mg	1000 mg	→
Magnesium[1]	300 mg[3] - 350 mg[4]	300 mg[3] – 400 mg[4]	↑
Chromium[2]	50 µg - 200 µg	30 µg – 100 µg	↓
Iron[1]	10 mg[4] -15 mg[3]	10 mg[4] - 15 mg[3]	→
Iodine[1]	200 µg	180 - 200 µg	→
Copper[2]	1.5 mg - 3.0 mg	1.0 mg - 1.5 mg	↓
Manganese[2]	2.0 mg - 5.0 mg	2.0 mg - 5.0 mg	→
Molybdenum[2]	75 µg - 250 µg	50 µg - 100 µg	↓
Selenium[2]	20 µg - 100 µg	30 µg - 70 µg	↓
Zinc[1]	12 mg[3] - 15 mg[4]	7 mg[3] - 10 mg[4]	↓

[1] Recommended intake
[2] Estimates for appropriate intake
[3] Female
[4] Male

The recommended intake for calcium, magnesium, iron, iodine and manganese is largely unchanged with the new nutrient reference values (D-A-CH, 2000) compared with the DGE recommendations from 1991. For chromium, copper, molybdenum, selenium and zinc lower reference values for nutrient intake are given.

3.3 Tolerable total daily intake of minerals

Besides the EC Scientific Committee on Food (SCF), other bodies have also derived safe upper limits for daily intake for individual vitamins and minerals. Mention should be made here in particular of the Nordic Council of Ministers (Food) and the US-Food and Nutrition Board. In English-speaking countries these upper limits are described as **"Upper Safe Intake Levels"** or as is common within SCF **"Tolerable Upper Intake Levels (UL)"**. Table 4 gives an overview of the different recommendations.

Tolerable Upper Intake Level (UL) stands according to SCF, unless otherwise stated, for the daily maximum intake level of a nutrient (from all sources) for which it is assumed that it is unlikely to constitute a health risk to man. Different ULs can be derived for various age groups. The UL is not a recommended daily intake level. The UL refers to the general population including sensitive individuals of all ages. Individuals who receive additional nutrients on doctors' orders under medical supervision are not included in this assessment. Furthermore, special sub-groups of the population were not taken into account when determining the ULs e.g. in the case of specific genetic predispositions or specific diseases (FNB, 1997). This means that these groups of individuals are particularly predisposed to damaging effects (SCF, 2000).

The following table gives an overview of the ULs defined by different bodies:

Table 3: Upper Intake Level for the total daily intake of minerals for adults

Minerals		**Upper Intake Level** (US-FNB, 2001) (> 19 years)	**Upper Safe Intake Level** (Nordic Council, 2001)	**Tolerable Upper Intake Level** (SCF, 2000, 2001) (> 18 years)
Sodium	mg			—[3]
Potassium	mg			—[3]
Chloride	mg			—[3]
Fluoride	mg	10		—[3]
Iodine	µg	1100	1000	—[3]
Magnesium	mg	350[6]		250[5]
Calcium	mg	2500	2500	—[3]
Phosphorus	mg	4000	5000	—[3]
Iron	mg	45	60	—[3]
Zinc	mg	40	45	—[3]
Copper	mg	10		—[3]
Manganese	mg	11		x [1]
Molybdenum	mg	2		0.6 [2]
Chromium	µg	N.D.[4]		—[3]
Selenium	µg	400	300	300

[1] Assessed by SCF, an Upper Level however was not derived
[2] Corresponding to 0.01 mg/kg body weight (SCF Opinion, 2000 h)
[3] Not yet reassessed by SCF but envisaged for the derivation of upper levels
[4] N.D.: not definable as no reports of adverse drug reactions. Intake should be only from foods.
[5] Refers to the addition of magnesium salts to food supplements or fortified foods.
[6] Refers only to food supplements not to other foods and water

When scientific bodies lay down tolerable intake levels for minerals as mentioned in table 3, this is generally data about total intake from all sources including food supplements and fortified foods and not data about tolerable upper levels or upper limits for individual products. An exception was made in the case of magnesium. This is data only about intake due to the addition of magnesium salts to food supplements or fortified foods.

3.4 Risk characterisation

3.4.1 General population

The risk potential from additional mineral intake from food supplements and/or fortified foods lies in the adverse drug reactions caused by overdosing due to uncontrolled consumption and the degree of severity of these effects in relationship to the consumption level of the nutrient. The following diagram presents the dose-frequency relationship. As a rule, the distribution of intake for normal nutrient intakes (from food) is below the Tolerable Upper Intake Level (UL) which means that no adverse health effects are to be expected. An uncontrolled supplementation can cause a potential health risk for some of the population i.e. when the UL is exceeded due to cumulative intake from all nutrient sources.

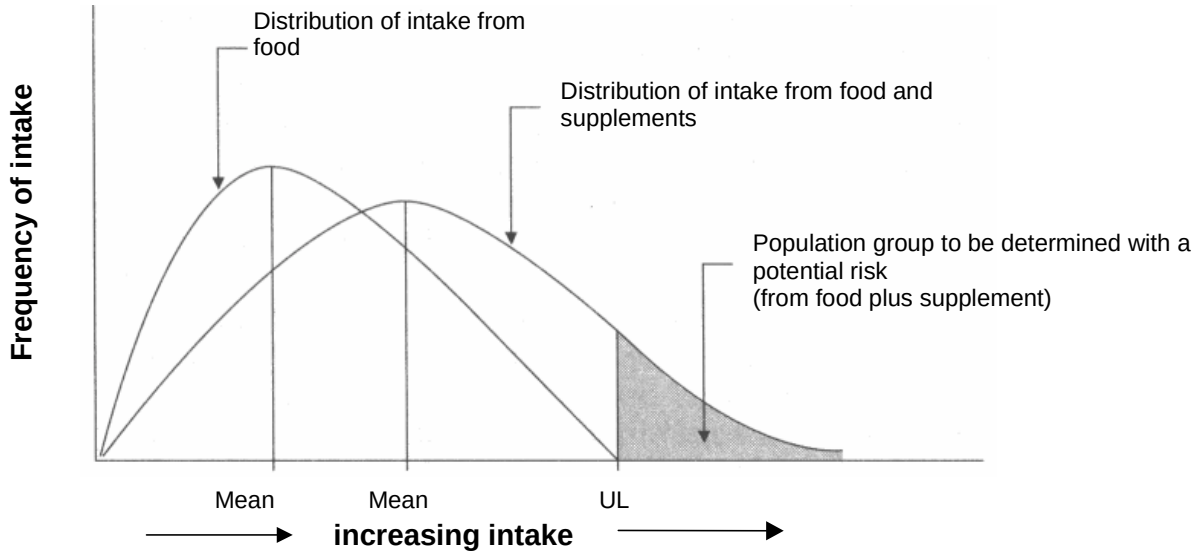

Diagram 1 Theoretical model for the risk potential of a nutrient, with and without supplementation

Besides exceeding the UL for a nutrient, there is a further risk potential in the interaction between nutrients and their competition for intake mechanisms which may lead to undesirable nutrient imbalances.

Both risk potentials are increased when the daily tolerable total intake of several nutrients is exceeded in an ongoing manner. The estimation whether the resulting adverse effects in a concrete case are additive or multiplicative, must be examined separately for each nutrient and each nutrient combination. For a scientific risk assessment of additional nutrient intake from food supplements it is therefore essential to derive a UL for each nutrient concerned and to correlate this value with up-to-date consumption data.

Depending on the mineral and the level of intake, adverse health effects may be mild or severe, acute or chronic, reversible or permanent. They are described in numerous publications and are mentioned, for instance, in the corresponding SCF opinions within the framework of the development of Tolerable Upper Intake Levels (UL) for vitamins and minerals (SCF, 2000 a-h).

3.4.2 Special population groups and individuals who are particularly vulnerable

The metabolism of a healthy individual is able to keep nutrient concentrations at a steady level over a wide range of fluctuation due to his highly complex regulatory metabolic network. In the human metabolism minerals are involved with co-ordinated and specialised protein activities which only function in an optimal manner within defined concentration ranges. Within this mechanism, genetically related activity differences in the proteins concerned, depending on the homozygotic or heterozygotic distribution of the alleles which encode them (variations of a gene), may vary considerably between individuals and be clinically noticeable in the border ranges.

One example is the genetically related haemochromatosis (C282Y mutation in the HFE gene), which can lead in a homozygotic genotype in adults because of increased iron resorption from the intestines to an iron overload disease with diverse, irreversible clinical symptoms like for instance hepatomegaly, diabetes mellitus, arthritic joint disorders or cardiac symptoms. In predisposed individuals of this kind the regular intake of bioavailable iron in the upper range of tolerable daily intake increases the risk of disease.

Genetic predispositions may vary considerably from group to group. Codetermining factors in the occurring of adverse effects are age, gender and health condition of the person concerned and his or her consumption behaviour. The geological conditions of the habitats play also a role in the unconscious daily mineral intake through foods. They have a considerable influence on the degree of the natural mineral content of drinking water and agricultural products. In the view of the BgVV, this is another reason why conventional foods for general consumption should not as a rule be fortified with minerals (cf. chapter 1.2).

