Published by A. Domke, R. Großklaus, B. Niemann, H. Przyrembel, K. Richter,
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Use of Minerals in Foods

Toxicological and nutritional-physiological aspects

Part II

Imprint

BfR Wissenschaft

A. Domke, R. Großklaus, B. Niemann, H. Przyrembel, K. Richter,
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Use of Minerals in Foods –
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1 Preface

BfR (previously BgVV) has been involved since 2000 in the risk assessment of vitamins and minerals, including trace elements, in foods. External experts were also invited to participate in the drawing up of this two-volume report now available in the series "BfR-Wissenschaft". The aim was to obtain as solid a consensus as possible on scientific risk assessment. Technical experts from the German Nutrition Society (DGE), the Senate Commission on Food Safety (SKLM), the German Research Foundation (DFG), the Federal Institute for Medicinal Products and Medical Devices (BfArM), the Federal Research Centre for Nutrition and Food (BFEL), the Robert Koch Institute (RKI), the German Institute of Human Nutrition (DIfE) and the Research Institute of Child Nutrition (FKE) in Dortmund as well as individual experts took part. Part II of the report examines the "Use of Minerals in Foods – Toxicological and Nutritional-Physiological Aspects". Part I is also published in the series "BfR-Wissenschaft" as edition 04/2005 and is entitled "Use of Vitamins in Foods – Toxicological and Nutritional-Physiological Aspects".

The report is intended as a basis for discussion and a decision-making for risk managers in Germany and the European Union when setting maximum levels for nutrients in food supplements and fortified foods. The setting of maximum levels was announced in Articles 5 and 13 of "Directive 2002/46/EC of the European Parliament and the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements". The proposal for a "Regulation on the addition of vitamins and minerals and of certain other substances to foods" (COM (2003) 671 of 10 November 2003 in conjunction with Article 16 of that Regulation) also envisages the setting of maximum levels for vitamins and minerals by the European Commission with the support of the Standing Committee on the Food Chain and Animal Health.

When setting maximum levels of this kind, consideration must be given both to the likely safe daily intakes of a vitamin and mineral (so-called tolerable upper intake levels) and to the uptake of these nutrients from common foods by the population. At the same time, the recommended daily intakes for a nutrient should be taken into account when setting a maximum level in a food. Whereas tolerable upper intake levels have been derived or defined by various scientific bodies, this report endeavours to identify ways of calculating maximum levels of vitamins and minerals in a single food from tolerable upper intake levels, daily intake and recommended daily intake.

Such "combined" maximum levels should allow supplementation levels sufficient for correcting nutrient deficits in population groups without exceeding the tolerable daily intake levels (to a major degree). Depending on the desired level of protection, various options for setting maximum levels are outlined in this two-volume report and the respective advantages and disadvantages are discussed. This does not constitute in any way a pre-emption of a political decision in favour of one of the identified options. This decision is to be taken on the Community level in Europe.

Professor Dr. Dr. Andreas Hensel
President of BfR

2 Glossary and Abbreviations

ACE beverages	Beverages fortified with provitamin A and the vitamins C and E
ADI	Acceptable Daily Intake
AFSSA	French Agency for Food Safety, Expert Committee on Human Nutrition
ATBC Study	Alpha-Tocopherol, ß-Carotene Cancer Prevention Trial
BfArM	Federal Institute for Medicinal Products and Medical Devices
BfR	Federal Institute for Risk Assessment
BGA	Federal Health Office
BgVV	Federal Institute for Health Protection of Consumers and Veterinary Medicine
CARET Study	ß-Carotene Cancer and Retinol Efficiency Trial
CAS Number	Chemical Abstracts Service. System which allocates a number to a chemical substance (= CAS Number)
D-A-CH	Deutsche, Österreichische und Schweizerische Gesellschaft für Ernährung: Deutsche Gesellschaft für Ernährung e.V. (DGE), Österreichische Gesellschaft für Ernährung (ÖGE), Schweizerische Gesellschaft für Ernährungsforschung (SGE) and Schweizerische Vereinigung für Ernährung (SVE) (German, Austrian and Swiss nutrition societies)
DGE	Deutsche Gesellschaft für Ernährung e.V. (German Nutrition Society)
DiätVO - Verordnung über diätetische Lebensmittel	Ordinance on Foods for Special Dietary Purposes
DINF	Dietary Intake by Normal Food (upper percentile)
DONALD Study	Dortmund Nutritional and Anthropometric Longitudinally Designed Study
EAR	Estimated average requirement
EFSA	European Food Safety Authority
EPIC Study	European Prospective Investigation into Cancer and Nutrition-Study
Estimated values	Values for nutrients for which human requirements cannot yet be determined with the desired accuracy. The estimated values do, however, provide good pointers for adequate and safe intake (D-A-CH, 2000). ➢ **Reference values**
EU	European Union
EVM	Expert Group on Vitamins and Minerals
FDA	Food and Drug Administration (USA)
FF	Fortified foods
FNB	Food and Nutrition Board of the Institute of Medicine (IOM)
FS	Food supplements
FSA	Food Standards Agency (UK)
Guidance Level	Levels that would not be expected to be associated with adverse effects but acknowledging that such levels may not be applicable to all life stages or for life-long intake and where it was not possible to establish Safe Upper Levels. Guidance levels should not be used as Safe Upper Levels (Food Standards Agency. Safe Upper Levels for Vitamins and Minerals. Report of the Expert Group on Vitamins and Minerals. London, 2003)
Guidance values	Orientation aid for nutrient levels if there is a need, on health grounds, for intake to be controlled within specific ranges but not within strict limit values (D-A-CH, 2000) ➢ **Reference values**
IOM	Institute of Medicine of the National Academy of Science (NAS)
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LMBG	Food and Other Commodities Act
LOAEL	Lowest observed adverse effect level; lowest intake (or experimental dose) of a nutrient at which an adverse effect has been identified (FNB: Dietary Reference Intakes. Applications in Dietary Assessment. Food and Nutrition Board, Institute of Medicine. National Academic Press, Washington D.C., 2000)
MEF	Multi-Exposure Factor = estimated number of food supplements and fortified foods with the respective nutrient
MRDR Test	Modified Relative Dose Response Test
NAS	National Academy of Science (USA)
NHS	Nurses' Health Study

Continuation Glossary and Abbreviations

NOAEL	No observed adverse effect level; the highest intake (or experimental dose) of a nutrient at which no adverse effects have been observed in the individuals studied (FNB: Dietary Reference Intakes. Applications in Dietary Assessment. Food and Nutrition Board, Institute of Medicine. National Academic Press, Washington D.C., 2000)
NFCS	National Food Consumption Study
OTC products	Over-the-counter products
Percentile	A specific value in a set of ordered data below which a specific percentage of the data fall. For instance, the 10 percentile is the value which 10% of the data fall below and 90% of the data fall above.
PHS	Physician's Health Study
PRI	Population Reference Intakes of SCF
RDA	Recommended dietary allowances
Recommendations	Amounts of nutrients derived from levels of average requirements and increased by the two-fold standard deviation. The intake of these amounts covers requirements in almost 98% of all individuals in a population and protects against damage to health (D-A-CH, 2000) ➢ **Reference values**
Reference values	Levels for nutrients which are assumed to protect almost all persons in the respective population group from food-related damage to health and which ensure they can function fully. Furthermore, they are intended to build up a certain body reserve which is immediately available for sudden increases in requirements without any impairment to health (D-A-CH, 2000). A distinction is made between: ➢ **Recommendations** ➢ **Estimated values** ➢ **Guidance values**
Safe Upper Level (SUL)	Represents an intake that can be consumed daily over lifetime without significant risk to health. (Food Standards Agency. Safe Upper Levels for Vitamins and Minerals. Report of the Expert Group on Vitamins and Minerals. London, 2003)
SCF	Scientific Committee on Food
TDI	Tolerable daily intake
TL	Tolerable level in a single dietary supplement or in an individual fortified food product; Maximum level for individual food supplements or individual fortified foods
Tolerable Upper Intake Level (UL)	➢ The maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. (Scientific Committee on Food: Guidelines of the Scientific Committee on Food 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) ➢ The highest average daily nutrient intake level likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases. (FNB: Dietary Reference Intakes. Applications in Dietary assessment. Food and Nutrition Board, Institute of Medicine. National Academic Press, Washington D.C., 2000)
UF	Uncertainty factor
Upper Intake Level (UL)	The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. (Nordic Council: Addition of vitamins and minerals. A discussion paper on health risks related to food and food supplements. Copenhagen 2001, TemaNord 2001: 519)
VERA	Nutrition survey and risk factor analysis
VitaminV - Verordnung über vitaminisierte Lebensmittel	Ordinance on Vitaminised Foods

3 Introduction

3.1 Description of the problem

The market of food supplements and fortified foods (conventional foods with added vitamins and/or minerals) is diverse and growing. It is, therefore, important to lay down uniform provisions and set maximum levels for these products to protect consumers from possible adverse health effects but also from misleading advertising. Directive 2002/46/EC adopted by the European Parliament in June 2002 is a first step towards the uniform regulation of food supplements in Europe. Firstly, the Directive contains a positive list of all substances that can be added to food supplements in the Member States of the European Union. The next step, which is planned, is to set maximum levels – referred to the daily dose recommended by the manufacturer.

The "Proposal for a Regulation of the European Parliament and of the Council on the addition of vitamins, minerals and certain other substances to food", which was submitted in November 2003 by the European Commission, aims to bring about the standardisation of provisions concerning the addition of vitamins and minerals to conventional foods (CEC, 2003). This proposal also envisages setting maximum levels for vitamins and minerals.

Both documents, Directive 2002/46/EC and the Proposal for a Regulation, call for other sources of vitamin and mineral intakes to be taken into account when setting maximum levels.

In this context, BfR has prepared this report on the toxicological and nutritional aspects of the use of vitamins and minerals in foods. In contrast to the work done by the European Scientific Committee on Food (SCF), the American Food and Nutrition Board (FNB) and the British Expert Committee on Vitamins and Minerals (EVM), this was not to constitute another attempt to derive tolerable upper intake levels for vitamins and minerals. Instead, the goal was to derive proposals for maximum levels of vitamins and trace elements in individual food supplements and for the nutrient fortification of individual conventional foods bearing in mind the assessments undertaken by scientific bodies, other relevant study findings and the data available for Germany on nutrient intake and supply situation.

This report only addresses the addition of vitamins and minerals to conventional foods including food supplements whereas foods for special dietary purposes (e.g. complete/incomplete foods for special medical purposes) and medicinal products are explicitly excluded. Furthermore, the proposed maximum levels mainly refer to adults, perhaps additionally to children and adolescents, but not to young children or infants as they are already taken into account in the Ordinance on foods for special dietary uses.

In January 2002 a report was already published which looked at the addition of minerals ("Toxicological and Nutritional-Physiological Aspects of the Use of Minerals and Vitamins in Foods. Part I: Minerals and Trace Elements") (BgVV, 2002). In the meantime tolerable upper intake levels for several substances (calcium, zinc, copper, chromium, iodine) have been derived and published by the EU Scientific Committee on Food (SCF). This report updates the publication from 2002. Given its size, this report was broken down into two documents. Both are published in the series BfR-Wissenschaft. Part I is called "Use of Vitamins in Foods – Toxicological and Nutritional-Physiological Aspects" (BfR-Wissenschaft 04/2005). Part II bears the number 05/2005 in the BfR-Wissenschaft series and is entitled "Use of Minerals in Foods – Toxicological and Nutritional-Physiological Aspects". Both publications are available subject to a charge from the BfR Press and Public Relations Office.

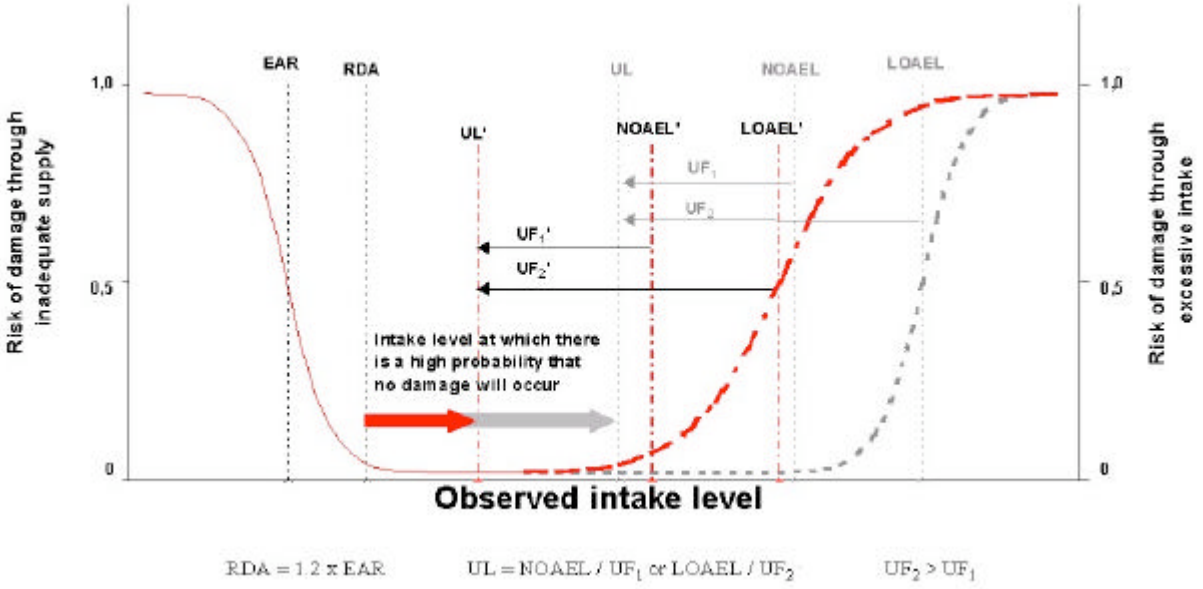
3.2 Principles for the risk assessment of vitamins and minerals including trace elements

The setting of tolerable upper levels for the daily intake of vitamins and minerals calls for comprehensive risk assessment based on generally recognised scientific data taking into account nutritional-physiological requirements.

The risk assessment of vitamins and minerals varies greatly from that of chemical residues or contaminants in foods. The special feature of essential nutrients, like minerals and vitamins, is that besides the risks related to high intakes there are also risks of inadequate supply or deficiency. In this context, the different sensitivities of individual consumer groups have to be taken into account as well (Dybing *et al.*, 2002; Grossklaus, 2002).

In the case of the classical toxicological procedure to set safe intakes or upper levels, the adverse effects identified are first placed in relationship to the dose (hazard characterisation). Based on the toxicological parameters like, for instance, NOAEL (No Observed Adverse Effect Level) and LOAEL (Lowest Observed Adverse Effect Level), tolerable upper intake levels (UL) are derived by the EU Scientific Committee on Food (SCF) or the European Food Safety Authority (EFSA) or other bodies using uncertainty factors (UF). SCF defines the UL as the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans (SCF, 2000).

Figure 1: Relationships between the recommended daily allowance (RDA) and LOAEL, NOAEL and the derivation of the UL for nutrients



using the example of a nutrient with a large margin between LOAEL/NOAEL and RDA (...) or a small margin between LOAEL/NOAEL and RDA (-·-) (modified in accordance with FNB, 2001)

Moreover, when determining the tolerable upper intake level/upper safe intake level of vitamins and minerals, it should be borne in mind that the area between the risk of insufficient dietary intake or deficiency and the risk of overdose or occurrence of toxic side effects may vary considerably for different nutrients. This is shown in Figure 1. The graph depicts the relative risk of the occurrence of deficiency or the occurrence of adverse side effects depending on the intake level of a nutrient.

The recommended dietary allowance for a nutrient (RDA or PRI, see Glossary) indicates the amount of a substance for which the probability of deficiency in a population group is not more than 2.5%. Higher nutrient intake than the RDA/PRI may, depending on the nutrient, lead quickly (see Fig. 1 LOAEL') or may lead with a larger margin of safety to adverse side effects (see Fig. 1, LOAEL). The UL is the intake level at which chronic daily intake, with a high degree of probability, will not lead to adverse side effects. The exceeding of this dose goes hand in hand with a higher probability of the occurrence of adverse side effects. In general, the margin between the RDA and UL is large (see Fig. 1 RDA ? UL). However, there are nutrients like vitamin A, for which the margin between the RDA and the defined UL is small (see Fig. 1, RDA ? UL'). The use of these nutrients in food supplements or fortified foods is, therefore, linked to a higher risk of adverse side effects than in the case, for instance, for nicotinamide where there is a large margin between the RDA and UL.

Regarding hazard characterisation, there are *considerable gaps in knowledge* about some nutrients. Although animal studies are available for the derivation of NOAEL and/or LOAEL, their transferability to man is unsure and very few studies in human beings are available. In some cases there are major differences between the individual bioavailability of nutrients and often a toxicological assessment is only possible of the amounts taken in via supplements and not of total daily intake (Hages *et al.*, 1999). Moreover, there may be interactions amongst various nutrients or with other food components that have to be taken into account. Furthermore, consideration must also be given to differences in gender and age as well as special physiological conditions and specificities in dietary habits (Dybing *et al.*, 2002).

Because of these differences in quantitative risk assessment, indications can only be given on a case by case basis whether and, if so, to what extent measures are required or whether they are necessary in line with the principle of hazard avoidance or the precautionary principle and whether they are imperative or not absolutely imperative.

3.3 Method to derive maximum levels for individual products

3.3.1 Structure of the report

The assessment of individual vitamins and minerals (Chapters 4-17 (Part I) and Chapters 4-18 (Part II)) was undertaken using the following structure (Figure 2). The individual chapters are based on principles of risk analysis and are tailored to deriving maximum levels in individual products (food supplements/fortified foods) (CAC, 2003).

Figure 2: Structure of risk assessment for the derivation of maximum levels in individual foods

1	Summary
2	Nutrient description
2.1	Characterisation and identification
2.2	Metabolism, function, requirements
2.3	Exposure (dietary and other sources, nutritional status)
3:	Risk characterisation
3.1	Hazard characterisation (NOAEL, LOAEL)
3.2	Deficiency, possible risk groups
3.3	Excessive intake, possible risk groups
4	Tolerable upper intake level
4.1	Derivation of maximum levels in food supplements
4.2	Derivation of maximum levels in fortified foods
5	Gaps in knowledge (optional)
6	References

Based on the supply status, nutrients can be divided into four categories following the example of AFSSA (Agence Française de Sécurité Sanitaire des Aliments) (Table 1) (AFSSA, 2002).

Table 1: Supply categories taking into account intake and/or supply status

Supply category	Criteria
1	Risk of a clinically manifest deficiency or a depletion of body stores in specific age groups with specific physiological conditions, specific eating habits, in specific regions
2	Uncertainty about the risk of a clinically manifest deficiency or a depletion of body stores because of the lack of or the questionable validity of a biomarker, inadequate food tables, lack of epidemiological studies
3	No indication of inadequate nutrient intake or there is nutrient intake in the range of recommended intake
4	Indication of nutrient intake above recommended intake

modified in accordance with AFSSA, 2002

With regard to the risk that nutrients can cause adverse effects, they can, following the classification of the Nordic Council (2001), be roughly divided into three categories depending on how large the margin is between recommended/observed intakes and the defined UL (Table 2). However, in individual cases (e.g. manganese, beta-carotene; see Table 3) the criteria used to define risk categories could not be applied.