As the scientific derivation of the UL, as described in chapter 3.3, does not take into account special subgroups of the population e.g. with a specific genetic predisposition and as these groups of individuals are susceptible to health damaging effects possibly far below the

normal maximum daily intake level, individual considerations must be undertaken to protect them from overdose.

3.5 Principle to derive maximum levels for minerals in an individual food supplement

3.5.1 Previous procedure

In 1996 the BgVV used the following approach to lay down **upper limits for trace elements in food supplements:**

(a) $\frac{\text{upper + lower estimate}}{2}$ x 0,5

(b) $\frac{\text{Recommended daily intake}}{2}$

In all the cases in which estimates exist (a), half of the mean estimate range was selected, in all other cases (b) half of the recommended daily intake. The resulting values were either rounded up or down to full figures using the reference parameters of the DGE recommendations from 1991 with the exception of zinc and iron, where the reference parameters are the SCF PRI values (SCF 1993). The resulting upper limits are given in table 4.

Table 4: BgVV proposal from 1996 for upper levels for trace elements in food supplements compared with recommended daily intake

Nutrient		Recommended daily intake for adults according to DGE (1991)	Upper levels for intake through food supplements per day (BgVV, 1996)
Chromium	µg	50 – 200	60
Iron	mg	9 [1]	5
Iodine	µg	180 – 200	100
Copper	mg	1.5 – 3	1
Manganese	mg	2 – 5	2
Molybdenum	µg	75 – 250	80
Selenium	µg	20 – 100	30
Zinc	mg	9.5 [1]	5

[1] PRI values of SCF (1993)

These upper levels primarily described the tolerable maximum daily intake of minerals from food supplements overall. As long as it could be assumed that in general not more than one food supplement per day was consumed, these upper levels applied also for the daily consumption level specified by the manufacturer for individual products. As described below, this assumption can no longer be made today.

3.5.2 Future procedure

As far as we know, on the national and international levels, there is no binding procedure to derive maximum levels for the use of minerals in food supplements and fortified foods. Since the derivation of upper levels for minerals in food supplements by the BgVV in 1996, consumption behaviour towards this kind of foods and fortified foods has changed considerably. A new approach is, therefore, necessary to derive maximum levels or upper limits in individual products which is based on the following reflections.

A tolerable upper intake level of a mineral (UL) derived by the EC Scientific Committee on Food (SCF) which normally refers to intake from all sources, is still occupied by its intake through the normal consumption of solid and liquid foods up to a specific percentage. The difference between this intake and the UL is the remaining quantity of mineral intake which may be consumed from all other intake sources if the UL is not to be exceeded.

Based on this fundamental assumption the BgVV now suggests the following procedure:

First of all, dietary intake by conventional food (DINF) is deducted from the Tolerable Upper Intake Level of SCF (UL). Based on the precautionary principle, the highest available percentile from the corresponding studies should be used to protect the vast majority of consumers who do not suffer from a deficiency. As a rule these are data on the 95th or 97.5th percentile.Meanwhile, it must be considered, that a large group of consumers for the purposes of additional intake of vitamins and minerals not only consume a single food supplement (preparation or product) but in parallel also other foods which claim a purpose of that kind offered in various forms and compositions on what is now a very comprehensive market. This may lead to multiple exposures to individual minerals, which involves:

- Possible multiple exposure through foods of various **product categories** like
  - food supplements,
  - solid foods fortified with minerals (e.g. breakfast cereals and snack bars),
  - liquid foods fortified with minerals (e.g. refreshment and milk beverages);
- Multiple exposure by means of **similar products within one category** e.g. through consumption of two different food supplements on one and the same day which contain the same mineral among others;
- **Further exposure sources** like mineral and table water, foods whose minerals are admixed for technological purposes and medicinal waters and other medicinal products like effervescent powders and tablets which have not been prescribed by a doctor.

These various possibilities of multiple exposure can be summarised in a **multiple exposure factor (MEF)**. The magnitude of this factor can only be roughly estimated because of the inadequate data about the actual exposure of the consumer from all named sources. At present, the assumption is very realistic that comparable amounts of minerals may be taken in parallel from up to four different sources. This is why a multiple exposure factor of 4 as a rule is probably not too high. As this is, however, a variable parameter which must be adapted to the respective level of knowledge, cases are also conceivable in which this multiple exposure factor could have a different value for very good, substantiated reasons.

The derivation of the tolerable intake level (maximum level) for minerals with the daily ration of an individual food supplement leads to the following formula:

$$TL = \frac{UL - DINF}{MEF}$$

Heading:

UL	=	Tolerable Upper Intake Level (SCF) usually referring to the daily total intake		
DINF	=	Dietary Intake by Normal (conventional) Food (upper percentile)		
MEF	=	**Multi-**	=	Dietary Intake by Product Groups
		exposure	=	Dietary Intake by Similar Products
		Factor	=	Other Intake
TL	=	Tolerable Level (maximum level) in a daily dose of a single dietary supplement		

When the daily ration of the individual food supplement is known, the tolerable maximum level (ML) of the mineral can be calculated from this value in the corresponding food supplement in mg/kg.

3.6 Measures and regulatory proposals for food supplements

3.6.1 Maximum levels for minerals in individual food supplements

The amended draft for an EC Directive on food supplements (EU, 2000b) envisages a positive list of admissible minerals (Annex 1 of the draft Directive) and the positive list of admissible chemical compounds as the source of these minerals (Annex II of the draft Directive). The BgVV agrees with the draft directive that the substances which SCF has already assessed and accepted for use in infant and small children's food and in foods which are for a specific nutrition, should also be authorised for manufactureing of food supplements. Non-assessed minerals and their chemical compounds by contrast, should not be used in food supplements.

For the above-mentioned reasons the following substances should not be included in Annex I of the Directive:

a) Substances for which there are clear indications that the additional intake is associated with health risks for the population at large which are unacceptable. This is according to the European opinion for instance the case with manganese for which SCF has already undertaken a corresponding assessment (SCF Opinion, 2000 f).

b) Substances for which an essentiality for humans could not be proven up to now. This applies for instance to trace elements like boron, silicon, germanium, aluminium, nickel, tin or vanadium. We maintain our earlier recommendation to reject in principle their use in food supplements because we consider the lack of reliable data and the fact that an assessment has not been undertaken as major reasons for health protection.

c) Substances like sodium, potassium, chlorine and phosphorous, are available in adequate amounts in foods which means that their additional intake is not necessary.

d) Substances for which there is no nutritional requirement but are of prophylactic importance (e.g. fluoride), and of which the intake is already regulated in a corresponding national prophylaxis programme.

By way of deviation from the Commission proposal, only the following minerals should be included in Annex I of the planned Directive and thus be approved for use in food supplements: **molybdenum, selenium, chromium, copper, zinc, iron, iodine, calcium and magnesium**. The addition of all other minerals should not be authorised for nutritional purposes.

The addition of substances like sodium, potassium, chloride and phosphate, which form corresponding salts with the above mentioned minerals and which are necessary for technological purposes (e.g. to guarantee sufficient solubility and bioavailability), should be regulated in Annex II of the Directive.

So far for the minerals, which are to be included in Annex I of the Directive, there are no sufficiently validated data which could give reliable information about normal nutrient intake and about consumption habits with respect to food supplements and other fortified foods. There is a need here for considerable research. For that reason very limited valid data could be used in the formula developed by the BgVV for the derivation of maximum levels (cf. chapter 3.5.2). Furthermore, SCF has only derived upper levels for three of the minerals concerned (molybdenum, selenium and magnesium). Nevertheless, the BgVV believes for the reasons explained in the following chapter that it is acceptable to maintain its prior upper levels from 1996 (with the exception of manganese and constraints for molybdenum and selenium) for pragmatic reasons and to apply them to food supplements until sufficiently validated data are available which can be used in the formula. Furthermore, we also now propose an upper level for magnesium. The new maximum levels are presented in Table 5.

Table 5:
Maximum levels for minerals in the daily ration of individual products (as per: January 2002)

Minerals	Maximum level per daily ration of food supplement	Restrictions
Calcium	Individual evaluations are necessary as in the past until the final assessment by SCF	
Magnesium	**62.5** mg	Not for children under 4
Chromium	60 µg	
Iron	5 mg	
Iodine	100 µg	
Copper	1 mg	
Molybdenum	80 µg	Not for children under 7
Selenium	30 µg	Not for children under 7
Zinc	5 mg	

3.6.2 Nutritional and toxicological characterisation of relevant minerals in brief

3.6.2.1 Calcium

Calcium is of importance in various ways, e.g. for the structure of bones and teeth and in signal transduction, muscle contractions and blood clotting. Calcium resorption is variable and is influenced by several factors. The concentration in the plasma is regulated by hormones and is largely stable.