Table 2: Various degrees of probability that a nutrient leads to adverse side effects

Risk category	Criterion
High risk	Nutrients for which the margin between the RDA (or measured intake) and UL is low (factor <5)
Moderate risk	Nutrients for which the UL is 5 to 100 times higher than the RDA (or measured intake)
Low risk	Nutrients for which a UL cannot be defined because up to now no adverse side effects have been identified despite intake 100 times higher than the RDA

3.3.2 Principles to derive maximum levels for vitamins and minerals in food supplements and fortified foods

Whereas SCF and other scientific bodies have defined a Tolerable Upper Intake Level (UL) for the daily intake of a nutrient from all food sources, BfR has derived a daily maximum level (TL) of a vitamin or mineral in individual products.

3.3.2.1 Theoretical foundations

In Part I "Minerals and Trace Elements", which has already been published on the Internet, we proposed a procedure for the derivation of daily maximum levels for individual products which is presented once again here in detail (BgVV, 2002).

This sequential procedure and the separate derivation of daily maximum levels for food supplements and fortified foods aims to take account of multiple exposure which may result from the daily parallel consumption of both product categories (food supplements, fortified foods) and also of the parallel daily consumption of several products within a category (e.g. consumption of several food supplements per day). At the same time, this procedure aims to facilitate the flexible handling of multiple exposure and to reflect the specificity's of food supplements and fortified foods. Differences between the two categories result from the fact that food supplements contain nutrients in dosed form (e.g. capsules or tablets) and must carry information about recommended daily intake along with a warning not to exceed the stipulated daily dose. In contrast, the consumption of fortified foods is not based on the amount of vitamins and minerals contained therein but is mainly determined by factors like hunger, thirst, appetite and availability. In contrast to the situation with food supplements, consumption recommendations are not usual or could not be complied with. In addition,

appropriate consideration must be given to the fact that vitamins and/or minerals may be added to a wide range of processed foods.

3.3.2.1.1 Derivation of tolerable vitamin and mineral levels for additional intake through food supplements and fortified foods

The basic assumption is that the tolerable upper intake level of a vitamin or mineral (UL), derived by the EU Scientific Committee on Food (SCF) - that normally comprises intakes from all sources - is already used up to a certain degree through the normal consumption of solid and liquid foods. The resulting difference to the UL represents the respective residual amount (R) of vitamin and/or mineral intake which may be taken in altogether from all other intake sources if the UL is not to be exceeded. It, therefore, constitutes the amount available for additional intake from food supplements and fortified foods. In line with a precautionary approach, for the calculation of the residual amount (R) the highest percentile available from corresponding studies is used as the value for Dietary Intake by Normal Food (DINF). As a rule, these are data on the 95 or 97.5 percentile. This leads to the following formula:

Formula 1 ➔ R = UL – DINF

UL	=	Tolerable Upper Intake Level (SCF) usually referring to the daily total intake
DINF	=	Dietary Intake by Normal Food (upper percentile)
R	=	Residual or maximum amount for safe addition to foods including dietary supplements

3.3.2.1.2 Derivation of the total tolerable intake of a vitamin or mineral via food supplements or the total intake level for via fortified foods

The residual amount R calculated according to formula 1 constitutes the sum of the total tolerable intake of a vitamin or mineral from food supplements and fortified foods. The following applies:

Formula 2 ➔

Residual amount (R) = total tolerable intake via food supplements + total tolerable intake via fortified foods
or
total tolerable intake via food supplements + total tolerable intake via fortified foods = UL – DINF

The percentage of this residual amount allocated to food supplements or fortified foods for additional intake is freely selectable. It may be between 0 and 100% whereby, however, the sum of the two percentages may not exceed 100%.

For the individual vitamins and minerals the distribution between the two food categories should be selected in such a way that the derived maximum daily levels for food supplements or fortified foods still reach significant sizes. In cases of conflict a decision should be taken in favour of the addition to food supplements. Nevertheless, in the case of vitamins and minerals with large margins between the tolerable upper intake level and the 95 or 97.5 percentile of intake, it makes sense to divide the available (large) residual amount in equal parts between food supplements and fortified foods. By contrast, in the case of vitamins and minerals with small margins, e.g. zinc, it is recommended that the available (small) residual amount be allocated to the category of food supplements alone and therefore to be no fortification of conventional foods.

3.3.2.1.3 Derivation of maximum levels for individual food supplements (TL_{FS})

Based on the total tolerable intake level laid down for food supplements (see formula 2), the daily maximum level can be derived for individual products. In this context, consideration must be given to multiple exposure via the product category food supplements. No corresponding figures are available to estimate the possible multiple exposure. Although a scientifically based numerical value cannot be derived at the present time, it is justified from the precautionary angle to assume that vitamins and minerals under certain circumstances are taken in daily from two different food supplements. This is conceivable, for instance, in the case of the intentional intake of vitamins and minerals via multivitamin and mineral products and the additional intake of food supplements which are consumed and promoted for their content of other substances (herbs, extracts etc.) and which contain vitamins and minerals as well (thus leading to unintentional additional intake of these nutrients). In this context it is relevant that food supplements do indeed carry instructions not to exceed the recommended daily dose but no recommendation to pay attention to the corresponding contents of other food supplements consumed. By improving knowledge about the consumption of food supplements, a more reality-based factor can be indicated for taking into account possible multiple exposure which can be correspondingly adapted when deriving the daily maximum levels.

$$TL_{FS} = \frac{\text{Total tolerable intake via food supplements }^{*)}}{2}$$

*) Total tolerable intake via food supplements = UL – (DINF + total tolerable intake via fortified foods)

3.3.2.1.4 Derivation of maximum levels for individual fortified foods (TL_{FF})

When deriving daily maximum levels for individual fortified foods (individual products), attention must also be paid to possible multiple exposure which may result from the addition of vitamins and minerals to a wide range of processed foods. As in the case of food supplements, no corresponding figures are, however, available. Not least because of this fact, various methods are feasible for the derivation of maximum levels for individual fortified foods:

a) Derivation of maximum levels for individual products based on food portions (numerical multiple exposure factor)

Here the derivation is based on the number of portions of foods fortified with a specific vitamin or mineral which are consumed daily. In order to derive the maximum level per individual product, the total tolerable intake via fortified foods is divided by the number of portions of fortified foods consumed daily. The level obtained in this way may be contained in a normal portion of the food concerned. Here, too, from the precautionary angle, the assumption of a multiple exposure factor of 2 (i.e. consumption of 2 portions of a food fortified with the same nutrient per day) is justified. In the case of an extension of the fortification of foods and/or consumption of fortified foods, higher factors may be necessary or there may be a need for regular adjustment in line with market developments. The maximum level per portion could be derived as follows (multiple exposure factor = 2):

$$TL_{FF}/\text{Portion} = \frac{\text{Total tolerable intake via fortified foods }^{(**)}}{2}$$

(**) Total tolerable intake via fortified foods = UL – (DINF + total tolerable intake via food supplements)

b) Derivation of maximum levels for individual products based on energy content, adapted to the model by Flynn *et al.* (2003)

In line with the method used by Flynn et al., the derivation is based on the 95 percentile of energy intake which was estimated for consumers in the European Union as 3600 kcal. In the same way, a maximum fortification rate of conventional food is assumed to be 50% since vitamins and minerals can only be added to processed foods but not, however, to fresh foods like fruit, vegetables or meat. Their addition is also limited by a number of other factors (Flynn et al., 2003).

For the derivation of the daily maximum level, referred to an energy content of 100 kcal, this leads to the following formula:

$$TL_{FF}/100\ kcal = \frac{\text{Total tolerable intake via fortified foods}^{(***)}}{36 * 0.5}$$

(***) Total tolerable intake via fortified foods = UL – (DINF + total tolerable intake via food supplements)

Although a multiple exposure factor can only be estimated at present, BfR favours the portion-based approach (Option a) since in the case of a reference to energy density (Option b) a special provision would be necessary for the groups of energy-reduced foods and low-energy drinks. Furthermore, Option a) offers the advantage of a uniform portion-based method both for food supplements and fortified foods.

3.3.2.2 Practical implementation

The method presented above was developed in order to guarantee the uniform derivation of maximum levels for the various vitamins and minerals. However, when considering individual vitamins and minerals, for the vast majority the method was not applicable or not fully applicable to the derivation of maximum levels in food supplements and/or fortified foods or it did not lead to viable results. The available data – or more appropriately the sparse data – normally meant that cases had to be considered on an individual basis.

The reasons which restricted or ruled out the application of the method or did not lead to viable results are the following:

- SCF did not derive a UL (e.g. vitamin B_1, B_2, pantothenic acid, biotin) or the work on the derivation of a UL by SCF or EFSA has not yet been concluded (e.g. iron) (when this report was published);
- not enough data are available on the dietary intake of vitamins/minerals or supply status;
- the therapeutic dose would be exceeded (e.g. vitamin K);
- BfR has well founded reservations about ULs which have been defined already (e.g. vitamin E).

3.4 Tabular overview of the results

Table 3 provides an overview of the classification of vitamins and minerals (including trace elements) in the risk or supply categories. Tables 4 and 5 present the maximum levels proposed by BfR for the use of vitamins and minerals in food supplements and fortified foods.

Table 3: Overview of the classification of vitamins and minerals in supply and risk categories

Nutrients	Risk category (Classification according to Table 2)	Supply category (Classification according to Table 1)
Vitamins		
Vitamin A	high	2/3
Beta-carotene	high *	3
Vitamin D	high	1
Vitamin E	moderate	2/3
Vitamin K	moderate	2
Vitamin B_1	low	3
Vitamin B_2	low	3
Vitamin C	moderate*	3/4
Niacin		3/4
- Nicotinamide	low	-
- Nicotinic acid	high	-
Vitamin B_6	moderate	4
Folic acid	moderate *	1/2
Pantothenic acid	low	2
Biotin	low	2
Vitamin B_{12}	low	4
Minerals		
Sodium	high * (additional administration as NaCl)	4
Chloride	-	4
Potassium	high (FS)	2/3
Calcium	high	4 from 0-3 years after 1/3
Phosphorus	moderate	4
Magnesium	moderate *	2/3
Iron	high	1/2
Iodine	high	1
Fluoride	moderately high *	2
Zinc	high	2
Selenium	moderately high *	2
Copper	high	3
Manganese	high *	2/3
Chromium	low	2
Molybdenum	moderate	2

* Classification deviates from Table 2

Table 4: Proposed maximum levels for the use of vitamins and minerals in food supplements (FS) referred to the daily dose recommended by the manufacturer

Nutrients		Recommended daily intake for adults [1]	Proposal for maximum level in FS	Comments
Vitamins				
Vitamin A	µg	800	400 (only for adults)	for children aged between 4 and 10: 200 µg
Beta-carotene	mg	2-4 [2]	2	
Vitamin D	µg	5	5	for persons >65 years: 10 µg
Vitamin E (equivalents)	mg	11-15 [2]	15	
Vitamin K	µg	80 [2]	80	
Vitamin B_1	mg	1.3	4	
Vitamin B_2	mg	1.5	4.5	
Niacin	mg	17	17	no use of nicotinic acid
Vitamin B_6	mg	1.6	5.4	
Folate equivalents	µg	400	400 (as folic acid)	
Pantothenic acid	mg	6 [2]	18	
Biotin	µg	60 [2]	180	
Vitamin B_{12}	µg	3	3-9	
Vitamin C	mg	100	225	
Minerals				
Sodium	mg	550 [3]	0	
Chloride	mg	830 [3]	0	
Potassium	mg	2000 [3]	500	
Calcium	mg	1000-1200	500	
Phosphorus	mg	15 to <19 y: 1250 from 19 y: 700	250 (as phosphate)	
Magnesium	mg	15 to <19 y: 400/350 19 to <25 y: 400/310 25 to <65 y: 350/300 65 years and older:350/300 (m/f)	250	where appropriate, break down into 2 single doses
Iron	mg	15 to <19 y: 12/15 19 to <51 y: 10/15 51 y and older: 10/10 (m/f)	0	
Iodine	µg	180-200	100	
Fluoride [4]	µg	15 to <19 y: 3.2/2.9 19 to 65 y and older: 3.8/3.1 (m/f)	0	
Zinc	mg	7 (f) 10 (m)	2.25	no supplements for children or adolescents under the age of 18
Selenium	µg	30-70	25-30	
Copper	µg	from 15 y: 1000-1500 [2]	0	
Manganese	mg	2-5 [2]	0	
Chromium	µg	30-100 [2]	60	
Molybdenum	µg	50-100 [2]	80	maximum level not suitable for children under the age of 11

* (D-A-CH, 2000)
1 Recommended intake in Germany for adolescents and adults from age 15 (D-A-CH, 2000)
2 Estimated values for adequate daily intake (D-A-CH, 2000)
3 Estimated values for minimum intake (D-A-CH, 2000)
4 Guidance values for upper intake for caries prevention (D-A-CH, 2000)

Table 5: Proposed maximum levels for the fortification of conventional foods with vitamins and minerals referred to the expected daily portion of a food

Nutrients		Proposal for maximum levels in fortified foods	Comments
Vitamins			
Vitamin A	µg	no fortification	Except: Margarine and mixed fat products (10 mg/kg)
Beta-carotene	mg	no fortification	
Vitamin D	µg	no fortification	Except: Margarine and mixed fat products (2.5 µg/100 g) Edible oils (20 µg/L)
Vitamin E (equivalents)	mg	15	Where appropriate, linking of vitamin E fortification to the polyene fatty acid content of the food
Vitamin K	µg	80	
Vitamin B_1	mg	1.3	
Vitamin B_2	mg	1.5	
Niacin	mg	17	No use of nicotinic acid
Vitamin B_6	mg	1.2-1.6	
Folic acid	µg	200	Where appropriate, reassessment in the case of fortification of flour
Pantothenic acid	mg	6	
Biotin	µg	60	
Vitamin B_{12}	µg	3	Where appropriate, limiting addition of the vitamin to specific food groups
Vitamin C	mg	100	
Minerals			
Sodium	mg	no fortification	Exception: drinks, which are directly intended to balance substantial losses in the healthy consumer (e.g. as a consequence of heavy sweating)
Chloride	mg	no fortification	
Potassium	mg	no fortification	Instead addition of potassium only for the purposes of replenishment, where appropriate parallel reduction of table salt content in processed foods
Calcium	mg	only dairy substitutes	Calcium amounts like in dairy products
Phosphorus	mg	no fortification	
Magnesium	mg	15-28 mg/100 kcal or 22.5 mg/100 ml, referred to ready-to-eat food	
Iron	mg	no fortification	
Iodine	µg	no direct fortification of foods	Restriction to iodised salt as the suitable carrier food
Fluoride	µg	only table salt	250 mg/kg
Zinc	mg	no fortification	
Selenium	µg	no fortification	
Copper	µg	no fortification	
Manganese	mg	no fortification	
Chromium	µg	no fortification	
Molybdenum	µg	no fortification	

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4 Risk Assessment of Sodium

4.1 Summary

The calculations available for Germany on sodium intake indicate that the estimated values for minimum intake are clearly exceeded. The main share of dietary sodium comes from added salt or is ingested in in this form. Various bodies recommend cutting down salt intake. According to the DGE (German Nutrition Society) reference values, daily salt intake in adults should be 6 g or less; this would correspond to a maximum sodium level of 2.3 g. There are signs that the DGE parameter for salt intake is already exceeded in practice. The biochemical studies conducted to estimate sodium supply do not provide any evidence of deficiencies either (supply category 4).

Because of the special status of sodium chloride in sodium supply, it seems appropriate to take the reference value for salt intake rather than the estimated values for minimum sodium intake as the yardstick when classifying risks in accordance with Table 2 (Chapter 3.3.1). On this basis, BfR is of the opinion that the additional use of sodium for nutritional-physiological purposes is linked to a high health risk.

In the shape of its main source sodium chloride, sodium has been linked for some time with various diseases. For instance, it is discussed that high salt intake goes hand in hand with higher hypertension, nephrolithiasis or the risk of osteoporosis and could be associated with higher cardiovascular and overall mortality. Although there is not as yet any definitive scientific evidence to back these associations and there are still considerable gaps in knowledge, BfR recommends – also taking into account the already sufficient sodium intake from salt – refraining in principle from adding sodium to food supplements on the grounds of preventive health protection.

For the same reasons there are also fundamental objections to the sodium fortification of conventional foods for nutritional-physiological purposes. Nevertheless, the addition of sodium to products intended to compensate for significant sodium losses in healthy consumers (e.g. as a consequence of elevated losses through sweating after intensive physical activity), may make sense from the nutritional-physiological angle. It, therefore, seems appropriate to restrict the addition of sodium to specific food groups. Given the close links with fluid status, sodium fortification should be tied to products which make a significant contribution to fluid intake. No fortification of products which do not provide fluid should be permitted even if they are marketed for that purpose.

Estimated values for minimum intake	550 mg/day	
Reference value for daily salt intake	= 6 g/day (= 2.3 g sodium/day)	
Intake [g/day] (NFCS, 1994)	**m**	**w**
Median	3.64	2.79
P 2.5	1.81	1.41
P 97.5	6.62	4.92
Tolerable Upper Intake Level	Not yet defined (EFSA)	
Proposal for **maximum levels** in:		
Food supplements	No addition	
Fortified foods	Restriction to fortification of specific food groups	

4.2 Nutrient description

4.2.1 Characterisation and identification

Naturally occurring sodium has an atomic mass of 23. The alkali metal with the atomic number 11 mainly occurs in the valence rate +1 (Falbe and Regitz, 1998). Sodium is essential for man and is classified as a mineral.

Sodium and sodium compounds may be added to foods in Germany for various *technological* reasons (cf. see list of additive references, Additives Approval Ordinance – ZverkV, Additives Purity Criteria Directive 96/77/EC).

The addition of sodium salts for *nutritional-physiological* purposes has been permitted in Germany for some years to specific products for special dietary purposes but not to conventional foods. With the implementation of Directive 2001/15/EC of the European Commission of 15 February 2001 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses (Directive 2001/15/EC, 2001), the addition of sodium salts to foods for special dietary purposes was harmonised throughout Europe. According to this, the following 8 sodium compounds may be used (Annex 2 to the twelfth amendment to the Ordinance on Foods for Special Dietary Purposes of 31 March 2003):

- Sodium bicarbonate
- Sodium carbonate
- Sodium chloride
- Sodium citrate
- Sodium gluconate
- Sodium lactate
- Sodium hydroxide
- Sodium salts of phosphoric acid.