The BgVV pointed out in 1998 that the amount of minerals in food supplements, for which no upper levels had been laid down in 1996, did not exceed the single dose of the respective DGE recommendation per daily portion (BgVV, 1998). The D-A-CH reference value (2000) for calcium is 1000 mg per day for adults over the age of 18. For healthy adults 2500 mg calcium should not be exceeded (FNB, 1989; 2001; SCF, 1993; Nordic Council, 2001). At higher levels there is amongst other things an increased risk of hypocalcaemia and the formation of kidney stones (FNB, 1989; SCF, 1993). So far SCF has not derived an UL. Therefore, the formula described in chapter 3.5.2 cannot yet be used to derive a maximum level for individual food supplements. Given the diversity of food supplements, beverages and other foods for general consumption fortified with calcium, which are now on the market, it is however to be expected that after the derivation of an UL by SCF a maximum level will

have to be laid down for individual products which will be considerably lower than the D-A-CH reference value of 1000 mg.

Up to assessment by SCF and the derivation of a maximum calcium level for individual products, applications for exemptions or general ordinances [7] must be handled individually.

3.6.2.2 Magnesium

Magnesium acts as a co-factor in many enzymatic reactions and plays an important role in the synthesis of nucleic acids and protein. It also stabilises the physiological balance of calcium, potassium and sodium. The level of magnesium in foods varies considerably. Resorption is influenced by numerous factors like intake level, solubility and interaction with other elements whereby for instance age, physical activity and liquid intake are also of importance.

The average intake of magnesium from foods for European consumers is given as between 200 mg/day (Italy) and approx. 350 mg/day (Germany). For the United States of America the values are 323 mg/day for men and 228 mg/day for women (FNB, 1997). The data for European consumers (97.5th percentile) and for the USA (95th percentile) are between approximately 350 mg/day and 600 mg/day (Elmadfa et al., 1999; Heseker et al., 1992; Turrini et al., 1996; Hulshof and Kruizinga, 1999; FNB, 1997).

No adverse effects have been observed in healthy consumers in conjunction with magnesium intake via conventional foods for general consumption. This can be explained, amongst other things, by the lower availability as a consequence of the influence of other food ingredients compared with intake from food supplements. Easily soluble magnesium salts, like the ones found in food supplements and medicinal products or in water, are fully available in the stomach through the presence of hydrochloric acid. From oral doses of 360 mg/day upwards they can trigger minor diarrhoea in a few test persons. Effects of this kind were not observed at doses of 250 mg/day and below (SCF, 2001 b).

From this SCF derives an NOAEL of 250 mg/day for **additional** intake of easily soluble magnesium salts (e.g. chloride, sulphate, aspirate, lactate) and for compounds like magnesium oxide (MgO) from food supplements, water or other fortified foods and beverages. When using a safety factor of 1, SCF gives for this additional intake a tolerable

[7] That is a general order issued by a German Ministry allowing the trade with a product which normally is not dealable according to German laws.

upper intake level **(UL) of 250 mg/day**. The use of a safety factor 1 is justified by the existence of corresponding data for many human studies in which a large number of test persons of all age groups including pregnant women and children aged 4 upwards were observed. Given the lack of corresponding data for children aged between 1 and 3, the UL only applies to adults and children aged 4 or more. No UL for magnesium intake from all sources could be given (SCF, 2001 b).

If the proposed calculation is undertaken to determine the tolerable intake level (TL) of magnesium from individual food supplements, this leads to the following value:

$$\frac{250 \text{ mg}\ ^{1}\text{(UL)} - 0\ ^{2}\ \text{(DINF)}}{4\ \text{(MEF)}} = 62.5 \text{ mg (TL)}$$

Caption:

1 SCF Opinion, 2001 b
2 Value zero is to be used here because the UL does not apply to intake from all sources but only for targeted additional intake.

UL	=	Tolerable Upper Intake Level (SCF) usually referring to the daily total intake		
DINF	=	Dietary Intake by Normal (conventional) Food (upper percentile)		
MEF	=	**Multi-**	=	Dietary Intake by Product Groups
		exposure	=	Dietary Intake by Similar Products
		factor	=	Other Intake
TL	=	Tolerable Level in a daily dose of a single dietary supplement		

In the case of magnesium the UL refers to additional intake only (cf. chapter 3.6.2.2)

Because the Tolerable Upper Intake Level of SCF (UL) for **magnesium** only applies expressly to adults and children aged 4 and upwards, magnesium-containing food supplements should not be consumed by children under the age of 4.[8] Therefore products of this kind should contain the reference **"Not for children under the age of 4"**.

3.6.2.3 Chromium III

Chromium is ubiquitous and is essential for man in its tervalent form (chromium III). In biological systems and, by extension, in foods, it is normally present in this form. Oxidation into the more toxic chromium VI does not take place there (Dayan and Paine, 2001) or only on a very low scale. Chromium VI compounds are not stable in biological systems (FNB, 2001).

[8] As no data were available for children from 1 to 3 years, and since it was considered that extrapolation of the UL for older children and adults on the basis of body weight was inappropriate, no UL could be established for this age group (SCF, 2001 b).

By influencing insulin activity, chromium III intervenes in the metabolism of carbohydrates, lipids and proteins. The exact mechanism of action and the exact structure of the so-called "glucose tolerance factor", the biologically active form of chromium, could not be fully explained up to now.

Adverse effects in individuals, which were caused by a chromium deficiency, have only been observed up to now in patients who were not given any chromium whilst being fed intravenously. Animal studies showed that when suffering a chromium deficiency rats developed a glucose tolerance disorder, similar to that found with diabetes mellitus. Other symptoms were reduced growth, increased cholesterin and triglyceride values and reduced fertility (WHO, 1996 b).

The available studies on kidney, liver and reproduction toxicity caused by chromium III and on interactions with DNA do not permit up to now the derivation of a LOAEL or NOAEL, which was reason enough for the US Food and Nutrition Board (FNB) not to derive an upper intake level for soluble chromium III salts. FNB does however ask, because of the widespread use of chromium supplements, explicitly for increased research on the health assessment of high chromium intakes and advises caution in respect of the chromium intake from food supplements until corresponding data are available (FNB, 2001).

Generally speaking, we can assume a relatively large safety margin between requirement and toxic effect for tervalent chromium (ATSDR, 1993, IARC, 1990, WHO, 1988). The requirement assessment by DGE in 1991 in the amount of 50-200 µg/day was reduced with the new D-A-CH values in 2000 to 30 - 100 µg/day. Since however no anomalies (D-A-CH, 2000) were observed in humans even with regular consumption of 200 µg/day chromium daily, and trivalent chromium has a low level of toxicity, the recommended upper level of the BgVV from 1996 of 60 µg/daily ration can be maintained provisionally for chromium III until the laying down of upper levels for the tolerable daily intake by SCF for food supplements.

The situation must be assessed quite differently in conjunction with the increased use observed recently of chromium as **chromium picolinate** as a food supplement. Several case studies in humans are available which point to a series of adverse effects (Huszonek,1993; Reading and Wecker, 1996; Wasser et al., 1997; Cerulli et al., 1998; Martin and Fuller, 1998; Young et al., 1999). Several in vitro studies also point out toxic effects of chromium picolinate (Stearns et al., 1995; Speetjens et al., 1999; Voelker, 1999; Vincent,

2000). They also indicate that chromium is likely to accumulate in individual tissue (Nielsen, 1996 and Stearns et al., 1995).

The EC Scientific Committee on Food states that data on the bioavailability of organically bound chromium are of decisive importance for the assessment of chromium picolinate and that until sufficient data are available no statement is possible about the admissibility of the use of these chromium compounds in foods for special nutritional purposes (PARNUTS) (SCF, 1999).

This situation strengthens our opinion that the use of chromium picolinate in foods should be rejected. In this context the "compelling reasons of health protection" should not only be asserted for proven health damage or risks but also in line with the fundamental principle of risk minimisation in cases of suspicion, in cases in which health risks have not been absolutely proven but are described as possible in scientific discussion.

3.6.2.4 Iron

Iron is essential for man and is needed for numerous body functions. Around 60% of endogenous iron is bound to haemoglobin in the erythrocytes where it is involved in oxygen transport to the individual tissues and cells. 25% is bound to ferritin and haemosiderin and around 15% to myoglobin in muscle tissue and in enzymes.

In Germany the average iron intake by women is 11 mg/day and by men 13 mg/day. The recommended intake for men aged 19 upwards is 10 mg/day and for women during pregnancy 30 mg/day and during lactation 20 mg/day, otherwise 10-15 mg/day. A nutritionally related iron deficiency is observed far less frequently today than in the past. Signs of iron deficiency anaemia were found in approximately 0.6% of federal citizens whereby women were affected twice as often as men (D-A-CH, 2000).

Iron is absorbed from food depending on the binding type and the presence of other food ingredients like resorption inhibiting ligands like tannins, lignins, oxalic acid, phytates and phosphates, on very differing degrees. The resorption rate from animal products (haem iron) is 20% and more, whereas iron is only resorbed to around 5% from foods of plant origin (non haem iron). Ligands like ascorbic acid or citric acid stimulate resorption whereas the consumption of wheat bran, calcium salts, milk and soya products inhibit iron resorption. The same applies to medicinal products like ASS and antacid agents (D-A-CH, 2000).

The iron requirement results from iron losses of the body. Only 10% of the haemoglobin and myoglobin iron released during degradation is excreted, the rest is recycled. The overall loss is on average 1 mg / day. Menstruating women lose an additional 15 mg iron per month.