These same sodium compounds have now been taken over into the Directive of the European Parliament and Council 2002/46/EC of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements (Directive 2002/46/EC, 2002) and into the "Proposal for a Regulation on the addition of vitamins and minerals and of certain other substances to foods" of 10 November 2003. In Table 6 important sodium compounds and sodium-containing nutrient compounds are listed. They can either be used as additives within the scope of the Additives Approval Ordinance or as nutrients for nutritional-physiological purposes. It has been observed that the compounds sodium carbonate, sodium bicarbonate, sodium gluconate, sodium lactate, sodium hydroxide, sodium citrates and sodium orthophosphate may be used for both technological as well as nutritional-physiological purposes. Of the other sodium-containing nutrient compounds, sodium-L-ascorbate can for instance be used both as a source of vitamin C and for technological purposes. In this chapter we only examine the sodium compounds used for the nutritional-physiological purposes described above.

4.2.2 Metabolism, functions, requirements

Metabolism: In terms of volume, sodium is the most important cation in the extracellular space. The total body store of sodium in healthy human beings is 100 g or 60 mmol/kg body weight. 95% of this is to be found in the extracellular and 5% in the intracellular space. Around one-third is stored in bound form in bones as a reserve which means that around 70% of body sodium, corresponding to approximately 40 mmol/kg body weight, can be quickly exchanged. The sodium concentration in blood plasma is normally between 135 and 145 mmol/l, corresponding to 3105-3335 mg sodium/l (DGE/ÖGE/SGE/SVE, 2000; Falbe and Regitz, 1998; Grunewald, 2003; Löffler and Petrides, 2003).

The most important accompanying ion of sodium is chloride. Together they influence water status and extracellular volume (Preuss, 2001). The most important antagonist to sodium is potassium mainly as bicarbonate (Zimmerli et al., 1992).

Sodium can be quickly absorbed along the entire length of the intestines and distributed in the extracellular space. Beside a passive mechanism there is also the possibility of active sodium absorption. The sodium-potassium pump (Na^+-K^+-ATPase) is responsible for the coupled active transport of sodium from and potassium to the cells (Martindale, 2002; SCF, 1992; Seeger, 1994).

Sodium is mainly excreted by the kidneys where it is fully filtered glomerularly and can be reabsorbed up to 99% in the tubules (Grunewald, 2003; Preuss, 2001; Seeger, 1994). Depending on the amount taken up, on average 100-150 mmol/24 h are eliminated daily whereby excretion is subject to a 24-hour rhythm (Elmadfa and Leitzmann, 1990; Löffler and Petrides, 2003). At a level of daily sodium intake of 120 mmol/day (around 2.8 g sodium) and intact kidney function with a normal glomerular filtration rate, the sodium excreted in urine accounts for 0.5% of glomerularly filtered sodium. If sodium intake is doubled, excretion doubles to 1% of the glomerularly filtered amount. As this adjustment takes 3 to 5 days, sodium is temporarily retained during this period, i.e. it has a positive balance.

Only a small amount of around 5 mmol/24 h is excreted in faeces. The digestive juices do contain a high level of sodium but as they are normally reabsorbed in the intestine, the organism does not lose any sodium. By contrast, disruptions of reabsorption (e.g. diarrhoea) can lead to sodium loss. Sweat contains on average 25 mmol sodium/l. In the case of heavy sweating more than 0.5 g sodium can be lost per litre sweat (DGE/ÖGE/SGE/SVE, 2000; Elmadfa and Leitzmann, 1990; Greiling and Gressner, 1989; Löffler and Petrides, 2003; Stenger, 1987). Here the sodium amount increases with rising sweat volume but can also fall once acclimatisation has taken place (Preuss, 2001).

Regulation: Sodium and, by extension, water status can be controlled by the interaction between various hormones. The sodium concentration in the intracellular space is regulated by Na+/K+-ATPase. By contrast, the sodium concentration in the extracellular space, is regulated by the renin-angiotensin-aldosterone system (RAAS) and by the atrial natriuretic peptide (ANP) (DGE/ÖGE/SGE/SVE, 2000; Löffler and Petrides, 2003; Stenger, 1987).

Renin release, the key RAAS regulator, is controlled directly by the size of the extracellular volume and indirectly by means of pressor sensors in the high pressure system and volume sensors in the low pressure systems. The system is stimulated by reducing extracellular volume (e.g. sodium deficiency) or by a major drop in pressure. RAAS ensures an increase in the sodium level whereby angiotensin II plays a central role. This hormone triggers thirst and a desire for salt and leads to a release of the antidiuretic hormone (ADH) from the posterior lobe of the pituitary gland.

Although the thirst threshold varies in healthy individuals, an increase in osmolality of 1% is already perceived as thirst and leads to ADH release. Furthermore, RAAS increases sodium absorption in the proximal kidney renal tubule and stimulates the formation of the mineralocorticoid aldosterone in the adrenal cortex. Besides elevated sodium retention, aldosterone also leads to elevated potassium excretion. In the case of a high sodium volume the aldosterone level falls and superfluous sodium is excreted renally (Grunewald, 2003; Löffler and Petrides, 2003; Stenger, 1987).

By contrast, atrial natriuretic peptide (ANP), which is formed as a prohormone mainly in the right atrium, reduces the sodium store in the body. The trigger for secretion is an increase in atrium pressure, for instance through an expansion of plasma volume as a consequence of higher salt intake (Löffler and Petrides, 2003).

The sodium concentration in serum is not a yardstick for sodium store but for the store of free water. This means that hyponatraemia does not necessarily point to a sodium deficiency; it merely indicates that osmoregulation is disturbed or that the extracellular volume is elevated (Greiling and Gressner, 1989).

Functions: Sodium plays a role in a number of processes in the human body in conjunction with other electrolytes like chloride and potassium (Falbe and Regitz, 1998; Grunewald, 2003; Löffler and Petrides, 2003).

Its main tasks are to maintain extracellular volume, adjust osmotic pressure, regulate the acid-base balance, form hydrochloric acid in the stomach, activate enzymes (e.g. a-amylases) and form membrane potential, e.g. for nerve conduction and muscular excitation. Via the potassium-sodium pump sodium is also involved in the active transport of glucose to the cells.

In the case of intact osmoregulation any deviation from the normal sodium store leads to a corresponding change in extracellualr volume. In the case of an excessive offering of sodium the organism stores a higher level of water (oedemas, increased body weight). In the case of sodium deficiency a higher level of water is lost (exsiccosis, fall in body weight) (Greiling and Gressner, 1989). 1 mol (58.5 g) sodium chloride has an osmotic effect of approximately 2 osmol (Seeger, 1994). 3 g sodium (approximately 8 g sodium chloride) can bind 1 l water (Zimmerli et al., 1992).

Requirements: According to the DGE (German Nutrition Society) reference values (DGE/ÖGE/SGE/SVE, 2000), minimum sodium intake is estimated at 550 mg (24 mmol) per day. This value corresponds to just under 1 mmol sodium (23 mg) per 100 kcal or a salt intake of 1.4 g per day. Furthermore, it is recommended that the daily intake of salt in adults should be 6 g (corresponding to 2.3 g sodium) or less. This amount is easily reached with a balanced mixed diet as a consequence of the natural sodium content of foods and salt (= sodium chloride (NaCl)) added to processed foods (DGE/ÖGE/SGE/SVE, 2000; Elmadfa and Leitzmann, 1990). The Food and Nutrition Board (FNB) (2004) recently derived new reference values and laid down "adequate intake" values for sodium. Table 7 on page 45 contains the reference values of DGE (DGE/ÖGE/SGE/SVE, 2000), the National Academy of Sciences (NAS) (National Academy of Sciences, 1989), SCF (SCF, 1992) and the latest values of the Food and Nutrition Board (FNB) (FNB, 2004).

For nutrient labelling purposes the Scientific Committee on Food (SCF) of the European Commission (SCF, 2003) proposed the following Reference Labelling Values (RLV) for sodium per recommended daily dose: 600 mg for adults and 400 mg for children up to age 4.

Interactions: Beside interaction with other minerals like potassium, chloride and calcium (Frassetto et al., 2001; Preuss, 2001; Sellmeyer et al., 2002), there are diverse interactions with medicinal products (Bennett, 1997). For instance it is known that sodium restriction can potentiate the effect of various anti-hypertensive drugs. Calcium antagonists (like Verapamil) are an exception; in their case reduced sodium intake did not lead to any observed additive effects (Redón-Más et al., 1993). Thiazide-style diuretics combined with sodium restriction can reduce renal calcium excretion which may be of therapeutic relevance in conjunction with an inclination to form calcium-containing kidney stones. In addition information is available that sodium restriction when coupled with drug therapy, e.g. acetyl salicylic acid, non-steroid antiphlogistics or ACE inhibitors (= angiotensin converting enzyme inhibitors) can impair renal function. In the case of patients who have to undergo lithium treatment for manic depression, it can be observed that salt restriction, as a consequence of elevated tubular reabsorption of lithium, may increase the risk of lithium intoxication (Bennett, 1997; Mutschler, 1986).

4.2.3 Exposure (dietary and other sources, nutritional status)

Sources:
Overall, the natural sodium content in food is relatively low. Most sodium is added during food processing and preparation as sodium chloride. Around 95% of sodium intake comes from sodium chloride (Luft et al., 1992). Sodium chloride not only influences taste but also helps to achieve a certain consistency in some foods. Furthermore, salt is one of the oldest preservatives. In the food industry various sodium salts are used for technical purposes as auxiliaries and additives for food processing, for instance sodium phosphates, sodium carbonates, sodium nitrate, sodium cyclamate or sodium alginate (Wirths, 1981); see also Table 6, pages 43-44).

Fresh vegetables, pasta, rice, potatoes and fruit with a sodium content of less than 20 mg/100 g scarcely contribute at all to sodium intake. Eggs, fresh meat, milk and certain dairy products contain moderate sodium amounts (<120 mg/100 g Na). A high sodium content (>400 mg/100 g Na) is found in foods where salt was used during their production like bread, various types of biscuit, vegetable and fish cans, bucklings and mackerel. Hard smoked sausage and smoked ham are very salty foods with a sodium content of >1000 mg/100g as well as certain types of cheese or salted herrings (Muskat, 1985; Souci-Fachmann-Kraut, 2000; Wirths, 1981).

In line with the results of the nutrition survey (Mensink et al., 2002) conducted as a supplement to the Federal Health Survey in 1998, the most sodium (just under 30%) is taken up from spices (including other food ingredients like table salt, sauces and stock cubes), from bread (>20%), sausage goods and dairy products (approximately 15%) and from meat (just under 10%).

Furthermore, drinking, mineral and table water also contribute to sodium intake. For drinking water intended for human consumption the Drinking Water Ordinance 2001 envisages a limit value for sodium of 200 mg/l. The Mineral and Table Water Ordinance states that if a product claims to "contain sodium", the sodium content must be >200 mg/l. If it claims to be "suitable for a low-sodium diet", the sodium content must be <20 mg/l.

Food fortification: According to the information available to us no targeted sodium fortification of foods has been undertaken in Germany up to now for nutritional-physiological reasons for the general public.

One exception are beverages which are sold for the purposes of rehydration after sporting activity, so-called "functional drinks", "isotonic drinks" or sports beverages. According to Brouns and Kovacs (1997) the sodium content should at all events be >400 mg/l. Taking into account the sodium concentration in sweat of 413-1091 mg/l, the maximum sodium content should not exceed 1100 mg/l per beverage. Similar recommendations are to be found in a consensus statement published in 1993 according to which the sodium content in hypotonic and isotonic carbohydrate/electrolyte beverages should be more than 200 mg/l and maximum 1100 mg/l in order to ensure, if possible, rapid rehydration (Bauser et al., 1993). Well known product examples are *Gatorade*® and *Isostar*® activator with sodium contents of 410 and 700 mg/l (Schek, 2000).

Food supplements: Up to now BgVV was of the opinion that the minerals used in food supplements should not exceed the simple dose of the respective DGE recommendation per daily portion (BgVV, 1998). This opinion was further specified in a renewed assessment from 2002 (BgVV, 2002) according to which the additional intake of substances like sodium, which are sufficiently available in food, is not necessary. For these reasons it was recommended that the addition of sodium should not be permitted on nutritional-physiological grounds in food supplements.

Medicinal products: For the above sodium compounds used for nutritional-physiological purposes, a monograph is available as far as we know only for *sodium hydrogen carbonate* (BGA, 1993). The pharmacological, oral administration of the salt results from the constituents of the HCO_3^-/CO_2 buffer. For the application "alkalisation of urine" daily doses of 2 times 2-4 g are recommended. According to the medical inventory "Red List" (BPI, 2004), sodium hydrogen carbonate is also available in the form of coated tablets with 1 g (corresponding to 11.9 mmol Na^+ and 11.9 mmol HCO_3^-) for the oral treatment of metabolic acidosis too. In the case of conditions linked to chronic salt loss, daily doses of between 2.4 and 4.8 g NaCl are administered perorally in addition to adequate fluid intake. According to Martindale (2002) in serious cases the substitution of up to 12 g NaCl per day may be necessary.

Nutritional status:
Parameters/biomarkers: Because of the various sources of sodium and different preparation and processing practices *sodium uptake from food* is subject to major fluctuations (Loria et al., 2001; Ovesen and Boeing, 2002). Furthermore, sodium intake results from the sum of the natural sodium content in foods, sodium added during food processing and the use of salt in the kitchen and whilst eating. On the other hand, sodium losses of up to 75% may occur during cooking which makes it difficult to estimate sodium intake.

No suitable clinical-chemical parameters are available to assess sodium intake. It is known that sodium intake does not have a detectable impact on the *sodium concentration in blood serum* and is not a yardstick for the sodium store (Greiling and Gressner, 1989; VERA-Schriftenreihe, 1995a). As more than 90% of the added sodium is excreted in urine, *sodium excretion in 24-h urine* is currently deemed to be the best marker for sodium intake (Loria et al., 2001; Ovesen and Boeing, 2002; Wirths, 1981). However, this does not provide any complete basis for assessment either. It is indeed known that in healthy individuals sodium excretion increases in line with rising sodium intake. However when assessing certain parameters in 24-h urine, besides the correct conduct of urine collection, the use of further control parameters is also necessary (e.g. fluid intake, creatinine content in urine) (VERA-Schriftenreihe, 1995a).

Intake: *The National Food Consumption Survey (NFCS)* in its revised version (DGE, 1996) indicated mean daily intake in men depending on age of 3.2-3.4 g sodium and 2.4-2.7 g sodium/day for women. The average mean sodium intake of 3.2 g and 2.5 g sodium for men and women respectively corresponds to a salt intake of 8 and 6.3 g per day. It is, therefore, higher than the DGE reference value (DGE/ÖGE/SGE/SVE, 2000) for adequate NaCl intake. The highest intake values, measured at the 97.5 percentile, of 6.8 g sodium were observed in men over the age of 65 (VERA-Schriftenreihe, 1995b). Table 8 on page 43 gives the NFCS results in percentiles separately for age and gender.

The Nutrition Survey (Mensink et al., 2002) conducted as a supplement to the *Federal Health Survey 1998* produced the following results: the guidance value for sodium was clearly exceeded by men in all age groups. In women, a lower sodium intake was generally observed which was just under the guidance value. In principle, the authors point out that the adding of salt prior to or during the consumption of food could not be recorded. This means that actual sodium or sodium chloride consumption is probably higher than the intake indicated here. In deviation from the NFCS results, the highest intake values, measured at the 90 percentile, of 6.0 g sodium were found in 18-24 year-old men. With a few exceptions the medians from the NFCS (VERA-Schriftenreihe, 1995b) were higher than those obtained in the Federal Health Survey (Mensink et al., 2002). Table 9 on page 44 gives the results of the Federal Health Survey in percentiles separately for age and gender.

No reliable information is available on the proportion or the level of sodium intake from food supplements. However the taking of mineral supplements was also estimated in the Nutrition Survey (Mensink and Ströbel, 1999) conducted in 1998 as a supplement to the Federal

Health Survey. Based on these data supplementation with sodium does not appear to play any role in Germany.

Sodium concentration in serum/sodium excretion in urine: In the VERA Study the sodium concentration in serum and sodium excretion in urine were investigated in a representative random sample of >18 year-olds (VERA-Schriftenreihe, 1995a).

a) A value of 144 mmol/l was established as the limit value for sodium concentration in *serum* (reference range: 136-146 mmol/l). A value of 141 mmol/l was determined as the median for both men and women. Table 10 on page 46 gives the NFCS results (VERA-Schriftenreihe, 1995a) in percentiles separately by age and gender.

b) 283 and 225 mmol/24h in a reference range of 40-300 mmol/24 h were defined as the limit values for men and women. Median daily sodium excretion in 24-hour urine was 181 mmol for men and 135 mmol for women. In around 1 in 3 men and 1 in 8 women more than 200 mmol sodium was measured in 24-hour urine which would correspond to a salt intake of more than 12 g/day.

The highest prevalences of "unfavourable" measured values were observed in *serum* (taking into account the 10 and 90 percentiles) in women in the age group 55-64 (11.6% of the 173 women examined) and in men in the over 65 age group (12.6% of the 103 men examined). Comparison with sodium excretion in *urine* produced the following picture: whereas the majority of unfavourable measured values were observed amongst women in the 55-64 age group (14% of the 157 women examined), in the case of men it concerned the youngest age group of 18-24 year-olds (13.2% of the 91 men examined) (VERA-Schriftenreihe, 1995a).

Table 11 on page 46 gives the NFCS results (VERA-Schriftenreihe, 1995a) in percentiles separately by age and gender.

4.3 Risk characterisation

4.3.1 Hazard characterisation (LOAEL, NOAEL)

As a consequence of the considerable excretion capacity, hypernatraemia is scarcely to be expected even in the case of an excessive sodium burden. Each excessive sodium intake leads to an increase in the sodium concentration in extracellular fluid which is partially compensated by an increase in fluid volume. Chronically elevated sodium intakes can lead to oedemas (Elmadfa and Leitzmann, 1990). In the case of a not completely fully developed renal excretion function and inadequate hormonal regulation of renal sodium excretion, an elevated sodium burden can also lead to intoxication (e.g. in premature babies).

The various sodium compounds have differing degrees of hazard potential (Seeger, 1994). The known ones are alkali burns through sodium hydroxide solution (NaOH), e.g. through swallowing cleaning products. Accidental intoxications were observed in infants (Saunders et al., 1976) and in adults (Johnston and Robertson, 1977) as a consequence of accidental overdosing of table salt or mistaking table salt for sugar. Furthermore, there are known cases of resorptive intoxications through swallowing sea water (NaCl concentrations of around 450 mmol/l).

Salt itself or in a hypertonic solution is a local irritant and when taken orally normally leads to vomiting (Seeger, 1994). Whereas fatal incidents in conjunction with the use of sodium chloride as emetics have been observed (Barer et al., 1973), there is no chance of intoxication from the natural sodium content in foods (Seeger, 1994).

For healthy adults 35-40 g NaCl per day (corresponding to 14-16 g sodium) are deemed to be acutely toxic. The acute lethal dose for human beings is given as 0.75 to 3 g/kg. In the case of serum concentrations of >160 mmol/l there is a threat of severe clinical consequences; concentrations of >200 mmol/l normally proved fatal. Symptoms can be observed shortly after taking acute toxic doses which manifest in great thirst, motory restlessness, tremor, muscle rigidity, ataxia, dyspnoea, coma and cardiac failure (Elmadfa and Leitzmann, 1990; Seeger, 1994; Zimmerli et al., 1992).