An oversupply of iron can lead to effects which, depending on dose and sensitivity of the persons concerned, may range from minor gastrointestinal irritations to severe poisonings. A few interactions with other elements are also of importance. Increased iron intake reduces for instance the resorption of zinc.

Iron ions (Fe^{2+} und Fe^{3+}) form hydroxyl radicals ($-OH^{\bullet}$) with oxygen species like NO or H_2O_2, and with other transition metal ions. The hydroxyl radical is itself a strong oxidant which rapidly reacts with organic molecules. For instance, it may form with cell component parts secondary radicals from proteins, lipids or nucleic acids which, in turn, react with other cellular macromolecules and trigger a chain reaction (Marquardt und Schäfer, 1994). These reactions may lead to considerable functional disturbances of cell membranes and to corresponding cell damage.

Acute toxic effects are observed at doses between 20 and 60 mg/kg body weight whereby in the lower dose range gastrointestinal irritations are predominant and in the upper dose range besides liver and kidneys also the central nervous system, the cardiovascular and the haematological systems are affected (FNB, 2001).

Today, increased iron intake is viewed far more critically than in the past. The reason is the assumption that on confirmation of the hypotheses of "oxidative damaging effects of iron", far more people than before would have to be viewed as particularly sensitive to iron. This suspicion is backed more particularly by results from transferrin receptor studies and studies with individuals who are heterozygous for the iron storage disease haemochromatosis. No further details are discussed at this point. In the EC Scientific Committee on Food (SCF) work is currently being done on an opinion on iron and the derivation of an UL.

After considering all validated findings it is tenable to tolerate the use of iron in individual products up to a provisional maximum level of 5 mg/daily ration food supplment until a definitive assessment is made by SCF.

3.6.2.5 Fluoride

Humans take in fluoride from solid foods (fish, seaweed and seafood are all rich in fluoride), drinking water, mineral water, black tea, fluoride-containing toothpaste and oral hygiene products and, in some cases, from fluoridised table salt and special fluoride-containing medicinal products. The total intake of fluoride in the population fluctuates depending on eating habits and regional differences in the fluoride levels in drinking and mineral waters (Hunt und Stoecker, 1996). According to estimates the daily intake of fluoride by adults in Germany is between 0.4 and 1.5 mg (Bergmann, 1983; Heseker, 1999; WHO, 1996 a).

The EC Scientific Committee on Food (SCF) has not made any specific recommendations for fluoride because there is no special requirement for fluoride ("There does not appear to be a specific physiological requirement for fluoride") (SCF, 1993; SCF, 1997). The WHO was also unable to lay down a value for a possible fluoride requirement. It noted that there is no evidence of clinical symptoms of fluoride deficiency in humans and there are no diagnostic parameters which correlated with fluoride deficiency (WHO, 1996 a). Germany, Austria and Switzerland merely issue guidance values for the appropriate intake of fluoride (3.1-3.8 mg/day for adults) (D-A-CH, 2000).

Because in certain regions, e.g. in areas with very low levels of fluoride in drinking water, the daily target **fluoride intake for caries prophylaxis** is not reached by some consumers from food alone, measures for local and systemic caries and fluoride prophylaxis are recommended on the national level (BgVV, 1999). **Since an overdose of fluoride can have adverse effects (for instance dental and skeletal fluorosis), the intake paths for fluoride must be restricted.**

Besides supply through the above foods, only one form of systemic fluoridisation should be chosen, either **fluoridised table salt** or special **fluoride supplements as medicinal products.** In addition to the two first-mentioned measures, fluoride can also be administered **locally** in **fluoride-containing toothpaste** (in adults and children from the age of 6). The intake of fluoride from other additional sources like e.g. food supplements would lead to the uncontrolled intake of this trace element. Adverse effects on health could not be ruled out. For that reason, fluoride should not be used in food supplements.

3.6.2.6 Iodide

Germany is still considered to be an iodine deficiency area even if the iodine supply in recent years has improved considerably (D-A-CH, 2000). It is assumed, that only 1.3% of the people examined have a sufficient iodine intake (optimum 180-200 µg/day, maximum up to

300 µg/day). In Germany according to the WHO criteria, the entire population suffers from a "Degree 1" iodine deficiency (Manz et al., 1998). Compared with other countries with sufficient iodine supply like for instance Switzerland or the USA, thyroid diseases caused by iodine deficiency in Germany are still a health problem. According to the results of the integrated study “Iodine Monitoring 1996” the average iodine intake of men and women is 126 µg and 111 µg/day respectively. The median was 116 µg and 106 µg/day. The 95th percentile was 209.6 and 185.8 µg/day. Compared with the intake recommendations there is an average supply deficit of around 60-80 µg iodine/day (intake reference value: 180-200 µg/day). This corresponds to one-third of the recommended intake. The supply deficits (approx. 40-50%) of pregnant women and puerperant women are considerable which means that a good iodine supply through basic foods plus 100 (-200) µg iodine/day in tablet form is recommended to cover the increased need (230-260 µg/day).

The chosen method to improve the iodine supply status of the population is the use of iodised table salt (WHO/UNICEF/ICCIDD, 1996). Iodine supply in food through iodised table salt and products manufactured with it, is interpreted by the statutory fixed maximum level regulation (**15-25 mg** iodine/kg salt) in such a way, that even if normal table salt were to be completely replaced by iodised salt to reach at best the intake of 200 µg iodine/day recommended by the Deutschen Gesellschaft für Ernährung e.V. (German Society for Nutrition).

For groups of people, who for instance have a higher iodine need according to the D-A-CH recommendations like pregnant and lactating women, easily dosable iodine preparations are available as medicinal products. For food supplements up to now the BgVV has accepted an upper level of 100 µg/daily ration; this does not apply to diet foods.

WHO stated an upper tolerable intake level of 1000 µg iodine per day. The USA and Canada have laid down a "Tolerable Upper Intake Level" of 1100 µg/d (US-FNB, 2001). Germany, however, like other countries, (Bürgi et al., 1982; Phillips et al., 1988), as a consequence of a long-term iodine deficiency, can expect to see unrecognised functional autonomies of the thyroid gland, particulary in older people. Under these circumstances the iodine intake from food for adults should not in general exceed 500 µg/day (D-A-CH, 2000). With that level, as a rule, no acute, severe hyperthyreoses will be triggered even in the case of existing compensatory autonomy of the thyroid gland. However, depending on the stage of development of the autonomy and the iodine dose, hyperthyreoses are to be expected (Livadas et al., 1977). The frequency of that kind of hyperthyreoses will fall considerably with ongoing improvements to the iodine supply of the population (Baltisberger et al., 1995).

According to iodine monitoring the maximum iodine intake, including iodine tablets, of men and women is 437.8 and 414.3 µg per day (Manz et al., 1998).

For reasons of preventive health protection the upper level of 500 µg total iodine intake per day currently described as safe in Germany should not be exceeded as otherwise old people in particular with an unrecognised autonomy of the thyroid gland would be exposed to the health risk of a life-threatening derailment of the thyroid gland function (hyperthyreosis). The exemptions granted up to now for the direct fortification of foods with iodine in the case of butter and eggs should remain the exceptions. Other exemptions should not be granted. In the long term iodine should only be supplied through iodised salt. Firstly this makes the controlled intake of iodine possible and secondly, it prevents oversupply which cannot be ruled out in the direct fortification of foods. In the meantime, the alternative is to add iodine to medicinal products or food supplements with a maximum level of 100 µg/day.

3.6.2.7 Copper

Copper is essential for man and a necessary component in various enzymes. For instance in oxidases it is involved as a catalyst in the reduction of molecular oxygen. Copper also plays an important role in caeruloplasmin, an important plasma protein which is of importance for binding iron to transferrin (cf. 3.6.2.4). Disruptions in the function of the caeruloplasmin lead to the intracellular accumulation of iron.

Descriptions of the oral toxicity of copper are contradictory. The inadvertent intake of 15-75 mg copper is said to already cause gastrointestinal disorders. (Aaseth and Norseth, 1986). Other authors report that vomiting and heartburn were observed as reversible effects at oral doses of 10-15 mg. According to Bergquist and Sundbom (1980) the emetic dose is 25-75 mg. Copper taken in with drinking water already led at far lower doses to toxic effects. Individuals complained about stomach irritations after consuming drinking water with a copper content of 3 mg/l (WHO, 1993). Toxic effects following the short-term oral intake of larger amounts of copper are normally reversible (Aaseth and Norseth, 1986), whereas the longer lasting intake of large amounts of copper may lead to irreversible damage. Copper-driven liver damage is observed almost only in patients with the Wilson's disease aside from the diseases in children described below.

Copper is mainly excreted by the gallbladder. In the case of a surplus of copper, biliary excretion is considerably increased. Since this excretion mechanism doesn’t develop its full

capacity until the first years of life, infants are more at risk than adults in the event of a surplus of copper despite their higher copper requirement. A high copper intake triggered, beside other possible factors, a disease which has become known as "Indian Childhood Cirrhosis" (ICC) and is deemed to be the main trigger for the onset of "Idiopathic Copper Toxicosis" (ICT) (FNB, 2001).