FNB (2004) recently chose an **LOAEL** (Lowest observed adverse effect level) for "dietary sodium" of 2.3 g (100 mmol sodium)/day on the basis of studies by Johnson et al. (2001), MacGregor et al. (1989) and Sacks et al. (2001). Blood pressure was selected as the critical end point. No **NOAEL** (No observed adverse effect level) could be determined (cf. also Chapter 4.4).

4.3.2 Risks which can be linked in the long-term to high sodium or salt intakes

4.3.2.1 Cardiovascular risk factors and mortality

a) *Hypertension:* Sodium or salt intake has long been discussed in conjunction with primary hypertension. Here it is important that sodium obviously influences blood pressure only in the form of sodium chloride but not in the form of other sodium compounds. Since, however, 95% of sodium comes from sodium chloride, this aspect scarcely has any practical relevance (Luft et al., 1992).

A threshold value, upwards of which sodium chloride influences blood pressure is not known, i.e. no information in available on the dose-response relationship. According to Fodor et al. (1999) a major restriction on sodium intake to 100 mmol is necessary in people with normal blood pressure in order to reduce systolic blood pressure by 1 mmHg. In hypertonic individuals who are older than 44 years, greater effects are described: systolic/diastolic blood pressure change of 6.3/2.2 mmHg per 100 mmol sodium.

Some people react more sensitively to salt than others ("salt sensitivity"). Seemingly, this trait is genetically anchored. Other factors which influence this are age, race, gender, body weight and hormonal factors. There seems to be a close link between obesity, high blood pressure, insulin resistance and salt sensitivity. However up to now we still do not have a general definition of salt sensitivity or a method to identify salt-sensitive individuals. Nor do we know anything about the pathophysiological mechanisms responsible for differing sodium or salt sensitivity. The share of salt-sensitive individuals amongst the normotonics is estimated to be around 30% and amongst hypertonics 50%. It is higher in the black population than in the white and more frequently found in women than in men. People of a more advanced age (in whom hypertension also occurs more frequently) are more often salt-sensitive than young people. As potassium and sodium act as antagonists in blood pressure regulation, increasing importance has been attributed recently to potassium intake and the sodium-potassium relationship in food (Luft and Weinberger, 1997; Luft, 1993; Schorr-Neufing, 2000).

Whether salt restriction can effectively prevent the development of hypertension, has been a subject of controversial debate for years (BgVV, 2001). Some are of the opinion that there is no evidence that the development of the multi-factorial disease hypertension could be prevented through a population-wide salt restriction. Furthermore, existing major restrictions in intake only have a minor influence on normal blood pressure (Alderman, 2000; BgVV, 2001; Fodor et al., 1999).

From a comprehensive meta analysis (Jürgens and Graudal, 2003) of randomised and controlled studies, which were published between 1966 and December 2001, the conclusion was drawn that no general restriction in sodium intake should be recommended to the Caucasian, normotensive population because of the limited effects on blood pressure. A short-term reduction in sodium intake had only led to a drop in blood pressure of 1%. The authors suspect that the limited influence on blood pressure could be attributed to parallel hormonal changes (increases in renin, aldosterone and noradrenaline levels in the plasma). Furthermore, more extreme reductions in sodium intake of 200 mmol led to observations of significant increases in plasma cholesterol, LDL cholesterol and plasma triglycerides.

b) *Left ventricular hypertrophy*: Another cardiovascular risk factor, which seems to be associated with high sodium or salt intake, is left ventricular hypertrophy (Perry, 2000).

The observation of a study group from the National Health and Nutrition Examination Survey revealed that high sodium intake was an independent risk factor for the development of cardiac insufficiency in overweight but not in normal weight individuals (He et al., 2002).

c) *Mortality:* Different results are available on the relationship between salt intake and mortality.

In a prospective Finnish study spanning 5 years the influence of salt intake was examined on cardiovascular mortality in more than 2000 participants. Independently of other cardiovascular risk factors, higher sodium excretion was observed to lead to increased mortality and morbidity amongst men but not amongst women (Tuomilehto et al., 2001). He et al. (1999) noted that in the case of overweight but not of normal weight individuals there is a significant relationship between high sodium intake as well as cardiovascular disease risk and overall mortality. According to this a 100 mmol higher sodium intake is associated with a 32% higher stroke incidence, an 89% higher stroke mortality, a 44% higher mortality from coronary heart disease and a 39% higher cardiovascular or overall mortality.

According to WHO (FAO/WHO, 2003) there is convincing evidence that high sodium intake can be classified as a risk factor for cardiovascular disease. It is estimated that a reduction in sodium intake by 50 mmol/day would lead to a 50% saving in antihypertensive therapeutics and could reduce the number of deaths from stroke or cardiovascular disease by 22 and 16% respectively.

Other publications point to an inverse correlation between sodium intake/excretion and cardiovascular mortality (Alderman et al., 1995; 1998; Alderman, 2000). This is attributed to the observation of an inverse association between salt intake and plasma renin activity and the presence of a high renin level coupled with an elevated heart attack risk.

According to a comprehensive, systematic evaluation of studies published up to July 2000 which had been conducted in a randomised and controlled manner over a period of at least 6 months, it is still not clear what long-term impact changed salt and sodium intake has on cardiovascular mortality and morbidity or what link there is between salt intake and mortality (Hooper et al., 2002; 2003). In the opinion of BgVV it has not yet been proven that salt restriction in the healthy general population could lead to a reduction in mortality or in the long-term to a fall in the frequency of hypertension along the lines of primary prevention (BgVV, 2001).

4.3.2.2 Carcinoma risk

Older studies from Asia have linked the consumption of salted foods to the onset of stomach carcinomas. It is suspected that high salt concentrations damage the protective intestinal mucosa and can, therefore, promote tumours (Hirohata and Kono, 1997; Sugimura, 2000). Other epidemiological studies point to a correlation between high salt consumption and the emergence of nasopharyngeal and colon carcinomas (FSA, 2003; Seeger, 1994).

In Japanese studies it was estimated that a reduction in salt intake from 13.4 to approximately 8 g/day could reduce the incidence of stomach cancer by around 65%. Cohen and Roe (1997) came to the conclusion that there are no signs of an association between salt intake and the risk of gastro-intestinal carcinomas. They do not, therefore, see any reason to assume that reducing sodium chloride intake could have a favourable impact on carcinoma incidence. A Dutch cohort study, which was conducted over an observation period of 6.3 years, revealed a non-significantly increased risk between salt intake (both from natural salt contained in foods as well as from salt added during food processing) and stomach carcinoma incidence (Van den Brandt et al., 2003). A prospective study from Japan over 11 years showed a significant, dose-related association between salt intake and stomach cancer in men but not in women (Tsugane et al., 2004).

These controversial comments show that there are major gaps in knowledge in this area too.

4.3.2.3 Nephrolithiasis risk

High sodium chloride intake, as it increases calcium excretion, is seen as a risk factor for the formation of kidney stones. Per 100 mmol (2300 mg) NaCl around 1 mmol Ca (40 mg) more are excreted. It is assumed that individuals, who already tend towards calcium-containing kidney stones, are more at risk of forming calcium-oxalate-containing concrements with a high sodium diet (Massey and Whiting, 1995).

4.3.2.4 Osteoporosis risk

Furthermore, higher salt intake by means of the related higher calcium excretion, is linked to a greater risk of osteoporosis. However, up to now no clear association could be established between reduced bone density and elevated sodium chloride intake (Burger et al., 2000; FSA, 2003). Cohen and Roe (2000) came to the conclusion that high sodium or salt intake is not an important risk factor for osteoporosis and that a reduction in salt intake from 9 to 6 g/day is not an effective way of preventing osteoporosis. It would seem that calciuria following sodium intake is also subject to major individual fluctuations and is dependent on the respective sodium and salt sensitivity. More recent studies indicate that the "bone-absorptive" effect of high salt intake can be weakened through the administration of potassium citrate or potassium bicarbonate (Frassetto et al., 2001; Harrington and Cashman, 2003; Sellmeyer et al., 2002).

4.3.2.5 Risk of kidney damage

High salt intake is linked to adverse effects on kidney function, particularly in the case of an existing renal dysfunction (Boero et al., 2002).

4.3.2.6 Burden on water status

The additional intake of 100 mmol NaCl for instance imposes a burden on water status by increasing the obligate urine excretion volume by around 240 ml at a maximum urine osmolality of 830 mosm/kg (Manz and Wentz, 2003). Mild dehydration probably constitutes a risk factor for various diseases like urolithiasis (Siener and Hesse, 2003) or obstipation (Arnaud, 2003).

4.3.3 Deficiency, possible risk groups

4.3.3.1 Deficiency

The sodium-preserving mechanisms in the human organism are very effective. A sodium deficiency cannot normally occur under physiological conditions and a balanced diet (Löffler and Petrides, 2003).

A distinction is made between various forms of hyponatraemia (chemical laboratory tests: serum sodium content of <130 mmol/l) which may be caused by the following factors (DGE/ÖGE/SGE/SVE, 2000; Elmadfa and Leitzmann, 1990; Greiling and Gressner, 1989; Grunewald, 2003; Löffler and Petrides, 2003):

"Loss hyponatraemia": Sodium deficiency through losses via

- the *gastro-intestinal tract* (e.g. through persistent vomiting or heavy diarrhoea);
- the *kidneys* (e.g. reabsorption disorders in the kidney "salt loss kidney", polyuria or diuretics abuse, hypoaldosteronism (e.g. Addison's disease)), the *skin* (e.g. heavy sweating >3 l/day, losses in conjunction with extensive skin lesions, losses in conjunction with mucoviscidosis through abnormally high sodium concentrations in sweat).

"Distribution hyponatraemia": Internal sodium losses in third space situations in which there is a sequestration of extracellular fluid in the intestines (ileus), in large body cavities (e.g. transsudates) or in subcutaneous tissue (oedemas). Hyponatraemia as a consequence of disrupted fluid homeostasis ("*water surplus*" for instance in conjunction with the Schwartz-Bartter Syndrome with pathologically elevated ADH secretion) is not a sign of emptied sodium stores. Nor does it permit any conclusions about total body sodium.

The clinical picture of hyponatraemia largely depends on the speed at which shifts in fluid occur. In the case of genuine "deficiency hyponatraemia" different symptoms are described depending on the scale of loss. In the case of a minor deficiency (NaCl losses of around 20 g) there may be symptoms like apathy, inactivity, headache, loss of appetite and calf cramp. A moderate deficiency (NaCl losses of around 35 g) may go hand in hand with thirst, general weakness, anorexia, vomiting, hypotension and tachycardia. A severe deficiency with NaCl losses of up to 50 g NaCl can lead to coma (Bolte and Lüderitz, 1971; Elmadfa and Leitzmann, 1990).

In the literature various changes are described following salt restriction which themselves can be linked to an increase in cardiovascular morbidity and mortality (Chrysant et al., 1999; Chrysant, 2000; Egan and Lackland, 2000; Graudal et al., 1998; Iwaoka et al., 1988; Luft et al., 1992; Mensink et al., 2002; Weder and Egan, 1991), e.g.:

- Changes in *hormone status* along the lines of counter-regulation (elevated renin, aldosterone, noradrenaline and insulin levels);
- Adverse effects on *cholesterol metabolism* (increase in LDL and total cholesterol, drop in HDL cholesterol);
- Increase in *blood viscosity* and thrombocyte aggregation;
- Occurrence of *hyperuricaemia.*

4.3.4 Possible risk groups for deficiency

Up to now no risk groups for a purely dietary sodium deficiency have been identified from the healthy population with conventional eating habits. During pregnancy (because of the increa-

se in maternal extracellular fluid) and during breastfeeding (because of the sodium content in human milk), it is assumed that there is an increased need which can, however, be easily covered through diet (DGE/ÖGE/SGE/SVE, 2000). In healthy individuals there may be cases of higher sodium losses through sweat as a consequence of intense physical activity or periods spent at high temperatures which can lead to a critical nutritional status.

A sodium deficiency normally only occurs in conjunction with congenital (e.g. mucoviscidosis) or acquired diseases as a consequence of elevated losses, if no corresponding substitution occurs (cf. Chapter 4.3.3).

The calculations available for Germany on sodium intake indicate that the reference values (both the estimated values for minimum intake of 550 mg/day for adolescents and adults as well as the acceptable intake of maximum 6 g NaCl/day) are on average exceeded. The biochemical studies undertaken to estimate sodium status do not provide any indication of deficiency (supply category 4).

4.3.5 Relative excess, possible risk groups

4.3.5.1 Relative excess and pathological sodium regulation

- Hypernatraemia cannot be triggered by food, i.e. through the consumption of a high salt diet. An elevated sodium store is normally caused by diseases linked to dysfunctional excretion via the kidneys, more rarely through an excess in food. Hypernatraemia is normally associated with inadequate water intake or excessive water losses. In chemical laboratory tests hypernatraemia is normally discussed in conjunction with serum sodium contents >150 mmol/l. The following causes may be relevant (Bolte and Lüderitz, 1971; Greiling and Gressner, 1989; Herold, 1987; Löffler and Petrides, 2003; Martindale, 2002):

- *Primary hyperaldosteronism (Conn's Syndrome):* The clinical picture is caused by adenomas or carcinomas of mineralocorticoid-forming cells in the adrenal cortex. Sodium retention is elevated and potassium excretion increased as a consequence of pathologically elevated, autonomous aldosterone secretion.

- *Secondary hyperaldosteronism:* In the case of this clinical picture the focus is on increased aldosterone production and secretion through the adrenal cortex as a consequence of overactivity in the renin-angiotensin system. Conditions of this kind are found in conjunction with extensive oedemas (e.g. in the case of cardiac failure) or in the case of extensive ascites (e.g. in the case of cirrhosis of the liver).

- *Renin hypersecretion:* Renal artery stenosis is a classical situation.

- *Diabetes insipidus:* In the case of this clinical picture a deficiency of the antidiuretic hormone (ADH) leads to polyuria coupled with the inability to concentrate urine.

- *Water deficiency:* Disruptions in water and electrolyte status are encountered relatively frequently in geriatric medicine. Older people often suffer from hypernatraemia in conjunction with fluid deficiency which is often difficult to diagnose (Adrogué and Madias, 2000; McGee et al, 1999; Palevsky et al, 1996; Thomas et al., 2003; Weinberg and Mnaker, 1995).

The symptoms may range from a reduction in skin turgor, weakness, tiredness, thirst, fever, somnolence, confusion, cramps, tachycardia, hypertension down to death.

4.3.6 Possible risk groups in conjunction with increasing supplementation with sodium/salt

The possible risk groups for sodium supplementation or increased salt intake are in principle all patients who already have an excess or all the pathological conditions associated with sodium retention (cf. Chapter 4.3.5). In this context patients should also be mentioned who have a salt-sensitive hypertension. This is because in the reverse situation it is known that certain patients with arterial hypertension can benefit from a reduction in salt intake. Since high salt intake can lead to elevated calcium excretion, risks in conjunction with the development of nephrolithiasis and osteoporosis cannot be ruled out.

In line with the DGE recommendations (DGE/ÖGE/SGE/SVE, 2000) no advantages but rather disadvantages are to be expected from intakes of more than 6 g salt/day corresponding to an amount of 2.3 g sodium. Taking into account the intake levels which were determined in the food consumption studies (Mensink et al., 2002; VERA-Schriftenreihe, 1995b) the vast majority of the German population would already be exposed to disadvantages without supplementation.

4.4 Tolerable upper intake level for sodium

Up to now no risk assessment of sodium has been undertaken by the expert bodies of the EU. The EU Scientific Committee on Food (SCF) expressed its view in 1992 that excessive intake of 200 mmol (= 4.6 g) sodium would go hand in hand with a significant risk of hypertension. It was, therefore, proposed that adults should restrict maximum sodium intake to 150 mmol/day, corresponding to **3.5 g/day** (SCF, 1992) in order to prevent hypertension and the related risks. It can be observed that this recommendation would correspond to a daily amount of maximum 9 g salt and would be 50% above the current DGE recommendation (DGE/ÖGE/SGE/SVE, 2000) of maximum **6 g salt/day (corresponding to 2.3 g sodium)**.

Up to now the Nordic Council (2001) has not derived an *Upper safe intake level* for sodium. The Expert Group on Vitamins and Minerals of the United Kingdom (EVM) (FSA, 2003) decided to do a risk assessment of the compound sodium chloride because of the sparse data situation concerning the toxicity of chloride. The Expert Group did not feel it was in a position to establish a *safe upper level* and concluded that sodium chloride cannot generally be deemed to be suitable for use in food supplements.

FNB (2004) recently established a common "**Tolerable Upper Intake Level (UL)**"[♦] of **2.3 g (100 mmol) sodium per day** (corresponding to 5.8 g sodium chloride) for adolescents (from age 14), adults of all ages and women during pregnancy and breastfeeding. Taking into account the respective mean energy intakes, the following ULs for children were derived from this value: 1.5 g (65 mmol)/day (1-3 years), 1.9 g (3 mmol)/day (4-8 years), 2.2 g (95 mmol)/day (9-13 years). Because of the direct effect of ingested sodium on blood pressure, that is deemed to be proven in both hypertensive and normotensive individuals, blood pressure was chosen as the critical endpoint. It can be noted that the LOAEL (2.3 g sodium) defined by FNB when converted to salt corresponds to the amount which should not be exceeded daily by adults according to DGE (DGE/ÖGE/SGE/SVE, 2000). Since an uncertainty factor (UF) of approximately 1.6 would lead to a UL below the reference value for adequate intake (see Table 7), a UF of 1 was established. It was admitted that there is no threshold value for sodium and that blood pressure is influenced by various other factors like for instance age, race, weight, gender, genetic predisposition or other dietary factors. Furthermore, attention was drawn to methodological problems in the conduct of the studies.

♦ The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals (FNB, 2004).

The different comments and recommendations reflect the uncertain data situation and the lengthy controversial debate about the subject salt/sodium and blood pressure. Against the backdrop of differing salt sensitivity and the disputed effects of sodium restriction in conjunction with normal blood pressure, the question is raised whether the selected endpoint can be deemed to be convincing. According to BfR the following aspects are of particular relevance in the risk assessment of sodium. They should be taken into account when deriving maximum levels:

- Sodium status is closely linked to water status. Depending on this and other electrolytes, it is subject to major fluctuations.
- The sodium concentration in serum is not a yardstick for sodium store. There is no correlation between serum sodium and dietary sodium.
- The sodium-preserving mechanisms in the human organism are very effective. This means that under physiological conditions and a normal diet, there cannot be any significant sodium deficiency. The sodium-retaining capacity of the body seems, in terms of development, to be more defined than the ability to excrete an excess.
- In healthy individuals sodium status is regulated through changes in excretion rate and cannot be determined from the level of dietary intake.
- Up to now no concrete requirement figures could be formulated for sodium. Whereas there seems to be a relatively good correlation between the estimated values for minimum sodium intake of various bodies (e.g. DGE (DGE/ÖGE/SGE/SVE, 2000) and National Academy of Sciences (1989)), major deviations can be observed in respect to the intake values described as acceptable (e.g. between DGE (DGE/ÖGE/SGE/SVE, 2000) and SCF (1992)). This estimation is supported by the reference values for adequate sodium intake only recently established by FNB (2004).
- According to the current level of knowledge there are no signs that sodium intake is suboptimal in the German population. There is no need for the targeted addition of sodium for nutritional-physiological purposes to improve sodium supply or to protect from deficiency.
- By contrast, based on the available data it can be assumed that high sodium intake constitutes a greater problem for the German population than low intake. There are signs that the target described by DGE as desirable for salt intake is already exceeded in practice. The major share of dietary sodium comes from salt or is added in this form. It, therefore, seems appropriate to give more consideration in the risk classification to the intake values for salt currently described as acceptable and less to the estimated values for minimum sodium intake.
- At present there are no signs that high sodium intake could be linked with a health advantage or a benefit for the healthy population under the living conditions here. Instead, high sodium intake is linked with health risks.

Taking into account these aspects BfR believes that the additional use of sodium for nutritional-physiological purposes involves a high risk to health. Sodium should, therefore, be classified as a nutrient in the highest risk group.

4.4.1 Derivation of a maximum level for sodium in food supplements

In other Chapters of our report maximum levels were calculated for some micronutrients for use in food supplements using the following formula:

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

Legend:

UL	=	Tolerable Upper Intake Level (SCF) usually referring to the daily total intake
DINF	=	Dietary Intake by Normal Food (95. or 97.5. percentile)
MEF	=	Estimated Number of Consumed Products
TL	=	Tolerable Level in a single dietary supplement or fortified food

Based on the available data it is not possible to use this formula to derive a safe and tolerable maximum level in food supplements. It has already been mentioned that the competent EU expert body has not yet undertaken a risk assessment of sodium. The Expert Group on Vitamins and Minerals of the United Kingdom (FSA, 2003) did do a risk assessment of the compound sodium chloride but did not feel it was in a position to derive a UL.

The UL of 2.3 g sodium/day for adults recently set by the US-American FNB (2004) corresponds to the value for salt intake described as desirable by DGE. On average it is already achieved or even exceeded according to the food consumption studies available for Germany (Mensink et al., 2002; VERA-Schriftenreihe, 1995b).

A series of epidemiological studies indicates that there may be an association between high sodium intake and certain risks of disease. For instance, based on the available findings it cannot at present be ruled out that longer-term sodium intake above the recommendation – specifically in the form of sodium chloride – could increase the cardiovascular risk and the risk of carcinomas or osteoporosis.

In the opinion of BfR this experience should be taken into account along the lines of a precautionary approach when setting maximum levels for sodium even if there is no scientific backing for these findings. BfR supports the opinion last adopted by BgVV (2002) that the addition of substances like sodium which are already sufficiently available in foods, is not necessary and should not be undertaken. This estimation correlates with the EVM conclusion (FSA, 2003) that in general sodium chloride is not considered suitable for use in food supplements.

4.4.1.1 Possible management options

Taking into account the available data and the above comments, there is only one management option:

a) Upholding the existing opinion that no sodium be added to food supplements for nutritional-physiological purposes.

   Taking into account the supply situation of the German population, the instruction by DGE not to exceed the guidance value of 6 g NaCl/day and the potential risks discussed in conjunction with high NaCl intake, there are no recognisable grounds for using sodium in food supplements for nutritional-physiological purposes. Hence, within the framework of preventive consumer health protection food should not be fortified with sodium.

4.4.2 Derivation of a maximum level for sodium in fortified foods

In this case, too, BfR supports the opinion last defended by BgVV (2002) that the additional admixture of substances like sodium which are already available in sufficient amounts in foods or diet, is not necessary and should not be done.

Because of the existing gaps in knowledge, the supply situation of the German population, the potential risks linked to high sodium intake (especially as NaCl) and in order to avoid the accumulation of high sodium doses from various products, BfR does not see any grounds for a fundamental extension of current practice. Exceptions could be justified at best for specific products which are intended to replace larger losses of sodium and fluids.

4.4.2.1 Possible management options

Based on the above comments, there are the following management options:

a) Continuation of the existing practice with no addition of sodium for nutritional-physiological reasons to conventional foods.

   As the supply situation of the average German population with sodium is deemed to be met and the average daily NaCl intake is even above the recommended guidance value, there is no need for fortification on nutritional-physiological grounds. Taking into account the current supply situation in Germany and the potential risks discussed, health risks cannot be ruled out in the context of preventive consumer health protection.

b) Restricting fortification to specific groups of foods.

   The targeted sodium fortification of foods intended to balance significant losses in healthy consumers (e.g. elevated losses through sweating after intense physical activity) may make sense from the nutritional-physiological angle. Given the close links with the fluid balance, fortification with sodium should be linked to those products which contribute significantly to fluid intake. The fortification of products which do not provide fluid should not be permitted even if they are marketed for this purpose.

In the opinion of BfR a high health risk is linked to the additional use of sodium for nutritional-physiological purposes. Hence, there is no justification for extending the current practice of using sodium in food supplements or for the fortification of conventional foods.

The ubiquitous presence, the wide distribution of sodium, the intake of sodium above the recommendations and more recent, albeit controversial, findings about the potential risks of high sodium, more specifically sodium chloride intake, advocate, along the lines of Option a) that sodium should not be added to food supplements. BfR, therefore, recommends that sodium should not, in principle, be used in food supplements.

Also in the case of conventional foods, aside from a few concrete exceptions within the meaning of Option b), there should be no fortification with sodium for nutritional-physiological purposes (Option a).

Table 6: Overview of important permitted sodium compounds and other sodium-containing nutrient compounds

Sodium compound	Directives (2003/46/EC and 2001/15/EC)	E-No. (Reference list 1998, ZZulV)	Use as food additive	Molecular formula	CAS Number	EINECS (Directives 96/77/EC; 95/31/EC)
Sodium acetate (red salt), Sodium diacetate		E 262 (i) E 262 (ii)	Generally authorised	$NaC_2H_3O_2$ $NaC_4H_7O_4$ x nH_20	127-09-3	204-823-8 204-814-9
Sodium carbonates Sodium carbonate ("soda") Sodium bicarbonate (=sodium hydrogencarbonate) Sodium sesquicarbonate (=sodium monohydrogen dicarbonate)	 + +	E 500 (i) (ii) (iii)	Generally authorised	 Na_2CO_3 $NaHCO_3$ $Na_2(CO_3)$ x $NaHCO_3$ x 2 H_2O	 497-19-8 144-55-8 	 207-838-8 205-633-8 208-580-9
Sodium citrates Monosodium citrate Disodium citrate Trisodium citrate	+	E 331 (i) (ii) (iii)	Generally authorised	 $C_6H_7O_7Na$ $C_6H_6O_7Na_2$ $C_6H_5O_7Na_3$	 6132-04-03 68-04-2	 ? 205-623-3 200-675-3
Sodium gluconate	+	E 576	Generally authorised	$NaC_6C_{11}O_7$	527-07-1	208-407-7
Sodium lactate	+	E 325	Generally authorised	$C_3H_5O_3Na$	72-17-3	200-772-0
Sodium chloride	+			NaCl	7647-14-5	
Sodium malates Sodium malate Sodium hydrogen malate		E 350 (i) (ii)	Generally authorised	 $C_4H_4Na_2O_5$ x 1/2 H_2O $C_4H_5NaO_5$		 ? ?
Sodium sulphates Sodium sulphate Sodium hydrogen sulphate		E 514 (i) (ii)	Generally authorised	 Na_2SO_4 $NaHSO_4$	 7757-82-6 7681-38-1	 ? ?
Sodium tartrates Monosodium tartrate Disodium tartrate		E 335 (i) (ii)	Generally authorised	 $C_4H_5O_6Na$ $C_4H_4O_6Na_2$	 6106-24-7	 ? 212-773-3
Sodium hydroxide	+	E 524	Alkaline substance	NaOH	1310-73-2	215-185-5
Sodium hypochlorite			Bleach	NaOCl	7681-52-9	
Sodium alginate		E 401	Thickners, solvents and carriers for dyes	$(C_6H_7NaO_6)_n$	9005-38-3	?
Sodium salts of edible fatty acids		E 470	Emulsifiers, separating agents		141-01-5	205-447-7
Sodium compounds of various amino acids Sodium glutamate		E 621	Flavour-influencing substances	 $NaC_5H_8NO_4$ x H_2O	 6106-04-3	205-538-1
Sodium hexacyanoferrate (II)		E 535	Flow agent	$Na_4[Fe(CN)_6]$	13601-19-9	237-081-9

Continuation of Table 6: Overview of important permitted sodium compounds and other sodium-containing nutrient compounds

Sodium compound	Directives (2003/46/EC and 2001/15/EC)	E-No. (Reference list 1998, ZZulV)	Use as food additive	Molecular formula	CAS Number	EINECS (Directives 96/77/EC; 95/31/EC)
Sodium nitrite		E 250	Substances with various actions	$NaNO_2$	7632-00-0	231-555-9
Sodium nitrate		E 251	Substances with various actions	$NaNO_3$	7631-99-4	231-554-3
Sodium orthophosphates	+	E 339	Substances with various actions			
Mononsodium orthophosphate		(i)		NaH_2PO_4	7558-80-7	231-449-2
Disodium orthophosphate		(ii)		Na_2HPO_4	7558-79-4	231-448-7
Trisodium orthophosphate		(iii)		Na_3PO_4	7601-54-9	231-509-8
Sodium diphosphates		E 450	Substances with various actions			
Disodium diphosphate		(i)		$Na_2H_2P_2O_7$	7782-85-6	231-835-0
Trisodium diphoshate		(ii)		$Na_3HP_2O_7$	10101-89-0	238-735-6
Tetrasodium diphosphate		(iii)		$Na_4P_2O_7$	13472-36-1	231-767-1
Sodium sorbate		E 201	Preservative	$NaC_6H_7O_2$		?
Sodium benzoate		E 211	Preservative	$NaC_7H_5O_2$	532-32-1	208-534-8
Sodium compounds of parahydroxibenzoic acid ("PHB esters")		E 215 E 217 E 219	Preservative	$NaC_9H_9O_3$ $NaC_{10}H_{11}O_3$ $NaC_8H_7O_3$		252-487-6 252-488-1 ?
Sodium formiate		E 237	Preservative	$NaCHO_2$	141-53-7	
Sodium-orthophenyl phenolate		E 232	Preservative	$NaC_{12}H_9O \times 4\ H_20$		205-055-6
Sodium sulphite, sodium hydrogen sulphite, sodium disulphite		E 221 E 222 E 223	Substances developing sulphur dioxide	Na_2SO_3 $NaHSO_3$ $Na_2S_2O_5$	7757-83-7 7631-90-5 7681-57-4	231-821-4 231-921-4 231-673-0
Benzoic acid sulphimide-sodium ("saccharin")		E 954	Sweetener	$NaC_7H_4NO_3S \times 2\ H_2O$		204-886-1
Sodium cyclamate		E 952	Sweetener	$NaC_6H_{12}NO_3S$	139-05-9	205-348-9
Sodium-containing trace element compounds						
Sodium ferric diphosphate	+					
Sodium iodide	+			NaJ	7681-82-5	
Sodium iodate	+		For the production of iodised salt	$NaJO_3$	7681-55-2	
Sodium selenate	+					
Sodium hydrogen selenite	+					
Sodium selenite	+			Na_2SeO_3	10102-18-8	
Sodium molybdate	+			Na_2MoO_4	7631-95-0	
Sodium fluoride	+			NaF	7681-49-4	
Sodium-containing vitamin compounds						
Riboflavin-5'-phosphate, sodium (Vitamin B_2)	+					
Sodium-D-pantothenate (pantothenic acid)	+					
Sodium-L-ascorbate (Vitamin C)	+	E 301	Generally authorised	$C_6H_7O_6Na$	134-03-2	205-126-1

Table 7: Reference values for sodium of DGE (DGE/ÖGE/SGE/SVE, 2000), the National Academy of Sciences NAS (1989)), SCF (1992) and FNB (2004)†

Age (years)	Estimated values for minimum intake DGE (mg/day)		Estimated values for minimum requirements NAS/USA (mg/day)		Acceptable intake ranges SCF (mg/day)		Reference values for adequate intake FNB/USA (mg/day)	
Children	1 up to under 4	300	1 year	225			1 up to 3 years	1000
	4 up to under 7	410	2-5 years	300			4 up to 8 years	1200
	7 up to 10	460	6-9 years	400			9 up to 13 years	1500
	10 up to under 13	510	10-18 years	500			14 to 18 years	1500
	13 up to under 15	550						
Adolescents		550					19 up to 50 years	1500
and			Over 18 years	500	Adults	575-3500	51 up to 70 years	1300
Adults							>70 years	1200
Pregnant women	+69		+69				1500	
Breast-feeding women	+138		+135				1500	

Table 8: Daily sodium intake (in g) by gender (F = Female, M = Male) and age (from: Nationale Verzehrsstudie Band XI, VERA-Schriftenreihe 1995b)

Age (years)		4-6	7-9	10-12	13-14	15-18	19-24	25-50	51-64	>/= 65
Estimated values for minimum intake (mg) (DGE/ÖGE/SGE/SVE, 2000)		410	460	510	550	550	550	550	550	550
P 2.5	F	0.94	1.22	1.34	1.43	1.25	1.22	1.32	1.42	1.40
	M	1.08	1.30	1.43	1.50	1.70	1.78	1.83	1.84	1.65
P 25	F	1.43	1.85	2.05	2.12	2.03	2.10	2.23	2.29	2.17
	M	1.62	1.95	2.25	2.56	2.81	2.93	2.97	2.96	2.70
Median	F	**1.77**	**2.27**	**2.46**	**2.68**	**2.52**	**2.66**	**2.77**	**2.82**	**2.73**
	M	**1.99**	**2.40**	**2.81**	**3.19**	**3.52**	**3.58**	**3.65**	**3.64**	**3.41**
P 75	F	2.17	2.79	3.05	3.28	3.19	3.20	3.39	3.49	3.41
	M	2.46	3.01	3.43	3.93	4.33	4.36	4.47	4.42	4.24
P 97.5	F	3.29	4.15	4.50	4.72	5.04	4.69	5.07	5.36	5.11
	M	3.64	4.23	5.16	6.31	6.64	6.53	6.61	6.56	6.80

† Conversion factors:
1 mmol sodium = 23 mg sodium;
100 mmol sodium = 2300 mg sodium = 6 g NaCl
1 g sodium = 2.5 g NaCl

Table 9: Daily sodium intake (in g) by gender (F = Female, M = Male) and age

Age groups (years)		18-24	25-34	35-44	45-54	55-64	65-79
Estimated values for minimum intake (mg) (DGE/ÖGE/SGE/SVE, 2000)		550	550	550	550	550	550
Mean	F	**2.6**	**2.6**	**2.7**	**2.6**	**2.5**	**2.4**
	M	**4.1**	**3.7**	**3.7**	**3.4**	**3.2**	**3.0**
Standard deviation	F	0.7	0.8	0.9	0.9	1.0	0.8
	M	1.4	1.2	1.7	1.4	0.9	0.9
P 10	F	1.7	1.7	1.9	1.7	1.5	1.6
	M	2.6	2.4	2.4	2.2	2.1	1.9
Median	F	**2.5**	**2.5**	**2.6**	**2.5**	**2.4**	**2.3**
	M	**3.8**	**3.6**	**3.4**	**3.2**	**3.0**	**2.9**
P 90	F	3.5	3.7	3.7	3.6	3.3	3.2
	M	6.0	4.9	4.9	4.9	4.2	4.1

(From: Mensink et al.: Beiträge zur Gesundheitsberichterstattung des Bundes. Was essen wir heute? Ernährungsverhalten in Deutschland. Robert Koch Institute, Berlin 2002)

Table 10: Sodium concentrations in serum (in mmol/l) by gender (F = Female, M = Male) and age

Age groups (years)		18-24	25-34	35-44	45-54	55-64	>65
Reference ranges	F						136-146
(mmol/L)	M						136-146
P 2.5	F	137.0	136.0	135.0	136.0	136.0	137.0
	M	135.0	137.0	137.0	137.0	137.0	137.0
Median	**F**	**140.0**	**140.0**	**140.0**	**140.0**	**142.0**	**142.0**
	M	**141.0**	**141.0**	**141.0**	**141.0**	**141.0**	**142.0**
P 97.5	F	145.0	145.0	144.0	145.0	147.0	147.0
	M	144.0	146.0	145.0	147.0	145.0	147.0

(From: VERA-Schriftenreihe, Band V: Versorgung Erwachsener mit Mineralstoffen und Spurenelementen in der Bundesrepublik Deutschland, 1995a)

Table 11: Sodium excretion in urine (in mmol/24h) by gender (F = Female, M = Male) and age

Age groups (years)		18-24	25-34	35-44	45-54	55-64	>65
Reference ranges	F						40-300
(mmol/24h)	M						40-300
P 2.5	F	49.1	47.1	42.1	64.3	61.7	51.5
	M	46.7	56.0	56.7	59.5	88.2	94.6
Median	**F**	**114.9**	**128.9**	**126.0**	**146.7**	**142.1**	**133.2**
	M	**167.7**	**160.5**	**169.6**	**182.7**	**200.3**	**187.9**
P 97.5	F	274.3	288.8	291.7	301.2	327.5	305.5

(From: VERA-Schriftenreihe, Band V: Versorgung Erwachsener mit Mineralstoffen und Spurenelementen in der Bundesrepublik Deutschland, 1995a)

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5 Risk Assessment of Chloride

5.1 Summary

The food consumption surveys conducted in Germany indicate that the chloride intake of the population is far higher than the estimated minimum intake values. The values for 24-h urine excretion, which directly correlate with chloride intake, confirm these results. There is not one group in the population which is not adequately supplied with this nutrient (supply category 4).

The risk of adverse health effects from the use of chloride in foods cannot be assessed on the basis of the available data. Nor is it possible to classify the nutrient in one of the risk categories defined by BfR.

As the German population takes in adequate or high amounts of chloride (as NaCl) through the consumption of processed foods, the explicit use of chloride for nutritional-physiological purposes in food supplements or fortified foods is not advised on precautionary grounds. BfR recommends to accept chloride as an addition to food supplements or for food fortification only when it is to be added together with another nutritional-physiologically relevant nutrient (e.g. calcium chloride, magnesium chloride).

Estimated value for minimum intake	830 mg/day	
Intake [mg/day] (NFCS, 1994)	**m**	**f**
Median	5.5	4.1
P 2.5	2.7	2.1
P 97.5	9.6	7.1
Tolerable Upper Intake Level	Not defined	
Proposal for **maximum levels** in: Food supplements	Addition only in conjunction with nutritional-physiologically relevant cations (CaCl, MgCl, ZnCl etc.)	
Fortified foods	No fortification except in conjunction with nutritional-physiologically relevant cations	

5.2 Nutrient description

5.2.1 Characterisation and identification

Chloride is an inorganic nutrient whose essentiality has been proven for man. It is the most frequent anion in extracellular fluid. In nature it is very widespread in conjunction with sodium (NaCl = CAS No. 7647-14-5), potassium, (KCl = CAS No. 7447-40-7) or calcium ($CaCl_2$ = CAS No. 10043-52-4).