The need estimated by DGE in 1991 of 1.5-3.0 mg/day was reduced to 1.0-1.5 mg/day in 200 in the new D-A-CH values. Other bodies stated requirements below 1 mg/day (WHO, 1998). The dietary intake of copper by conventional food is given with values between 0.94 - 2.2 mg/day; for children it is frequently below 1 mg/day (WHO, 1998). In the USA medians are given for upper intake by food which for men are in the range of 1.2 to 1.6 mg/day and for women of 1.0 to 1.1 mg/day. People who consume copper supplements (in 1996 15% of adult US citizens) take in on average an additional 0.3-0.5 mg/day (FNB, 2001). The gastrointestinal resorption rate is regulated homeostatically and is high compared with other metals (e.g. cadmium or lead). Depending on the composition of the food it is between 30 and 50%. Proteins, amino acids, citrates or oxalates increase resorption; fibres, a high calcium or phosphate supply and phytate reduce it (Marquardt and Schäfer, 1994). In the case of resorption there is also a direct interaction between copper and zinc. Studies in rats have shown that doses below 1 µg can be absorbed by more than 50%. Studies in humans with labelled copper showed an average resorption rate of 57%. In a study with four women a rate of 49 to 65% was determined. There are reports that a few low molecular copper compounds with high lipophilia and copper salicylates are almost fully resorbed (Aaseth and Norseth, 1986).

When considering the data available up to now and the relatively large safety margin between requirement and toxic effect (WHO, 1996 a; FNB, 2001), the upper level recommended by the BgVV from 1996 of 1 mg as a maximum level in the daily ration of a food supplement can be provisionally retained until the laying down of upper levels for the tolerable daily intake of copper by SCF.

3.6.2.8 Manganese

Manganese was reassessed by the EC Scientific Committee on Food (SCF) (SCF Opinion, 2000 f). The available data clearly show that overly high manganese intake both in humans and animals can trigger adverse effects. **No oral NOAEL could be determined** from the available animal experiments. That is why SCF decided not to stipulate a tolerable upper

intake level for manganese. Instead, it explicitly stated that the gap between the dose range in which adverse reactions occur in humans and the levels of manganese taken in through food is very narrow and that given the neurotoxicity and a potentially higher sensitivity of specific sub populations, manganese intake beyond what is normally ingested through beverages and solid foods carries the risk of potentially adverse effects which are not balanced by any recognisable benefits from additional manganese intake (SCF Opinion, 2000 f).

The US Food and Nutrition Board (US-FNB) assumes, in its assessment of manganese[2] intake by food, more or less the same scale as SCF. It notes that the consumer with a diet which is typical in the western world takes in up to 10.9 mg manganese per day. In the case of special vegetarian diets up to between 13 and 20 mg manganese may be taken in per day. As no adverse effects have been observed so far in consumers with a typical western diet, which could be attributed to manganese, FNB considers a daily manganese intake by food of 11 mg as a reasonable NOAEL. Using an uncertainty factor of 1 it derives a tolerable upper intake level (UL) of 11 mg/day.

The BgVV shares the opinion of the SCF, that given the inadequate data available for man and the lack of animal experiment NOAELs for critical end points, there is so much uncertainty that the derivation of a numerical UL cannot be justified. Aside from that, it is also clear in the assessment of US FNB that there is no scope for additional intake of manganese from food supplements. In this context there is no disagreement with the European opinion that intake which goes beyond what can normally be taken in from beverages and solid foods may be associated with the risk of potential adverse effects.

The BgVV, therefore, recommends that as of now no general ordinances or exemptions be granted any longer for food supplements to which manganese has been admixed.

3.6.2.9 Molybdenum

In animal experiments critical effects on reproduction can be identified for molybdenum, particularly in respect of foetal development. There are no corresponding findings for human beings. From a study in rats over a period of 9 weeks a NOAEL of 0.9 mg/kg body weight

[2] http://www4.nas.edu/IOM/IOMHome.nsf/Pages/Food+and+Nutrition+Board

was derived. When applying a safety factor of 10 for sensitive populations and a further safety factor of 10 for gaps in knowledge about toxicokinetics and the reproduction toxic effects in man, SCF derived a tolerable upper intake level for molybdenum of **0.01 mg/kg** body weight (SCF Opinion, 2000 h). That means **600 µg/person** (60 kg). This upper level also applies to pregnant and lactating women but not to children and adolescents because in further animal experiments clear adverse effects on the growth of young rats were observed. The following tolerable upper intake levels were derived for molybdenum in children, adolescent and adults (SCF, 2000 h):

Age in years	**Tolerable Upper Intake Level (UL) (µg/day)**
1 - 3	100
4 - 6	200
7 - 10	250
11 - 14	400
15 - 17	500
from 18	600

WHO quotes consumption data, which were researched by Parr et al. (1992) for the period from 1970 to 1991 on the basis of published literature and which refer to adults (WHO, 1996 b). However, these data are not as reliable and as representative as would be required to derive maximum levels according to the formula proposed in chapter 3.5.2. As already presented in chapter 3.2, the data from Anke et al. (2000) about molybdenum intake are not representative so we do not believe it makes sense to use these values in the above formula. We, therefore, suggest that as long as no reliable data has been collected in Germany about molybdenum supply, the previous BgVV upper level of 80 µg should be retained as the maximum level for the use of molybdenum in individual food supplements.

Given the above-mentioned reproduction toxic effects, we therefore do not feel it to be acceptable for precautionary reasons to place molybdenum-containing food supplements for children on the market. Calculations using WHO data (1996 b) and bearing in mind the guidance values for average energy intake of children (D-A-CH, 2000) show that at least in children under 7 years of age the corresponding tolerable upper intake level (UK) of 200 µg per day can be considerably exceeded already through the intake of just one single food supplement which contains the maximum level of 80 µg molybdenum per day ration. Because the data quoted by WHO are not so reliable and representative as would be desirable here and furthermore only refer to adults (and therefore would have to be adapted to the energy intake of children), there is a need for research. For the above precautionary

reasons we, therefore, believe it is justified to issue a **warning** that these products are not suitable at least **for children under 7.**

3.6.2.10 Selenium

For selenium there are numerous studies which deal both with the advantages of this element and also with its toxicity. They also include studies in human beings which permit, in the opinion of SCF despite some remaining uncertainties, the laying down of tolerable upper intake levels (SCF, 2000 g).

For the derivation a NOAEL of 850 µg/day was initially used which comes from a study in humans involving 349 people. At this level of intake no clinical symptoms of selenium intoxication could be observed any more. The above NOAEL also applies to more sensitive individuals. Remaining uncertainties are taken into account with an uncertainty factor of 3. This leads to a rounded tolerable upper level for the intake of selenium from all food sources of 300 µg per day and adult. SCF has no information that the upper level should not also apply to pregnant and lactating women. For children and adolescents it applies correspondingly for the respective body weight. The **tolerable upper intake levels for selenium in children, adolescents and adults (SCF Opinion, 2000 g)** are listed below:

Age in years	Tolerable Upper Intake Level (UL) (µg/day)
1 - 3	60
4 - 6	90
7 - 10	130
11 - 14	200
15 - 17	250
from 18	300

WHO quotes consumption data, which were researched by Parr et al. (1992) for the period from 1970 to 1991 on the basis of published literature and which refer to adults (WHO, 1996 b). However, these data are not as reliable and as representative as would be required to derive maximum levels according to the formula proposed in chapter 3.5.2. As already presented in chapter 3.2, the data from Anke et al. (2000) about selenium intake are not representative so we do not believe it makes sense to use these values in the above formula.

For selenium as for molybdenum it can be said that, despite the existing tolerable upper intake levels, a tolerable maximum level for use in food supplements cannot be calculated until representative data are available on selenium uptake in Germany. We, therefore, suggest that the previous BgVV upper level of 30 µg be retained as the provisional maximum level for the use of selenium in individual food supplements.

Since SCF has derived lower tolerable upper intake levels for children than for adults, we believe for precautionary reasons, as was done for molybdenum, that it is not tenable to place selenium supplements for children on the market. When doing calculations with the WHO data (1996 b) and bearing in mind the guidance values for the average energy intake of children (D-A-CH, 2000) it was shown that at least in children under the age of 7 the corresponding tolerable upper intake level (UL) of 90 µg per day can already be exceeded thourgh the intake of conventional foods. Because the data from WHO are not as reliable and as representative as we would like them to be and only refer to adults (and therefore have to be adapted to the energy intake of children), there is a need for research. For the above-mentioned precautionary reasons we believe it is justified to demand a **warning** that these products are not suitable at least **for children under the age of 7**.

3.6.2.11 Zinc

The new DGE-D-A-CH values for zinc are between 3 and 10 mg/day depending on age group and gender. It has been sufficiently proven that the recommended daily intake of zinc is reached or even exceeded through a normal diet with common foods, drinking water and beverages.