In the European Directive on Food Supplements, chlorine is listed as a mineral for use in food supplements. According to Annex II of that Directive it may be used as calcium chloride, magnesium chloride, sodium chloride, manganese chloride, potassium chloride, chromium chloride and zinc chloride. The same applies to food fortification in accordance with the Annex in the Proposal for a *Regulation on the addition of vitamins and minerals and of certain other substances to foods* (COM(2003) 671 final of 10 November 2003).

Furthermore, the chloride compounds tin(II) chloride (E 512), potassium chloride (E 508), calcium chloride (E 509) and magnesium chloride (E 511) are authorised as additives within

the EU. Ammonium chloride is no longer explicitly listed as an additive but may be used as an aroma component in liquorice products (including chewing gum).

5.2.2 Metabolism, function, requirements

Metabolism: Depending on the metabolic situation in the organism, chloride is taken up actively or passively. In the proximal small intestine passive resorption takes place during which chloride follows the electrochemical gradient produced during cation transport. By contrast, chloride resorption takes place actively in the distal small intestine and in the colon in exchange for bicarbonate anions. The uptake rate of chloride from food is more than 90%. In the intercellular space the chloride ion concentration is 110 mmol/l (1 mmol chloride = 35.5 mg), whereas the concentration in the intracellular space of 5 mmol/l is relatively low. For comparison: in the intercellular space the sodium concentration is 145 mmol/l and in the intracellular space it is 10 mmol/l (1 mmol sodium = 23 mg) (Greger, 1994). The distribution of the electrolytes between the extracellular and intracellular space is regulated by Na^+, K^+-ATPase which pumps out Na^+ from the cells in exchange for K^+. As chloride follows the movement of sodium in order to maintain the electrochemical balance, active sodium transport leads to chloride also passing into the extracellular space. Transport through the cell membranes is via the chloride channels.

High concentrations of chloride can be found in spinal fluid and in intestinal secretions, particularly as hydrochloric acid in the stomach. The total body amount of chloride is approximately 33 mmol/kg body weight. In the case of an adult weighing 70 kg this means around 2,310 mmol (~100 g). 90-95% of dietary chloride is normally excreted by the kidneys (Preuss, 2001). In the case of normal kidney function 170 litres extracellular fluid are filtered every day with a total of 1.5 kg NaCl. Of this more than 99% is reabsorbed via the nephrons. The renal excretion rate is roughly 10 g NaCl (= 6 g Cl^-) per day. It is reduced by excessive excretion in sweat (Greger, 1994). Normal perspiration varies between 0.11 and 3 l per day and is linked to NaCl excretion of up to 0.25 g/day (= 0.15 g Cl^-). Approximately 0.25 g NaCl (= 0.15 g Cl^-) per day are also excreted in faeces (Preuss, 2001). In the case of diarrhoea, when excretion is particularly stimulated, loss via faeces can be very high (Greger, 1994). As chloride is normally excreted together with sodium, high chloride loss is generally to be expected in situations/disorders involving a high sodium loss, too.

The renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, the atrial natriuretic peptide (NAP), the Kallikrein-Kinin system and various intrarenal mechanisms perform important functions in the regulation of (sodium and) chloride excretion.

Function: Chloride plays an important role in regulating fluid and electrolyte status. With hydrogen ions it forms hydrochloric acid (HCl) in the stomach and is important for protein metabolism, the resorption of other minerals and for activating the intrinsic factor of vitamin B_{12} uptake. Together with sodium and potassium, chloride is also essential for nerve and muscle cell functions. The continuing exchange between chloride and bicarbonate ions supports a balanced pH and regulates CO_2 excretion.

Requirements: There are no exact studies on chloride requirements. Based on the amount of chloride excreted daily of approximately 530 mg, an intake of 750 to 900 mg/day is recommended. The chloride requirements of an infant weighing 5.8 kg were estimated to be 3.6 mmol/day in the 1980s (Manz, 1985). The Food and Nutrition Board was not able to establish a (EAR or) RDA for chloride given the lack of dose-response studies. Instead it proposed Adequate Intake (AI), which is equimolar to that of sodium because chloride is almost only taken up from food in conjunction with sodium. The following table compares the estimated values for minimum chloride intake (DGE/ÖGE/SGE/SVE, 2000) with the American AI values for the various age groups (IOM, 2004):

Table 12: Reference values for chloride

Age	Estimated values for minimum intake[1] (mg/d)	Adequate Intake [2] (mg/d)
Infants		
0-4 months	200	180*
4-12 months	270	570**
Children		
1-3	450	1500
4-6	620	
7-9	690	1900
10-12	770	
13-14	830	2300
Adults	830	2300***
51-70		2000
>70		1800

DGE, ÖGE, SGE, SVE, 2000) and of the FNB (IOM, 2004)
* 0-6 months
** 7-12 months
*** Adults <50 years of age including pregnant and breastfeeding women
[1] DGE/ÖGE/SGE/SVE, 2000
[2] IOM, 2004

It is noticeable that the American values from age 6 months onwards are roughly twice or three times higher than the D-A-CH estimated values. This could be due to the fact that the American values are based on sodium intake from conventional foods (western diet) from which the equimolar chloride intake levels were calculated (IOM, 2004). By contrast, in the D-A-CH estimated values minimum sodium intake is defined on the basis of the obligatory losses from faeces, skin and perspiration. The necessary chloride intake per day is derived as the equimolar amount (DGE/ÖGE/SGE/SVE, 2000).

5.2.3 Exposure (dietary and other sources, nutritional status)

Sources:
Food: Chloride is almost exclusively taken up in conjunction with sodium. The natural chloride content in foods is below 0.36 mg/g. Furthermore, salt is the most important source for the intake of chloride (and sodium). Beverages may also contain a high level of sodium chloride. This applies in particular to tomato and vegetable juices but also to some mineral waters. Liquorice products are a source of chloride which should not be underestimated. Ammonium chloride (NH_4Cl) is added to them as aroma in order to produce the typical flavour for liquorice. According to the Aroma Ordinance (AromenVO) a maximum level of 20 g/kg food has been laid down for the use of ammonium chloride in foods (AromenVO, Annex 5, 1998). If the maximum admissible level of ammonium chloride has been exhausted, the consumption of 50-100 g liquorice would lead to an ammonium chloride intake of 1-2 g (= 0.66-1.3 g Cl^-). This means that the consumption of liquorice products by individuals, who eat large amounts of them, could lead to exceptionally high chloride intake. Human milk contains 11.3 mmol chloride per litre. The ratio of the cations (Na^+ (6 mmol/l) and K^+ (12 mmol/l)) to the chloride anions is 1.6.

Food supplements: It is not known whether food supplements have been specifically manufactured with chloride added. Chloride is, however, an accompanying ingredient in food supplements when for instance magnesium or zinc is added as chloride compounds.

Medicinal products: NaCl concentrates, which are added to infusion solutions, are administered intravenously for the correction of disruptions of sodium and chloride status (in the case of hypochloraemia and hyponatraemia).

Nutritional status:
Intake: Around 2-8 g chloride per day are taken in from a normal diet. On a diet free of added salt, the intake of chloride occurring naturally in food is approximately 600 mg per day. As chloride is taken up in conjunction with sodium as salt, actual intake depending on the processing or preparation of foods and individual nutrition habits is far higher. Average salt consumption in Germany is around 8 g per day and person (men = 8 g/day, women = 7 g/day) (DGE/ÖGE/SGE/SVE, 2000). The chloride intake from salt consumption is consequently 4.85 (men) and 4.2 g (women) per day. This is also confirmed by the figures of the National Food Consumption Study (NFCS). According to them, mean salt intake in adult men is 9.3 and in women 7.2 g per day (Heseker et al., 1994). This corresponds to chloride intake of 5.6 g (men) and 4.3 g (women) per day.

Plasma concentrations: In the VERA Study the serum concentrations of chloride were measured. Given the manifold endocrine regulation of serum electrolyte values, they remain largely steady in healthy individuals and are not, therefore, suited for drawing conclusions about electrolyte intake. The chloride concentrations in the serum are similar to those of sodium. Independently of intake, there is, however, in the case of chloride as for all other electrolytes a clear age factor in the serum values. In the case of women this deviates slightly from that of the sodium concentration. The maximum is already reached in women aged 25-44 years.

The reference range for chloride in the serum is 98-108 mmol/l. The reference range for the excretion of chloride in urine is 100-250 mmol/24h (Greiling and Gressner, 1995 in: Kohlmeier et al., 1995). The median of serum values is 106 mmol/l in both men (n=835) and women (n=1097). In both genders the 2.5 percentile is 101 and the 97.5 percentile is 111 mmol/l (Kohlmeier et al., 1995). In contrast to the serum values the excretion values of chloride clearly correlate with the intakes and there is a significant difference between men and women. In men (n=698) the median is 172.4 mmol/24h. The 2.5 percentile is 60.92 and the 97.5 percentile is 334.8 mmol/24h. In women (n=954) a median of 126 mmol/24h was identified. The 2.5 percentile is 46.92 and the 97.5 percentile is 277.16 mmol/24h (Kohlmeier et al., 1995).

5.3 Risk characterisation

5.3.1 Hazard characterisation (NOAEL, LOAEL)

The toxicity of chloride-containing salts is mainly due to the corresponding cations. There are no known cases of chloride toxicity in man. However, very little information is available about the effects of lengthy high dietary chloride intake. Ammonium chloride, which is used as an aroma in liquorice products, can lead to adverse effects in man at intakes of 100 mg/kg/day; this can have a major effect on the acid-base balance. Ammonium chloride intake increases renal acid load and reduces the pH of urine. Infants, old people and individuals with kidney diseases (renal tubular acidosis, tubular disorders, chronic renal deficiency, aldosterone deficiencies) but also people with elevated endogenous acid production may experience extensive and lengthy retention acidosis if they have a high intake of ammonium chloride.

It is known that in the case of salt sensitive high blood pressure a reduction of salt intake can lead to a short-term reduction in blood pressure. Both sodium and chloride ions seem to be responsible for this since selective dietary sodium intake without parallel chloride load reduces the increase in blood pressure or even prevents it completely (Boegehold and Kotchen, 1989; Kurtz et al., 1987; Reusch and Luft, 1991). However opinions differ as to whether a dietary measure of this kind can have positive effects in the long-term (mortality, disease rate, blood pressure). Furthermore, it is still unclear via which mechanisms NaCl can impact on blood pressure particularly as blood pressure is influenced by the interplay of many factors like genetic predisposition, BMI and the regulatory mechanisms of the nervous system, hormone system and kidneys (Stipanuk, 2000) but also by the level of potassium and pro-

bably also of calcium intake from food. In the Federal Health Survey 1998 hypertension was identified in just under 30% of men and approximately 27% of women (Thamm, 1999).

On the basis of the dose-response studies concerning the association between sodium and salt intake and blood pressure, FNB derived a LOAEL of 2300 mg sodium per day. It was observed that sodium intake below the AI is more favourable for normal blood pressure than higher intake. Since a series of other factors, in addition to sodium intake, influence blood pressure, no NOAEL could be identified.

5.3.2 Deficiency, possible risk groups

With a normal diet sufficient amounts of chloride (in conjunction with sodium) are consumed. This means that there are practically no cases of chloride deficiency in healthy individuals. Chloride deficiency can, however, occur for instance during diarrhoea and/or severe vomiting. The related high excretion of chloride leads to an elevated bicarbonate ion concentration and to a shift in the acid-base balance (hypochloraemic metabolic alkalosis). Acid-base balance normally is kept stable at pH values between 7.37-7.43. The Bartter Syndrome, an autosomal recessive hereditary disease with chronic diarrhoea and deficient chloride reabsorption, leads to hypochloraemia, similar to disorders in the renal tubule and to cystic fibrosis. This is coupled with high losses of chloride in sweat (Bartter et al., 1962 in: IOM, 2004). In all these cases more chloride is lost than sodium resulting in hypochloraemia without hyponatraemia. Metabolic alkalosis is linked to hypokalaemia (elevated potassium excretion because of stimulated aldosterone secretion). This, in turn, leads to an elevated binding of calcium ions to albumin, thereby reducing the calcium concentration in serum. The symptoms of metabolic alkalosis are muscle weakness, polyuria, hypoventilation, loss of appetite and lethargy.

In infants and small children chloride losses – mostly as a consequence of diarrhoea, vomiting or in conjunction with an infection – can be very high. Metabolic alkalosis was observed in the 1980s in infants who had mistakenly been given infant formula with overly low chloride levels. The typical consequences of chloride deficiency in infants are failure to grow, lethargy, gastro-intestinal disorders, anorexia and muscle weakness (Manz, 1985). The late effects observed in these children were speech development disorders (Malloy et al., 1991 in: IOM, 2004).

5.3.3 Excessive intake, possible risk groups

The consumption of large amounts of salt and potassium chloride leads to high chloride intake which can normally be balanced through increased excretion in urine, sweat and faeces. In the case of disorders of the sodium-chloride metabolism, e.g. heart failure, or in the case of kidney diseases when excretion is disturbed, complications may arise from high intake levels of chloride.

Furthermore, the chloride concentration in the organism (= hyperchloraemia) increases in the case of:

- inadequate water intake
- dehydration of long duration
- fluid losses via the kidneys or intestines or diarrhoea (HCO_3 losses lead to a higher chloride level)
- infusion of solutions with a high chloride content
- chronic hyperventilation (respiratory alkalosis)
- administration of adrenal cortex hormones with mineral corticoid effects/corticoid therapy.

The food consumption studies conducted in Germany indicate that the chloride intake of the population is far higher than the estimated values for minimum intake. The values for 24h urine excretion, which correlate directly with chloride intake, confirm these study results. There is no population group which is not adequately supplied with this nutrient (supply category 4).

5.4 Tolerable upper intake level for chloride

DGE considers that salt intake of 6 g per day is adequate for adults. It stresses that no benefits are to be expected from higher intake but that adverse effects on health cannot be ruled out (DGE/ÖGE/SGE/SVE, 2000). Salt consumption in Germany roughly corresponds to this recommendation. On average between 1g (women) and up to 2 g (men) are ingested in addition to this recommendation.

Based on the LOAEL for sodium, FNB derived a UL for sodium and for chloride, too. Given that an uncertainty factor >1 would lead to a UL below the AI, the uncertainty factor 1 was used and a UL for sodium of 2300 mg/day was derived for adults. It was assumed that chloride occurs equimolar to sodium in foods which means that from the UL for sodium a UL for chloride of 3600 mg/day could be calculated for adults. This UL also applies to pregnant and breastfeeding women whereas for children ULs were extrapolated from the value for adults (IOM, 2004):

Age (years)	UL [mg/d]
1 – 3	2300
4 – 8	2900
9 - 13	3400
14 - 18	3600
Adults	3600

Salt intake of 6 g, described as the maximum desirable daily intake in Germany, corresponds to a chloride intake of 3.5 g/day. Thus, the daily maximum value recommended by the D-A-CH societies is supported by the ULs derived by FNB.

However, it was assumed both for the daily maximum level (salt) recommended in Germany and for the derivation of the UL by FNB that sodium (in conjunction with chloride) is the substance which causes adverse effects at high doses. Therefore, the UL derived for chloride can only be used in conjunction with sodium, i.e. for the consumption of salt. Also, in the case of high chloride intakes in conjunction with other cations, toxicity seems to be due to the corresponding cations rather than to chloride intake itself. However, little information is available about what effects of long-time high chloride intake from food are to be expected.

5.4.1 Derivation of a maximum level for chloride in food supplements and fortified foods

In the case of healthy individuals with a conventional western diet, there is no risk of inadequate chloride intake. The data for Germany confirm that the population is (more than) adequately supplied with this nutrient. As there are no known advantages for healthy individuals arising from additional chloride intake and there is uncertainty about whether chronically high chloride intake may have toxic effects in man, BfR recommends to accept chloride in food supplements and fortified foods only up to the level which results from the deliberate addition of essential minerals like zinc, magnesium or calcium when they are used as chloride compounds.

The risk of adverse effects on health in conjunction with the use of chloride in foods cannot be assessed on the basis of the available data. Nor is it possible to classify the nutrient in any of the risk categories defined by BfR.

Since the German population takes in adequate or high amounts of chloride (as NaCl) daily particularly through the consumption of processed foods, BfR advises against the explicit use of chloride for nutritional-physiological purposes in food supplements of fortified foods on precautionary grounds. BfR recommends to accept the addition of chloride to food supplements or for the fortification of foods only if it is to be added together with another nutritional-physiologically relevant nutrient (e.g. calcium chloride, magnesium chloride).

5.5 Gaps in knowledge

There is uncertainty about the toxicity of chloride in conjunction with the intake of high levels over a long period.

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6 Risk Assessment of Potassium

6.1 Summary

The data available for the Federal Republic of Germany on the nutritional status of potassium do not point to inadequate potassium intake in healthy children, adolescents or adults (supply categories 2/3). Older people with inadequate food intake who frequently take certain medicines are at risk.

It is the opinion of BfR that the use of potassium in food supplements involves a high risk of adverse reactions. In the case of the fortification of food with potassium there may, under certain circumstances, be a high risk only for people with disturbed potassium excretion. BfR has established a UL of 1000 mg for additional intake. On the grounds of preventive health protection it recommends setting the maximum level for food supplements at 500 mg and foregoing any targeted fortification of foods. Instead, greater use should be made of the restoration option in processed foods since large amounts of water-soluble potassium compounds may be lost during processing. From the preventive angle this should be coupled with a parallel reduction in salt content.

Estimated values for minimum intake	2000 mg/day	
Intake [mg/day] (NFCS, 1994)	**m**	**f**
Median	3300	2860
P 2.5	1930	1440
P 97.5	5640	4640
Tolerable Upper Intake Level	1000 mg/day (only for supplements)	
Proposal for **maximum levels** in: Food supplements	500 mg/daily dose	
Fortified foods	No fortification	

6.2 Nutrient description

6.2.1 Characterisation and identification

Potassium (K^+) is in the 1st main group of the periodic system and, therefore, belongs to the group of alkali metals (CAS No. 7440-09-07). It has an atomic mass of 39,098. It is the seventh most abundant element in the earth's crust. Because of its properties potassium is a highly reactive element and does not, therefore, occur in nature as a pure substance. As a cation it forms compounds with minerals like clay stone, potash mica or other potassium salts. This report only assesses ionic potassium unless explicit reference is made to a potassium compound.

According to Commission Directive 2001/15/EC (of 15 February 2001 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses) and the Directive of the European Parliament and the Council 2002/46/EC (of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements), only the potassium compounds listed there may be used for nutritional purposes: potassium bicarbonate ($KHCO_3$) (CAS No. 298-14-6), potassium carbonate (K_2CO_3) (CAS No. 584-08-7), potassium hydroxide (KOH) (CAS No. 1310-58-3), potassium chloride (KCl) (CAS No. 7447-40-7), potassium iodide (KI) (CAS No. 7681-11-0), potassium iodate (KIO_3) (CAS No. 7758-05-6) etc.. Similarly, these compounds may be added to foods according to a Proposal for a Regulation of the European Parliament and the Council of 10 November 2003 (COM (2003) 671 final).

Some potassium compounds like, for instance, potassium citrate (E 332), potassium lactate (E 326), potassium orthophosphate (E 340) etc. may be added to foods for technological purposes (see list of references for additives, Additives Approval Ordinance, Food Additives Purity Criteria Directive 96/77/EG).

6.2.2 Metabolism, function, requirements

Metabolism: The total body store of potassium is 40-50 mmol*)/kg body weight which roughly corresponds to 140 g (3600 mmol) and 105 g (2700 mmol) for adult men and women respectively. However, only approximately 75% of the potassium load is rapidly exchangeable and is in a dynamic balance with the various body compartments. Insulin, catecholamines, aldosterone, magnesium and the acid-base balance are involved in distribution between the intracellular space and the extracellular space. The total store is an expression of the metabolic proportion of the body mass (lean body mass) and is, therefore, influenced by frame, age and gender (Aizman et al., 1998; Bia and DeFronzo, 1981; Burmeister and Bingert, 1967; He et al., 2003; Leggett and Williams, 1986; Sterns et al., 1981).

In contrast to sodium, potassium is largely localised (approximately 98%) in the intracellular space. The muscle cells (around 60%) contain a large amount of body potassium, followed by the erythrocytes (8%), liver cells (6%) and around 4% of the body store of potassium in other organs. Only 50-60 mmol are found in the extracellular space; the potassium concentration in the serum normally varies between 3.5 and 5.5 mmol/l. The "clinically measurably" extracellular potassium in the serum accounts for less than 2% of the total store. The low potassium concentration in the extracellular space is, nevertheless, very sensitive to fluctuations. Even minor deviations can lead to severe neuromuscular and muscular disorders (Allison, 1984; D-A-CH, 2000; Ensminger et al., 1995; Hartig, 1994; Preuss, 2001; Sterns et al., 1981).

90% of dietary potassium is absorbed in the upper small intestine through passive diffusion. In the colon potassium can be actively secreted in exchange for sodium as well as reabsorbed (Agarwal et al., 1994; Allison, 1984; Halm and Frizzell, 1986; Powell, 1987). In the body potassium is rapidly taken up intracellularly in the liver and muscles. Insulin and catecholamines are mainly involved in extrarenal regulation (Bia and De Fronzo, 1981). When in potassium balance around 90% of the potassium taken in orally is excreted within 8 hours and more than 98% within 24 hours in urine. Higher or lower intakes are not mirrored in changes in the plasma concentration since the regulation of the potassium balance is done via the kidneys within a small range. The precondition is normal kidney function which means that an increase in extracellular [K^+] stimulates aldosterone secretion. In the distal tubule this promotes reabsorption of potassium through the integration of a luminal potassium channel (NaCl-cotransport) and activation of Na^+/K^+-ATPase. In exchange the potassium secretion in the lumen is increased through ROMK (apical potassium channels). A potassium deficiency leads to a reduction in the ROMK protein level (down regulation) and a decrease in the reabsorption of NaCl (Bauer and Gauntner, 1979; Mennitt et al., 2000; Stanton and Giebisch, 1982; Young, 1988). Potassium excretion by the kidneys is very adjustable (Bhandari and Hunter, 1998; Giebisch, 2002; 1998; Ornt et al., 1987; Rabelink et al., 1990; Skoutakis et al., 1984; Stühlinger, 2003; Witzgall and Behr, 1986). The potassium concentration in the urine may fall to 10 mmol/l in the case of potassium deficiency. In the case of excess it may rise to more than 200 mmol/l (Hene et al., 1986; Rabinowitz, 1989). Overall in the case of a balanced potassium store around 85% is excreted via the kidneys and 12% via faeces. Minimum losses (3%) are caused by loss through sweating via the skin (Agarwal et al., 1994; Anke et al., 2003; BGA, 1991; Leggett and Williams, 1986; NRC, 1989; Preuss, 2001; SCF, 1993).

*) 1 mmol potassium corresponds to 39.1 mg.

Functions: Potassium is essential for normal growth and sustaining life. As the most important intracellular cation, potassium is involved in the activity of every cell:

- bioelectricity of the cell membranes, i.e. normal neuromuscular excitability, excitation formation and excitation conduction of the heart. Here, ion channels facilitate the rapid movement of ions through the hydrophobic barrier of the membrane. Characteristic examples for ion channels are the K^+ channel or Na^+ channel which convey neuro signals (Shieh et al., 2000; Tamargo et al., 2004);
- regulation of cell growth (Niemeyer et al., 2001; Shen et al., 2001);
- transepithelial transport processes in the kidneys and intestines, e.g. for glucose, aminoacids etc. (Preuss, 2001);
- impact on protective endothelial vascular functions (Ma et al., 2000; Young et al., 1995; Young and Ma, 1999);
- maintaining normal blood pressure (Krishna, 1990; Suter, 1998; Young et al., 1995; Tannen, 1987a);
- regulation of the acid-base balance by influencing renal net acid excretion (Frassetto et al., 2001; 1997; 1998; Manz, 2001; Remer et al., 2003; Remer, 2000; 2001; Sebastian et al, 2002; Tannen, 1987b);
- influencing the release of hormones (e.g. insulin from the beta cells) and
- carbohydrate utilisation and protein synthesis.

Furthermore, potassium is needed in intermediary metabolism for the synthesis and degradation of high energy phosphate compounds. Furthermore, some enzymes of glycolysis (the uptake of glucose in liver and muscle cells for glycogen synthesis is linked to potassium intake), oxidative phosphorylation and protein metabolism are dependent on potassium (Ensminger et al., 1995; Hartig, 1994; Preuss, 2001; Shieh et al., 2000).

Requirements: For the maintenance of potassium homoeostasis, the requirements of total energy intake are estimated that are needed for growth or maintenance of the cell mass (1 kg cell mass contains 92.5 mmol potassium). This is then proportional to the potassium load of the organism. In the case of infants almost 2 mmol potassium are calculated for 100 kcal, in line with the energy and potassium level in human milk. Because of rapid growth the necessary potassium level in infants in the first 4 months is 0.9 mmol/kg body weight/day and 0.4-0.5 mmol/kg body weight/day later in boys and girls up to age 12. During growth spurts in puberty it is 0.9 mmol/kg body weight/day (Fomon, 1993). In order to maintain normal body store and normal concentrations in the plasma and interstitial fluid, a minimum intake of approximately 1600-2000 mg/day is necessary in adolescents and adults (NRC, 1989).

During pregnancy or lactation there is no significant additional need for potassium which could not be met through a normal diet. Discussions focus on an additional requirement for athletes and heavy labourers who lose approximately 300 mg potassium/l after several hours constant strain through sweat (Breuer et al., 1991). Care should be taken to ensure adequate intake during incidents involving severe diarrhoea or vomiting. Laxatives and diuretics can also lead to high losses (D-A-CH, 2000).

A value of 2000 mg/day is given as the estimated value for minimum intake by healthy adults (D-A-CH, 2000). Based on balance measurements Anke et al. (2003) calculated normative requirements of potassium of 15 mg/kg body weight or 900 mg/day for women (60 kg body weight) and 1200 mg/day for men (80 kg bodyweight). The Scientific Committee on Food (SCF) of the European Commission indicates, as a Lowest Threshold Intake (LTI) for adults, a value of 40 mmol/day (1600 mg/day) in order to avoid a drop in potassium concentrations

in plasma and loss of total body potassium. No average requirements were established. A value of 80 mmol/day (3100 mg/day) was proposed as the Population Reference Intake (PRI) (SCF, 1993). Estimated values for the minimum intake of potassium and the PRI are compared in Table 13.

For the purposes of nutrient labelling a so-called Reference Labelling Value (RLV) of 2000 mg for adults and 1000 mg for children up to the age of 4 was proposed by SCF for potassium (SCF, 2003).

Table 13: Estimated values for a minimum intake of potassium (D-A-CH, 2000) compared with the PRI values

Age	D-A-CH, 2000 potassium (mg/day)	SCF, 1993 Population Reference Intakes (PRI) (mg/day)
Infants		
4 up to under 12 months	650	800
Children		
1 up to under 4 years	1000	800
4 up to under 7 years	1400	1100
7 up to under 10 years	1600	2000
10 up to under 13 years	1700	3100
13 up to under 15 years	1900	3100
Adolescents and **adults**	2000	3100
Pregnant and **lactating women**	–	3100

(SCF, 1993)

The Food and Nutrition Board of the USA and Canada believe that an Adequate Intake (AI) of 4.7 g/day (120 mmol/day) is adequate for all adults on preventive grounds. This potassium amount (from food) is necessary according to more recent findings in order to prevent, alleviate or delay the onset of chronic disorders or conditions like high blood pressure, salt sensitivity, kidney stones, loss of bone mass or strokes (Curhan et al., 1997; Hirvonen et al., 1999; Keßler and Hesse, 2000; Macdonald et al., 2004; Morimoto et al., 1997; Morris et al., 1999a; 2001; New et al., 2004; Schmidlin et al., 1999; Sebastian et al., 2002; Sellmeyer et al., 2002; Suter, 1999; Young et al., 1995). However, this body was not able to establish any Estimated Average Requirement (EAR) because of the lack of data on the dose-response relationship. Nor was it able to derive Recommended Dietary Allowances (RDA) which means that, at present, an AI is considered to be adequate (FNB, 2004).

Interactions: Interactions between potassium and sodium, magnesium and calcium (Marktl, 2003; Ensminger et al., 1995) as well as diverse interactions with medicinal products are of clinical relevance (Bjerrum et al., 2003; Fachinformation AstraZeneca, 2002; Fachinformation Novartis Pharma, 2002; Greenberg, 2000; Schwartz, 1975).

Potassium and sodium: It is important for sodium and potassium to be well balanced. Excessive sodium intake can lead to potassium depletion. Vice versa, potassium has a natriuretic effect. Hence the Na:K ratio in food is of more importance than the concentration of the individual cations. Aside from sodium, potassium is of major importance for the non-pharmacological regulation of blood pressure (Suter et al., 2002; Tobian, 1997). In epidemiological studies an inverse relationship was observed between potassium intake and blood pressure and an elevated risk of strokes. Furthermore, the blood pressure lowering effect of potassium in supplementation experiments could be proven (Ascherio et al., 1998; Barri and Wingo, 1997; Bazzano et al., 2001; Geleijnse et al., 1997; Khaw and Barrett-Connor, 1984; 1987; 1998; Siani et al., 1987; Svetkey et al., 1987; Suter, 1999). The first clinically controlled study by Sinai et al. (1991) concerning the influence of a switch to a high potassium diet by hypertensive individuals (n=27) showed a significant reduction in anti-hypertensive medication after one year (Siani et al., 1991). Another larger clinical intervention study also examined

the influence of potassium supplementation (96 mmol and 3754 mg/day) in combination with sodium reduction on blood pressure again in hypertensive men (n=287) taking antihypertensive medication. It was not able to confirm this effect (Grimm et al., 1988; 1990). In a meta analysis Whelton et al. compared the data from 33 clinically controlled intervention studies concerning the influence of potassium supplements on blood pressure. The test persons included hypertensive patients and normotensive individuals as the control group who, depending on the study, received different doses of potassium supplements. The result of the meta analysis was that potassium supplementation merely reduces blood pressure (systolic on average by 3.11 mm Hg and diastolic on average by 1.97 mm Hg). However, the effect was smaller in normotensive individuals than in hypertensive ones. The treatment success was greater in studies in which the test persons had been given a high sodium intake at the same time. Overall, the treatment duration was short and the dose was between 60 and 200 mmol/day, i.e. an amount of 2346-7820 mg. The higher dose does not normally stem from dietary intake alone. Many of the studies evaluated did not show convincing or demonstrated contradictory results (Whelton et al., 1997). In a more recent controlled clinical study, too, involving 59 healthy test persons, average arterial blood pressure could only be reduced by 7.01 mm Hg, systolic blood pressure by 7.60 mm Hg and diastolic blood pressure by 6.46 mm Hg in a low dose supplementation of 24 mmol potassium/day over six weeks. This amount of potassium (938 mg) roughly corresponds to the content in 5 portions of fresh fruit and vegetables (Naismith and Braschi, 2003). In a meta regression analysis involving a total of 67 clinically controlled studies examining the influence of sodium reduction or potassium supplementation on blood pressure, it was observed that sodium reduction and increased potassium intake can make a major contribution to preventing hypertension particularly in groups with higher blood pressure (Geleijnse et al., 2003).

A blood pressure lowering effect can also be achieved solely through the so-called DASH (Dietary Approaches to Stop Hypertension) diet (rich in wholemeal cereal products, fruit, vegetables, poultry, fish and nuts). Compared with a normal diet this diet contains less salt and saturated fats, a relatively high level of potassium but also a higher level of other nutrients like magnesium and calcium which are also said to lower blood pressure (Sacks et al., 2001; Vollmer et al., 2001; Zemel, 1997). For that reason a diet rich in fruit and vegetables (rich in potassium) should be recommended in combination with a moderate reduction of sodium intake since a sodium to potassium ratio of 1 or less has a favourable impact on blood pressure. It does not make sense to adjust potassium intake to high sodium intake. Nor does potassium supplementation lead to a clinically relevant reduction of blood pressure in individuals who already have a healthy diet (Campbell et al., 1999; Kübler, 1995; Obarzanek et al., 2003; Suter et al., 2002). Potassium intake obviously has an impact on salt sensitivity. This increases when potassium intake is marginal and, depending on dose, is suppressed when dietary potassium intake is increased. This may prevent or delay the onset of high blood pressure particularly in individuals whose potassium intake is too low (Coruzzi et al., 2001; Morris et al., 1999a; Schmidlin et al., 1999).

Potassium and magnesium: Potassium homoeostasis is closely linked to magnesium status. Magnesium is known to be the second most frequent intracellular cation. It plays a key role in intracellular potassium regulation. In many cases, potassium and magnesium losses coexist, triggered by massive gastro-intestinal cation losses as a consequence of diuretics, alcohol or antibiotics (Ryan, 1993). Hypomagnesaemia leads to renal potassium losses, the mechanism of which has not yet been clarified (Stühlinger, 2003). The interaction between potassium and magnesium takes place on various levels. It not only involves gastro-intestinal resorption and renal excretion but also endogenous distribution between the extracellular and intracellular compartments and above all various cellular processes. For instance a magnesium deficiency increases the permeability of K^+ through the K^+ channels which, in turn, has an impact on cardiac muscle action potential (Marktl, 2003).

Potassium and calcium: Furthermore, potassium has a positive impact on bone metabolism as a higher potassium intake prevents elevated calcium excretion induced through a high salt intake. Thus potassium promotes renal calcium retention in the kidneys and possibly prevents calcium loss from bones (Harrington and Cashman, 2003; Lemann et al., 1991; 1993; New et al., 2004). In this context, however, the influence of accompanying ions, the composition of food and age on the acid-base status must be taken into account (Barzel, 1995; Frassetto et al., 1996; Lemann, 1999; Massey, 2003; Morris et al., 1999b; Remer and Manz, 2001; Remer, 2000). In this way renal net acid excretion can be reduced through administering an alkalising potassium salt (e.g. potassium bicarbonate or tripotassium citrate). Particularly in post-menopausal women this increases the calcium and phosphorus balance and reduces bone resorption (Bushinsky, 2001; Frassetto et al., 2001; Morris et al., 1999b; Sebastian et al., 1994; Sellmeyer et al., 2002). A more recent study confirmed that independent of potassium intake neutralisation of mild metabolic acidosis caused by a so-called western diet (high proportion of animal protein and salt, fewer vegetable and fruit) is of major importance when it comes to preventing in the long-term the otherwise disadvantageous effects on bone metabolism (Maurer et al., 2003).

Interaction with medicinal products: Potassium-saving diuretics, aldosterone antagonists, ACE(Angiotensin-Converting Enzyme) inhibitors, non-steroidal antiphlogistics and peripheral analgesics reduce the renal excretion of potassium. An increase in the extracellular potassium concentration reduces the impact of cardiac glycosides. There is a risk of hypercalcaemia in conjunction with the parallel administration of potassium-containing medicinal products, table salt substitutes or supplements. On the other hand, there is a risk of hypocalaemia in the case of thiazide-style or loop diuretics. They increase potassium excretion which, in turn, strengthens the arrhythmogenic impact of cardiac glycosides. In combination with beta blockers to treat hypertension, too, one-third of patients had hypocalcaemia with serum potassium concentrations between 3.0 and 3.3 mmol/l; 19% even had values <3.0 mmol/l. This means there were frequent incidences of ventricular extrasystols in these patients (Allison, 1984; Bjerrum et al., 2003; Fachinformation AstraZeneca, 2002; Fachinformation Novartis Pharma, 2002; Gross and Pistrosch, 2003; Kamel et al., 1990; Lawson, 1975; Mandal, 1997; Ray et al., 1999; Schwartz, 1975).

6.2.3 Exposure (dietary and other sources, nutritional status)

Sources:

Drinking water: The average potassium content in drinking water is 5.7 (0.5-18) mg/l in EU Member States. Table waters in Germany contain on average 21.2 (0.9-322) mg/l (Großklaus, 1991).

Foods: Given its widespread distribution in the earth's crust, potassium is found in almost all foods of animal and plant origin. The main sources are plant foods like vegetables and fruit (890-6700 mg/kg) (21.3%), potatoes (2700-5700 mg/kg), rice (780-2890 mg/kg), pasta (530-2700 mg/kg) (19%) and bread/cereal products (940-3000 mg/kg) (8.2%). Approximately 10% is taken up from dairy products (800-1300 mg/kg), and around 17% from meat, poultry (1030-4100 mg/kg) and fish (1310-5000 mg/kg). 13.5% come from beverages whereby fruit juices (1570 mg/kg), milk (1570 mg/kg), alcoholic beverages (320-920 mg/kg), coffee (880 mg/kg) and tea (170 mg/kg) are the main sources. Potassium is normally found in fruit and vegetables as potassium citrate, potassium phosphate and other salts but only to a minor degree as potassium chloride. As a consequence of food preparation (steaming, boiling, chopping up) potassium losses of between 20 and 50% may occur (Egan et al., 2002; Food Standards Agency, 2001; Grossklaus, 1991; 1992; Helmke and Ney, 1992; Irmscher et al., 1988; Kersting et al., 2001; Kimura and Itokawa, 1990; Kopyt et al., 1985; Manthey, 1989; Souci et al., 2000).

Mature human milk (n=133) contains 480 ± 11 mg potassium per litre, and the concentration is relatively stable between the 6th and 12th month post-partum (Wack et al., 1997).

Food supplements: We do not know whether manufacturers of food supplements actually add potassium. Potassium is, however, an accompanying cation of compounds like potassium iodate or potassium-L-ascorbate. This is also backed by the fact that the difference in the mean values for potassium intake between men and women, who never or who take food supplements more than once a week was only 210 and 120 mg, particularly since these individuals are normally more health conscious and had a high nutrient diet (Mensink and Ströbel, 1999).