Various bodies, like for instance the SCF, DGE and the European Federation of Health Product Manufacturers Association (EHPM), advise against exceeding a daily zinc intake of 30 mg. The US-FNB defines an UL for zinc of 40 mg, the Nordic Council of 45 mg (FNB, 2001, Nordic Council of Ministers, 2001). There is no nutritional reason for additional intake through individual products clearly exceeding this need. It is rather to be expected that the fortification of foods with zinc could lead in a large proportion of the population to total intake (from all sources) which is above 30 mg. Until the expected laying down of tolerable upper intake levels by the SCF in the near future, we believe it is tenable to tolerate the use of zinc in food supplements up to the old BgVV upper level of 5 mg/food supplement daily ration as the provisional maximum level.

3.6.3 Protection of consumers against deceit

3.6.3.1 Minimum content of minerals and trace elements in food supplements

The minimum content of minerals in food supplements should be measured in such a way that the daily consumption amount stated by the manufacturer reaches 15% of the respective maximum level proposed bythe BgVV. The percentage is based on the Nutrient Labelling Regulation (NKV). Annex 1 of NKV states that only nutrients may be advertised which contain at least 15% of the daily requirement in 100 g or 100 ml of a ready to eat food. As the provisions of NKV do not apply to food supplements and the reference value 100 g or 100 ml would not make sense for food supplements in the form of pills, capsules, etc, we link our volume of 15% to the proposed maximum levels per daily ration.

A maximum level for calcium cannot yet be stated. According to the NKV 15% of the "recommended daily dose" of 800 mg given in Annex 1 of NKV is provisionally proposed. Provisionally, for calcium this means the minimum level of 120 mg in the daily ration.

3.6.3.2 Labelling

The purpose of mineral concentrates like food supplements is to supplement an undersupply of individual nutrients. The general safety of use of nutrient concentrates does not, therefore, result alone from the maximum values of approved doses but must in addition be validated through proper instructions for use and labelling of the product.

The main requirements for the labelling of food supplements have already been compiled in the German draft regulations on food supplements (of 29.06.2001) and need not be repeated here.

In respect of the warning for food supplements proposed in § 8, para 3, point 3 of the above draft, the BgVV proposes the following precise wording:

INFORMATION Eat a moderate and varied diet. Supplementing daily diet with individual nutrients only makes sense in the case of undersupply. The long-term consumption of nutrients beyond the daily requirement imposes a strain on the metabolism and does not bring with it any additional advantages. Avoid exceeding the recommended daily intake amounts.

3.7 Measures and regulatory proposals for fortified foods

It is urgently recommended to try and get the competent bodies of the EU to introduce greater differentiation into the preliminary draft for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND THE COUNCIL for the approximation of the laws of the Member States relating to the addition of nutrients to foods of 6 June 2000 (EU, 2000 d), (cf. chapter 1.2). Comprehensive approval of the addition of vitamins and minerals to conventional foods for general consumption in the preliminary draft would contradict the precautionary principle and would not be acceptable in the interest of general food safety in the envisaged form, as the intake amount of these foods is not oriented towards the amount of vitamins and minerals contained in them, but is determined by factors like hunger, thirst, appetite and availability. Therefore, fortification of conventional foods for general consumption can only be permitted as an exception in order to protect people from overdose when there are clearly proven preconditions for a nutrient deficiency or an undersupply of the population or population groups. All the same, there must be comprehensive scientific consensus about these preconditions.

In particularly substantiated exceptional cases fortification of conventional foods for general consumption should only then be possible, if firstly an endemic deficiency has been proven for the mineral, secondly it is guaranteed that the fortified food is only consumed by the target group regularly and in a foreseeable amount, and thirdly that the corresponding mineral is dosed to the food and admixed on a limited scale.

Fortification of conventional foods for general consumption should, if necessary, be conducted at best as a general (health) policy steered measure as has been done at present in respect of the addition of iodine to table salt, in Germany. The uncontrolled and non-differentiated fortification as an individual action by a manufacturer is not acceptable in our opinion.

If the opinion should gain the upper hand on the European level in conjunction with the discussion about the draft Directive concerning the addition of nutrients to foods that the fortification of conventional foods for general consumption should be allowed, maximum levels would also have to be derived for this. Furthermore, it would have to be guaranteed that these foods are correspondingly labelled and rendered visible to the consumer and that understandable information is provided as to which groups of persons should not eat these

foods or consume them with caution. The then necessary derivation of maximum levels in individual products should be conducted in the same way as proposed in this report for food supplements. The multi-exposure factor of the above-mentioned formula would then have to be correspondingly adapted.

In order to reach binding regulations for the fortification of foods for general consumption, like those for the iodisation of table salt, there is an urgent need for research about consumption behaviour and nutrient supply of the respective population (cf. chapter 3.8).

3.8 The need for research

The relevant consumption studies in Germany (National Consumption Study, Health Survey) do not take into account at all or only inadequately the new foods groups "food supplements", "fortified foods" and "functional foods" since they are based on analyses of conventional foods (cf. e.g. Federal Food Key). There is an urgent need for research in conjunction with supplementary studies.

The following preconditions must be met for a reliable risk analysis as the basis for the derivation of maximum levels in food supplements and in the fortification of foods:

1. For each individual nutrient a tolerable upper intake level (UL) must be defined. SCF has taken on board this task and initial assessments have already been published.
2. Current consumption data must be collected in order to be able to assess the nutrient supply of the German and European populations and special groups. In this context a distinction is to be made between intake from conventional, non-fortified foods, food supplements, fortified foods and other intake sources. On the basis of consumption studies of this kind, those foods which are suited for fortification should also be identified in especially substantiated cases.
3. Consumption data and data about the nutrient supply must be collected at regular intervals so that the type of nutrients which could be considered for supplements and/or fortification and the tolerable additional intake (maximum level) via the individual product can be adapted to the respective supply situation.

4 Glossary and Abbreviations

ATSDR US-Agency for Toxic Substances and Disease Registry
(The mission of the Agency for Toxic Substances and Disease Registry (ATSDR), as an agency of the U.S. Department of Health and Human Services, is to prevent exposure and adverse human health effects and diminished quality of life associated with exposure to hazardous substances from waste sites, unplanned releases, and other sources of pollution present in the environment.)

BGBl I Deutsches Bundesgesetzblatt I (Federal Health Gazette)

BgVV Federal Institute for Health Protection of Consumers and Veterinary Medicine

D-A-CH German, Austrian and Swiss Societies for Nutrition

DGE Deutsche Gesellschaft für Ernährung (The German Nutrition Society)
(The German Nutrition Society is a non-profit making organization and obliged to scientific facts. Its aims are to support the nutritional scientific research, to collect and to evaluate the results of related disciplines, to publish them in documentation and to find out where is a requirement for nutritional research. Furthermore, the coordination and assurance of quality of the nutrition education in the Federal Republic of Germany. Based on scientific facts about wholesome nutrition, the DGE helps to promote and maintain the health and fitness of the population.)

DINF Dietary Intake by Normal (conventuel) Food (upper percentile)

EU European Union

EC European Commission

FNB US-Food and Nutrition Board
(The Food and Nutrition Board (FNB) is a unit of the Institute of Medicine (IOM), part of the National Academy of Sciences (NAS). The NAS is a private, nonprofit corporation created by an Act of Congress, with a charter signed in 1863 by President Abraham Lincoln. The IOM, chartered under the NAS in 1970, acts as an adviser to the federal government on issues of medical care, research, and education. The IOM secures the services of eminent members of appropriate professions to examine policy matters pertaining to the public's health and occasionally undertakes studies on its own initiative.)

GSF Research Centre for the Environment and Health (up to 1990 Society for Radiation Research)

IARC International Agency for Research on Cancer.
(The International Agency for Research on Cancer is part of the World Health Organization. IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.)

KG	Bodyweight
LM	Foodstuffs
LMBG	German Foods and Other Commodities Act
LOAEL	Lowest Observed Adverse Effect Level
MEF	Multi-Exposure Factor
ML	Maximum Level
MONICA	WHO-Studie "Monitoring Trends and Determinants in Cardiovascular Disease" (Monitoring of trends and determinants of cardiovascular diseases. The project was launched at the end of the 1980s by WHO. Germany is one of the 20 participating countries. In the town of Augsburg and the surrounding districts Augsburg and Aichach/Friedberg, the population is examined randomly for high blood pressure and other risk factors.)
NEM	Dietary Supplement
NOAEL	No Observable Adverse Effect Level
PRI	Population Reference Intake (SCF, 1993)
SANCO	EC Directorate General Health and Consumer Protection Direction Générale de la Santé et de la Protection du Consommateur)
SCF	Scientific Committee on Food
TL	Tolerable Level in a daily dose of a single dietary supplement
UL	Tolerable Upper Intake Level
WHO	World Health Organisation

5 References

Aarts, T., ed., 1998. Nutrition industry overview. Nutr. Bus. J. 3 (9), 1-5.

Aaseth, J. and T. Norseth, 1986. Copper; In: Friberg, L. et al. (Hrsg.). Handbook on the Toxicology of Metals, Volume II, Elsevier, 1986.

Anke M., Groppel, B., Krause, U. et al., 1991. Trace Element Intake (Zinc, Manganese, Copper, Molybdenum, Iodine and Nickel) of Humans in Thuringia and Brandenburg of the Fed. Rep. of Germany. J. Trace Elem. Electrolytes Health Dis. Vol 5, 66-74.

Anke, M., Arnhold, W., Groppel, B., Kräuter, U., Müller, M.,1991. Die Spurenelementaufnahme Erwachsener (Zink, Kupfer, Mangan, Molybdän, Jod, Nickel) in den neuen Bundesländern Deutschlands. Mineralstoffe und Spurenelemente in der Ernährung der Menschen. Blackwell Wissenschaft, Berlin, 64-85.

Anke M., et al., Trace element intake and balance in adults in Central Europe. In: Roussel et al. (ed.), 2000. Trace Elements in Man and Animals. Plenum Publishers, New York, 2000.

ATSDR, 1993. Toxicological Profile for Chromium. Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services.

Bergmann, K. E. et al., 1983. Fluoridgesamtaufnahme im ersten Lebensjahr. Deutsche zahnärztliche Zeitschrift 38,145-147.

Bergquist, U. and M. Sundbom, 1980. Copper - Health and Hazard; Gov. Reports, Announcements & Index (GRA&I), Issue 14, 1981, Stockholm University - Fysika Institutionen.

BgVV 1998: Fragen und Antworten zu Nahrungsergänzungsmitteln. Informationsblatt BgVV, September 1998. http://www.bgvv.de

BgVV, 1996. Toxikologische und ernährungsmedizinische Aspekte der Verwendung von Spurenelementen in Nahrungsergänzungsmitteln. Unveröffentlichte Stellungnahme für das Bundesministerium für Gesundheit (FB1-2240-3596/96 vom 07.11.1996).

BgVV, 1999. BgVV recommends the use of fluoridised table salt for caries prophylaxis. When used properlz no health impairment. BgVV Press Relaese 10/99, 1 July 1999. http://www.bgvv.de (Presse).

Bürgi, H., Baumgartner, H., Steiger, G., 1982. Gibt es eine obere Verträglichkeitsgrenze der alimentären Jodzufuhr? Schweiz. Med. Wochenschr. 112, 2-7.

Cerulli J., D.W. Grabe, I. Gauthier, M. Malone, M.D. McGoldrick, 1998. Chromium picolinate toxicity. Ann Pharmacother 32, 428-31.

D-A-CH, 2000. Referenzwerte für die Nährstoffzufuhr. Deutsche Gesellschaft für Ernährung (DGE), Österreichische Gesellschaft für Ernährung (ÖGE), Schweizerische Gesellschaft für Ernährungsforschung (SGE), Schweizerische Vereinigung für Ernährung (SVE). Umschau Braus GmbH, Verlagsgesellschaft, Frankfurt a. M.,1. Auflage 2000, 179-184.

DAK, 1999. Repräsentative Studie der Deutschen Angestellten Krankenkasse DAK, durchgeführt vom Meinungsforschungsinstitut FORSA. Pressemitteilung 1999.

Dayan A.D. and A.J. Paine, 2001. Mechanisms of chromium toxicity, carcinogenicity and allergenicity: Review of the literature from 1985 to 2000. Human & Experimental Toxicology 20, 439-451.

Deutsches Institut für Ernährungsforschung Potsdam-Rehbrücke, 1998. Wer greift zu Vitamin- und Mineralstofftabletten? Pressemitteilung vom 19. Mai 1998.

DGE, 1998. Einsatz von Nahrungsergänzungsmitteln. DGE. Info (8), 114. Deutsche Gesellschaft für Ernährung.

DGE-Empfehlungen, 1991. Empfehlungen für die Nährstoffzufuhr, 5. Überarbeitung 1991 und 2. korrigierter Nachdruck 1995. Deutsche Gesellschaft für Ernährung. Umschau Verlag, Frankfurt / Main.

EU, 2000 a. Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND THE COUNCIL on the approximation of the laws of the Member States relating to food supplements (COM(2000) 222 final 2000/0080 (COD). Brussels, 8 May 2000). http://europa.eu.int/eur-lex/de/com/dat/2000/de_500PC0222.html

EU, 2000 b. Amended proposals for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND THE COUNCIL for the approximation of the laws of the Member States relating to food supplements. Brussels, 19 March 2001, COM(2001) 159 final, 2000/0080 (COD). http://www.europa.eu.int/eur-lex/de/com/pdf/2001/de_501PC0159.pdf http://europa.eu.int/eur-lex/de/com/reg/de_register_152030.html

EU, 2000 c. Guidelines of the SCF for the development of tolerable upper intake levels for vitamins and minerals (adopted on 19 October 2000). SCF/CS/NUT/UPPLEV/11 Final. 28. November 2000.

EU, 2000 d. Preliminary draft for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND COUNCIL for the approximation of the laws of the Member States for the addition of nutrients to foods. Brussels, 6 June 2000, SANCO.02-BM/cv.

EU, 2001. Tolerable upper intake levels for vitamins and minerals. http://www.europa.eu.int/comm/food/fs/sc/scf/out80_en.html

Elmadfa I., Burger P., Derndorfer E. et al., 1999; Austrian Study on Nutritional Status (ASNS). Österreichischer Ernährungsbericht. Bundesministerium für Gesundheit, Arbeit und Soziales. Wien 1999.

Fischer, B. et al.,1998. Die Einnahme von Vitamin- und Mineralstoffpräparaten in der Region Augsburg. Informationsblatt aus dem Institut für Epidemiologie der GSF.

Fischer, B., Döring, A., 1999. Häufigkeit der Einnahme von Vitamin- und Mineralstoffpräparaten. Ernährungs-Umschau 46 (2), 44-48.

FNB, 1989. Recommended Dietary Allowances. 10th Edition. Food and Nutrition Board, National Academy Press. Washington, D.C.

FNB, 1997. Dietary Reference Intakes for Calcium, Phosphorous, Magnesia, Vitamins D and F. Food and Nutrition Board, Institute of Medicine. National Academic Press, Washington D.C. pp 190-249.

FNB, 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zink. Food and Nutrition Board, Institute of Medicine. National Academic Press. Advance publication on the Internet:
http://www.nap.edu/catalog/10026.html

Hahn, A., und Wolters M., 2000 a. Nahrungsergänzungsmittel - Eine Bestandsaufnahme. Teil I: Einordnung, Marktsituation und Verbraucherverhalten. Zeitschrift für Ernährungsökologie 1 (3), 167-175.
http://www.scientificjournals.com/php/sjAbstract.php?doi=erno2000.07.009

Hahn, A., und Wolters M., 2000 b. Nahrungsergänzungsmittel - Eine Bestandsaufnahme. Teil II: Zielgruppen, Nutzen und Risiken. Zeitschrift für Ernährungsökologie 1 (4), 215-230.
http://www.scientificjournals.com/php/sjAbstract.php?doi=erno2000.09.013

Heseker H., Adolf T., Eberhardt W., Hartmann S. et al., 1992. VERA-Schriftenreihe, Bd. III: Lebensmittel- und Nährstoffaufnahme Erwachsener in der Bundesrepublik Deutschland. Wissensch. Fachverlag Dr. Fleck, Niederkleen, 179 and 182.

Heseker, H., 1999. Fluorid. Funktionen, Physiologie, Stoffwechsel. Empfehlungen und Versorgung in der Bundesrepublik Deutschland. Ernährungs-Umschau 46, 305-307.

Hulshof K.and Kruizinga AG: TNO Report 99516. Zeist, 1999. Vitamin and Mineral Intake in The Netherlands.

Hunt, C.D.and Stoecker B.J., 1996. Deliberations and evaluations of the approaches, endpoints and paradigms for boron, chromium and fluoride dietary recommendations; J. Nutr. 126, 2441-2451.

Huszonek J, 1993. Over-the-counter chromium picolinate. Am J Psychiatry 150, 1560-1.

IARC, 1990. Chromium and nickel welding. IARC Monographs on the evaluation of carcinogenic risks to humans, vol 49, Lyon.

Klipstein-Grobusch, K., Kroke, A., Voß, S., Boeing, H., 1998. Einfluß von Lebensstilfaktoren auf die Verwendung von Supplementen in der Brandenburger Ernährungs- und Krebsstudie. Z Ernährungswiss. 37, 38-46.

Lewis, K.A. and Hohl, R.J., 1997. Modulation of RAS expression in human malignant cells by dietary supplements. Nutrition 13 (10), 921-923.

Livadas, D. P., Koutras, D. A., Souvatzoglou, A., Beckers, C., 1977. The toxic effects of small iodine supplements in patients with autonomous thyroid nodules. Clin. Endocrinol. 7, 121-127.

Manz, F., Anke, M., Bohnet, H.G., Gärtner, R., Großklaus, R., Klett, Schneider, R., 1998. Jod-Monitoring 1996. Repräsentative Studie zur Erfassung des Jodversorgungszustands der Bevölkerung Deutschlands. Schriftenreihe des BMG, Bd. 110. Nomos Verl.-Ges., Baden-Baden.

Marquard, H. und S.G. Schäfer (Hrsg.), 1994. Lehrbuch der Toxikologie. Wissenschaftsverlag, Mannheim, Leipzig, Wien, Zürich

Martin W.R. and R.E. Fuller, 1998. Suspected chromium picolinate-induced rhabdomyolysis. Pharmcacotherapy 18, 860-862.

Mensink, G.B.M., Ströbel, A., 1999. Einnahme von Nahrungsergänzungspräparaten und Ernährungsverhalten. Gesundheitswesen 61 (2), 132-137.

Nielsen F.H., 1996. Controversial chromium. Does the superstar mineral of the mountebanks receive appropriate attention from clinicians and nutritionists? Nutr. Today 31, 226-233.

Nordic Council of Ministers, 2001. Addition of Vitamins and minerals: A discussion paper on health risks related to foods and food supplements. TemaNord 2001, 519.

Parr, R.M. et al., 1992. Human dietary intakes of trace elements: a global literature survey mainly for the period 1970 – 1991, data listings and references. International Atomic Energy Agency (IAEA), Vienna (Report IAEA-NAHRES-12).

Phillips, D. I., Nelson, M., Barker, D. J., Morris, J. A., Wood, T. J., 1988. Iodine in milk and the incidence of thyrotoxicosis in England. Clin. Endocrinol. 28, 61-66

Przyrembel, H., 1998. Nährstoffanreicherung in Lebensmitteln: Sinn und Unsinn. Rundgespräche der Kommission für Ökologie, Bd.15 "Lebensmittel im Wandel", S. 115-125. Verlag Dr. Friedrich Pfeil, München.

Reading S.A.J. and L. Wecker, 1996. Chromium picolinate. J. Florida M.A. 89: 29-31.

Ringel Heller I., Silverglade, B., 2001. Functional Food: Health Boon or Quackery? Bundesgesundheitsblatt 3, 214.

SCF, 2000. Scientific Committee on Food 2000. Guidelines of the Scientific Committee on Food
for the development of tolerable upper intake levels for vitamins and minerals.
SCF/CS/NUT/UPPLEV/11 Final. adopted on 19 October 2000.

SCF, 1993. Scientific Committee on Food 1993. Nutrient and energy intakes for the European Community. Reports of the Scientific Committee for Food, Thirty First Series. European Commission, Luxembourg.

SCF, 1997. Opinion On Arsenic, Barium, Fluoride, Boron and Manganese In Natural Mineral Waters. Scientific Committee on Food, SCF/CS/CNTM/NMW/5. Final, June 1997.
(expressed on 13 December 1996).
http://europa.eu.int/comm/food/fs/sc/oldcomm7/out09_en.html

SCF, 1999: Scientific Committee on Food: Opinion on substances for nutritional purposes which have been proposed for use in the manufacture of foods for particular nutritional purposes ("PARNUTS"). SCF/CS/ADD/NUT/20/Final, 12/05/99).

SCF, 2000 a. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Beta Carotene; Scientific Committee on Food, SCF/CS/NUT/UPPLEV/37. Final, 28 November 2000, (expressed on 19 October 2000).

SCF, 2000 b. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B2. Scientific Committee on Food SCF/CS/NUT/UPPLEV/33. Final, 7 December 2000.
(expressed on 22 November 2000).

SCF, 2000 c. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B6. Scientific Committee on Food SCF/CS/NUT/UPPLEV/16. Final, 28 November 2000.
(expressed on 19 October 2000)

SCF, 2000 d. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B12. Scientific Committee on Food SCF/CS/NUT/UPPLEV/42. Final, 28 November 2000.
(expressed on 19 October 2000).

SCF, 2000 e. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Folate. Scientific Committee on Food SCF/CS/NUT/UPPLEV/18. Final, 28 November 2000.
(expressed on 19 October 2000).

SCF, 2000 f. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Manganese. Scientific Committee on Food SCF/CS/NUT/UPPLEV/21. Final, 28 November 2000.
(expressed on 19 October 2000).

SCF, 2000 g. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Selenium. Scientific Committee on Food SCF/CS/NUT/UPPLEV/25. Final, 28 November 2000.

(expressed on 19 October 2000).

SCF, 2000 h. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Molybdenum. Scientific Committee on Food SCF/CS/NUT/UPPLEV/22. Final, 28 November 2000.
(expressed on 19 October 2000).

SCF, 2001 a. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B1. Scientific Committee on Food SCF/CS/NUT/UPPLEV/46. Final, 16 July 2001.
(expressed on 11 July 2001).

SCF, 2001 b. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level
of Magnesium. Scientific Committee on Food SCF/CS/NUT/UPPLEV/54. Final, 11 October 2001.
(expressed on 26 September 2001).

SCF, 2001 c. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level
of Biotin. Scientific Committee on Food SCF/CS/NUT/UPPLEV/55. Final, 10 October 2001.
(expressed on 26 September 2001).

Schellhorn, B., Döring, A., Stieber, J. 1998. Zufuhr an Vitaminen und Mineralstoffen aus Nahrungsergänzungspräparaten in der MONICA-Querschnittsstudie 1994/95 der Studienregion Augsburg. Z Ernährungswiss. 36, 198-206.

Sichert-Hellert, W., Kerstin, M., Manz, F., 2001. Changes in time-trends of nutrient intake from fortified and nonfortified food in German children and adolescents - 15 year results of the DONALD-Study. Eur. J. Nutr. 40, 49-55.

Sjölin, K., 2001. Zehn Jahre schwedisches Selbstregulierungsprogramm für “health claims” bei Lebensmitteln. Ein Rückblick. Bundesgesundheitsblatt 3, 219.

Slesinski, M.J., Subar, A.F., Kahle, L.L., 1995. Trends in use of vitamin and mineral supplements in the United States. The 1987 and 1992 National Health Interview Surveys. J. Am. Diet. Association 8, 921-923.

Speetjens J.K., R.A. Collins, J.B. Vincent, S.A. Woski, 1999. The nutritional supplement chromium (III) tris (picolinate) cleaves DNA. Chem. Res. Toxicol. 12. 483-487.

Stearns D.M., J.P. Wise, S.R. Patierno, K.E. Wetterhahn, 1995a. Chromium(III)picolinate produces chromosome damage in chinese hamster ovary cells. FASEB J. 9, 1643-1648.

Stearns D.M., J.J. Belbruno, K.E. Wetterhahn, 1995b. A prediction of chromium(III)accumulation in humans from chromium dietary supplements. FASEB J. 9, 1650-1657.

Streinz, R., 2001. Rechtliche Vorgaben für gesundheits- und krankheitsbezogene Angaben bei funktionellen Lebensmitteln. “Health Claims”. Bundesgesundheitsblatt 3, 227.

Turrini A., INRAN Rome. Vitamin and Mineral Intake in Italy. National Survey 1994-1996.

Van’t Veer P, Kardinal AFM, Bausch-Goldbohm RA and Kok Fj, 1993. Biomarkers for validation. Eur J Clin Nutr 47 (Suppl. 2): S58-S63.

Verbraucherzentralen, 2000: Nahrungsergänzungsmittel. Verbraucherzentralen Hessen, Nordrhein-Westfalen, Sachsen-Anhalt und Arbeitsgemeinschaft der Verbraucherverbände (AgV). © Hrsg. Verbraucherzentrale Baden-Württemberg e.V.

Verschuren, P.M., Trautwein, E.A., de Boer, B. et al., 2001. Perspektiven für Functional Foods. Bundesgesundheitsblatt 3, 205.

Viell, B., 2001. Funktionelle Lebensmittel und Nahrungsergänzungsmittel – wissenschaftliche Gesichtspunkte. Bundesgesundheitsblatt 3, 193.

Vincent J.B., 2000. The biochemistry of chromium. J. Nutr. 130, 715-718.

Voelker R.,1999. Cancer risk in diet supplement. JAMA 281, 1480.

Wasser W.G., N.S. Feldman, V.D. D'Agati, 1997. Chronic renal failure after ingestion of over-the-counter chromium picolinate. Ann. Intern. Medicine 126, 410.

WHO, 1971. Food Fortification, Protein-calorie Malnutrition. Joint FAO/WHO Expert Committee on Nutrition, eightieth Report. Technical Report Series No 477.

WHO, 1988: Chromium. IPCS Environmental Health Criteria, Document 61, World Health Organization, Geneva.

WHO, 1996 a: Guidelines for drinking-water quality, second edition, vol 2. World Health Organization, Geneva.

WHO, 1996 b: Trace elements in human nutrition and health, World Health Organization, Geneva.

WHO/UNICEF/ICCIDD, 1996. Recommended Iodine Levels in Salt and Guidelines for Monitoring their Adequacy and Effectiveness. WHO/NUT/96.13.

WHO, 1998: Copper. IPCS Environmental Health Criteria, Document 200, World Health Organization, Geneva.

Winkler, G., Brasche, S., Heinrich, J., 1997. Ernährungserhebung bei Erwachsenen in Erfurt 1991/92: Verzehr von Lebensmitteln und Supplementen. Z Ernährungswiss. 36 (2), 143-150.

Winkler, G., Döring, A., Fischer, B., 1998. Supplements as a source of micronutrient intake in middle-aged men in southern Germany: Results of the MONICA dietary survey 1994/95. Z Ernährungswiss. 37, 315-318.

Young P.C., G.W. Turiansky, M.W. Bonner, P.M. Benson, 1999. Acute generalized exanthematous pustulosis induced by chromium picolinate. J. Am. Acad. Dermatol. 41, 820-823.