Medicinal products: Potassium-containing coated tablets, tablets or effervescent tablets containing a dose of 50-100 mmol (1955-3910 mg) per day are authorised as pharmacy-only medicinal products for the treatment of hypocalcaemia (potassium deficiency syndrome). However, the daily dose should be broken down into several oral doses of no more than 20 mmol (782 mg). The medication should be taken at meal times in an upright position with sufficient fluid (BGA, 1991; Fachinformation Abbott, 2001; Fachinformation AstraZeneca, 2002). In the clinical area high potassium infusion solutions are normally administered parenterally as electrolyte concentrates to treat potassium deficiencies. Here the dose corresponds to the analytical values of the serum ionogram and acid-base status (Fachinformation Braun, 2002; Hartig, 1994).

Nutritional status:
Measurement parameters/biomarkers: At present there are no validated biomarkers to assess adequate potassium supply. Disruptions of the potassium status are diet driven only in the rarest cases and are largely balanced by the kidneys, the main regulatory organ of water and electrolyte status. The normal serum concentration (reference range) is 3.5-5.5 mmol/l*); concentrations below 3.5 mmol/l are a sign of hypokalaemia whereas values >5.5 mmol/l point to hyperkalaemia (Tietze, 1995). The serum concentration is, however, less indicative of potassium status and total body potassium status as the serum potassium concentration is influenced by many factors (pH of the extracellular fluid, energy metabolism of the cell, sodium status, renal function). In the case of a potassium deficiency it may even be elevated. Hence rapid changes may occur in the serum potassium concentration for instance because of shifts in the pH of the plasma in conjunction with respiratory disorders as a consequence of hyperventilation or hypoventilation. A drop in the plasma pH by 0.1 triggers an increase of the potassium concentration in the serum of approximately 1 mmol/l. Rapid changes of this kind occur through an exchange between the intracellular space and the extracellular space without any change in total body potassium reserves (Allison, 1984; Hartig, 1991; Singhal et al., 1991).

Measurement of potassium excretion in 24-hour urine is an indicator of potassium homoeostasis. If potassium excretion is <25 mmol/24h a deficiency is likely, at <10mmol/24h there is definitely a deficiency. 50 mmol/24h indicate a normal potassium status. The kidneys easily adapt to low or high potassium doses over up to 2-3 weeks. However, minimal excretion is 5 mmol/24 h. Intakes <10-20 mmol/day can no longer be compensated (Preuss, 2001; Singhal et al., 1991).

Parameters, too, of the acid-base status only provide indications of potassium homoeostasis. The total body store and the so-called exchangeable potassium can only be determined through potassium isotope measurements. Intracellular potassium determination is difficult. One option are muscle cells with approximately 160 mmol potassium/l. However they do not reflect in every case similar changes in all other cells (Hartig, 1991; Sjogren et al., 1988).

*) Potassium values in the serum are on average 0.3 mmol/l higher than in the plasma as potassium is released from thrombocytes during coagulation in the gel tube (serum). The reference values in the plasma: 3.6-4.5 mmol/l.

Intake: According to the National Food Consumption Study (NFCS) (1985-1988) the medians (2.5-97.5 percentiles) of potassium intake for women (n=1134) and men (n=854) were 2860 (1440-4640) and 3300 (1930-5640) mg/day respectively (Heseker et al., 1994). Referred to age and gender the median values established for daily potassium intake (2.5-97.5 percentiles) were 2680 (1410-4520) mg in >65-year-old women whereas the intakes were 3260 (1730-5870) mg in 19-24-year-olds and 3210 (1730-5040) mg in >65-year-old men (Adolf et al., 1995). More recent corresponding data from the Nutrition Survey 1998 for a total of 4030 persons indicated a mean intake (95% confidence interval) of 3240 (3210-3270) mg/day (Mensink and Ströbel, 1999). In the EPIC Study a median (10-90 percentiles) of 3200 (2000-4800) mg/day was determined in men (n=20045) in two German cohorts using a 24h dietary protocol (Schulze et al., 2001). Ovolacto vegetarians (women/men 3196/4577 mg/day) consumed on average 50-90% more potassium than people on a mixed diet (women/men 2130/2709 mg/day) (Anke et al., 2003). According to the Nutrition Report 2000 both women and men in all age groups were below the estimated values for minimum intake (DGE, 2000). In adults with a central European diet, daily intake was 2-3 g corresponding to 50-75 mmol per day. Under normal life conditions this amount is adequate (D-A-CH, 2000).

In the DONALD Study adequate potassium intake was observed in children and adolescents too. For instance the median (10-90 percentile) of potassium intake was 3159 (2423-6096) and 2657 (1810-3770) mg/day (Kersting et al., 2001) in 15-18 year-old male and female adolescents respectively.

Similar data were available from the United Kingdom. In food consumption surveys an average potassium intake of 2434-3187 mg/day was determined in the population (Food Standards Agency, 2001). In the USA, too, potassium status is adequate as confirmed by the Total Diet Study of the FDA (Egan et al., 2002).

Potassium concentration in the serum/potassium excretion in urine: In a representative random sample of the VERA Study linked to the National Food Consumption Study, the medians (2.5-97.5 percentiles) of the potassium concentrations in the serum of over 18-year-old men (n=836) and women (n=1097) were 4.199 (3.599-5.099) and 4.199 (3.499-5.099) mmol/l respectively. With increasing age a minor, statistically confirmed increase in potassium concentration in the blood serum could be observed (Erdinger et al., 1995).

The medians (2.5-97.5 percentile) of potassium excretion in 24-hour urine measured in these men and women were 76.45 (31.02-135.5) and 64.73 (27.1-113.8) mmol/24 h respectively. The values of the men were higher than those of the women in all age groups. Potassium excretion increased up to the 5th life decade (only significantly in women) and then fell slightly. The proportion of unfavourable excretion values (limit value for men <47 mmol/24 h and women <39 mmol/24 h) fell, but was only statistically signifiant in men, with increasing age from 16.5% amongst 18-24-year-olds to 4.8% amongst the over 65s. The prevalences derived from the limit values do not, however, say anything about the frequency of a deficiency risk. This question must be examined in conjunction with the overall status situation. Generally speaking it was shown that potassium intake determined to a major degree daily excretion in men and women. A clear increase in potassium excretion could be linked to a higher intake of potatoes, vegetables, fruit and milk (Erdinger et al., 1995).

6.3 Risk characterisation

6.3.1 Hazard characterisation (NOAEL, LOAEL)

Potassium, which is taken up as a natural ingredient from food, does not constitute a risk to healthy individuals (without medically or medicinally related disturbances of potassium excretion in urine). However, adverse reactions were observed in conjunction with excessive potassium intake from other sources (medicinal products, supplements or potassium-

containing table salt substitutes) in which various potassium salts are used for therapeutic purposes. For this reason a **Tolerable Upper Intake Level (UL)** cannot be derived on the basis of dietary potassium.

Hence, a distinction must be made in conjunction with hazard characterisation between:

1. Acute potassium intoxications as a consequence of intentional or unintentional intake of large amounts of potassium salts
2. Gastro-intestinal side effects after supplementation
3. Disturbances of potassium homoeostasis

on 1: Potassium intake from conventional foods has not led to any adverse effects in healthy consumers up to now particularly as healthy kidneys excrete excess potassium. However, if there is sudden enteral or parenteral intake of excess amounts of potassium salts, this may lead to a shift in the Na and K-ion balance with severe signs of intoxication. There are case reports in which mostly potassium chloride in tablets or potassium-containing table salt substitutes were taken in amounts of 6 to 94 g either by people intending to commit suicide or unintentionally. The individuals initially suffered nausea, vomiting, severe stomach pains and diarrhoea (Kallen et al., 1976; Restuccio, 1992; Riccardella and Dwyer, 1985; Su et al., 2001; Wetli and Davis, 1978).

SCF gives as an upper limit for acute toxicity an intake of 450 mmol/day (17.5 g/day). In healthy adults this leads to **hyperkalaemia**, i.e. an increase in the serum potassium concentration (above 5.5 mmol/l) (SCF, 1993). Values from 6.5 mmol/l are life-threatening, above 8 mmol/l mostly fatal as a consequence of ventricular arrhythmias followed by ventricular fibrillations or diastolic cardiac arrest (see also 6.3.4.1 excessive intake). However, intake of 150 mmol/day (5.9 g/day) may be dangerous in individuals who suffer from renal disorders and abnormal potassium retention without knowing it (Swales, 1991). Infants react more sensitively already at a dose of 1.5 g/day (Wetli and Davis, 1978). In fatal cases of hyperkalaemia, mucosa damage (ulcerations) and stenoses in the gastro-intestinal tract were observed because of high local concentrations (Peeters and Van Der Werf, 1998).

on 2: Potassium salts may trigger irritation and tissue damage at higher local concentrations. In the case of medicinal use of potassium chloride-containing tablets gastro-intestinal side effects like heartburn, nausea, vomiting, stomach pain and diarrhoea are frequently mentioned. In rare cases ulceration (ulcers), perforation and stricture/stenosis (narrowing) of the oesophagus or the small intestine, gastro-intestinal bleeding and skin rashes were observed (Fachinformation AstraZeneca, 2002; Lambert and Newman, 1980; Lawson, 1975; Leijonmarck and Räf, 1985; Skoutakis et al., 1984). The responsible factors are the easy solubility of the tablets and high local concentrations after administration. McMahon et al. tested the effects of potassium chloride (KCl) in wax capsules compared to potassium chloride in microcapsules in the gastro-intestinal mucosa in a controlled clinical study involving healthy test persons (n=48). Over a period of 7 days half of the test persons were given 1248 g (32 mmol) potassium as potassium chloride embedded in the wax substance 3 times a day whereas the other half were given the same doses of potassium chloride in microcapsules. The majority of the wax substance test persons (18 out of 24 test persons) showed clear endoscopically detectable damage to the gastro-intestinal mucosa in the study. In some cases there were even ulcers and lesions. The development of gastro-intestinal damage of this kind correlates closely with the pharmaceutical processing of the preparations and the transit time of the medicinal product. Potassium encapsulated in wax is rapidly released and can damage the mucosa at high local doses. By contrast, microcapsules only release their content slowly. The potassium is distributed and the physical contact with

the sensitive mucosa is minimised (McMahon et al., 1982). This study was repeated two years later in 225 test persons. It was confirmed that potassium encapsulated in wax causes more damage in the upper gastro-intestinal tract (McMahon et al., 1984).

In a controlled clinical trial involving 36 healthy adults over 8 days, no differences in the occurrence of erosions or ulcerations in the upper gastro-intestinal tract were observed at a dose of 70 mmol potassium/day (broken down into 5 individual doses) of potassium magnesium citrate compared with potassium citrate and placebo (Gonzalez et al., 1998). Modern preparations with delayed release are less dangerous. It is, nevertheless, recommended that the daily dose be broken down into several individual doses (maximum 20 mmol (782 mg) K^+/single dose) and taken at meal times with sufficient fluid, without chewing and seated in an upright position (Arnold et al., 1980; Fachinformation Novartis Pharma, 2002; Lowance et al., 1982; Senel et al., 1991; Skoutakis et al., 1984).

on 3: Disturbances of potassium homoeostasis are life-threatening because of the onset of hyperkalaemia and related complications. However, there are difficulties when setting the dose which leads to hyperkalaemia in healthy test persons as this depends not only on the amount ingested but also on potassium reserves and clearance time. Consequently, studies in which high doses of potassium were administered intravenously or to treat hypokalaemia or other clinical conditions cannot be used to derive a UL. The potassium concentration in the serum only reflects a very small fraction of the total body potassium store. In the case of normal potassium content in the body far less potassium must be ingested in order to increase the potassium concentration in the serum than in the case of emptied stores. This is because they first have to be refilled before a corresponding increase in the serum can be observed. In the case of the administration of potassium in concentrated form as a solution or supplement, there is a faster increase in the potassium concentrations in the serum than when larger amounts of potassium are ingested with food (Hene et al., 1986; Rabelink et al., 1990).

BfR is of the opinion that for the identification of the **LOAEL** (Lowest Observed Adverse Effect Level) or **NOAEL** (No Adverse Effect Level), the increase in the serum potassium concentration after oral exposure to potassium salts in healthy test persons at which health disorders may occur should be taken as the critical endpoint. After taking a high dose of on average 6.65 g (170 mmol) potassium in the form of potassium chloride or $KHCO_3$ of 60-100 mg potassium (1.5-2.5 mmol) per kg body weight, there was an increase in the serum potassium concentrations from 4.5 to 6.7-8.7 mmol/l in 7 normal adult test persons after 2-3 hours. At the same time, paraesthesis occurred in the hands and feet during this period with the exception of one test person with the lowest increase in the serum value to 6.7 mmol/l. In 3 of these test persons ongoing typical ECG changes (peak T wave) were observed as an expression of the influence of the potassium excess on cardiac activity. Aside from one test person the symptoms observed, including the ECG changes, continued over 3 hours and disappeared when the serum potassium concentrations returned to normal (Keith et al., 1942). The same authors administered 1.94 g (50 mmol) in the form of $KHCO_3$ and 27 to 43 mg potassium (0.7-1.1 mmol) per kg body weight as a bolus on an empty stomach to 5 further healthy test persons aged between 16 and 59. In 4 test persons there was a slight increase in the serum potassium concentrations from 4.3 to 4.8 on an empty stomach to 5.0 up to 5.4 mmol/l after 30 to 90 minutes. After 3 hours these values fell and returned to initial stomach values of between 4.2 and 4.7 mmol/l after 8 hours. Compared to the higher dose, a discrete increase in the serum potassium concentrations and the typical peak T waves in the ECG were observed but not any toxic side effects like paraesthesis in the hands and feet (Keith and Osterberg, 1946). In another older study involving 12 normal test persons, no increase in the potassium concentration in the serum was observed at a dose of 22 mg potassium (0.56 mmol) per kg body weight. However at a dose of 44 mg (1.12 mmol) per kg body weight there was also a slight increase (Zwemer and Truszkowski, 1936). Minor increases in

the serum from 4.75 to 5.75 mmol/l were also found after single oral exposure (67 mmol and 1 mmol/kg body weight) in test persons (n=2) with normal kidney function. However, the same dose led to an extensive ongoing hyperkalaemia (>6.5 mmol/L) (Winkler et al., 1941) in patients with acute or chronic nephritis (n=5). In the case of patients with chronic renal insufficiency hyperkalaemia was already triggered at a load of 0.5 mmol/kg body weight (Perez et al., 1984).

3.5-5.5 mmol/l are deemed to be normal values (Tietze, 1995). Single oral administration of 0.5 mmol K^+/kg body weight did not lead to any increase in the potassium concentration in the serum in healthy test persons whereas doses of 1 mmol/kg body weight did trigger a minor hyperkalaemia and already typical ECG changes without any other side effects. However it was only at doses of more than 1.5 mmol/kg body weight that there were cases of clear hyperkalaemia with typical ECG changes (peak and high T waves) and clinically relevant side effects (Keith et al., 1942; Perez et al., 1984; Schwartz, 1955). Transient hyperkalaemia was also observed postprandially in healthy test persons who were given large amounts of potassium (5 mmol/kg body weight) with a liquid formula diet over 5 days. The potassium concentrations in the serum after the meal were temporarily between 5 and 6 mmol/l without any other symptoms being observed (Gennari and Segal, 2003).

Based on the studies by Keith et al. (1942), the LOAEL in adults as resulting in a disturbance potassium homoeostasis is 4200 mg (107 mmol) and 1.5 mmol/kg body weight per day for potassium from additional intake from supplements. The NOAEL is 1400 mg (36 mmol) and 0.5 mmol/kg body weight and day (Perez et al., 1984; Schwartz, 1955; Zwemer and Truszkowski, 1936).

It must be noted that the data come from different studies and, in some cases, different patients. Furthermore, the serum potassium concentrations were obtained using various older methods and cannot, therefore, be directly compared with today's reference values. The trend towards the changes in values measured after oral exposure are, however, mostly comparable with other methods (Tietze, 1995). To that extent there is a some uncertainty in the quantitative risk assessment about what should be taken into account when deriving the UL.

6.3.2 Deficiency, possible risk groups

6.3.2.1 Deficiency

Only in the rarest cases diet is for a potassium deficiency responsible. A potassium deficiency is characterised by a reduction in the total potassium store of the body whereby hypocalcaemia, i.e. a potassium concentration in the serum <3.5 mmol/l, is not obligatory and normally occurs in combination with alkalosis (as a cause or consequence). In the extracellular space the potassium concentration may either be reduced, normal or elevated (Hartig, 1994; Kamel et al., 1990; Sjogren et al., 1988).

Potassium deficiency may be triggered by

- inadequate intake
- increased renal excretion (diuretics, renal insufficiency, osmotic diuresis in conjunction with diabetes mellitus
- elevated gastro-intestinal losses (vomiting, diarrhoea, fistula) or
- increased intracellular potassium uptake (acidosis treatment, glucose insulin therapy)

In the case of mild hypokalaemia (serum potassium 3.0-3.5 mmol/l) there are scarcely any symptoms. However, there may already be cardiac dysrhythmia. The ECG reveals QT prolongations and TU fusions which are, however, non-specific. In contrast to the typical ECG

changes in hyperkalaemia they are not so helpful when it comes to detecting hypokalaemia. Severe hypokalaemia (<2.5 mmol/l) goes hand in hand with general muscular weakness and frequently with atonia of the gastro-intestinal smooth muscles (obstipation down to paralytic ileus) (Agarwal et al., 1994; Allison, 1984; Hartig, 1994; Mandal, 1997; Preuss, 2001; Riggs, 1989; Stühlinger, 2003). Furthermore, as a consequence of reduced insulin secretion or insulin resistance there may be a disturbance of glucose tolerance which can be reversed by potassium supplementation (Helderman et al., 1983; Moldan et al., 1987; Norbiato et al., 1984; Plavinik et al., 1992).

6.3.3 Possible risk groups

Hypokalaemia is one of the most frequent electrolyte disorders in hospital. The main risk groups are older people. It is normally caused by inadequate food intake and frequent administration of medicines (diuretics, laxatives) (Allison, 1984; Bjerrum et al., 2003; Greenberg, 2000; Mandal, 1997; Paice et al., 1986; Riggs, 1989; Schwartz, 1975; Stühlinger, 2003; Touitou et al., 1987).

The data available for the Federal Republic of Germany on the nutritional status of potassium do not indicate any signs of inadequate potassium intake by healthy children, adolescents or adults (supply category 2/3). At present, there are no validated biomarkers for the assessment of adequate potassium supply. Older people with inadequate food intake and frequent administration of specific medicinal products are one particular risk group.

6.3.4 Excessive intake, possible risk groups

6.3.4.1 Excessive intake

Under normal circumstances the kidneys can excrete excess dietary potassium. Extrarenal regulation plays a more important role in the case of acute load. In the first 4-6 hours after acute potassium intake approximately 50% of the potassium is excreted by the kidneys. The other 50% is retained whereby more than 80% of this is transported to the cells. This uptake into the cells offers protection primarily against hyperkalaemia (Bia and DeFronzo, 1981). In the case of chronic exposure it takes between several days and 3 weeks for the kidney function to adapt to a potassium excess (Hené et al., 1986; Silva et al., 1977; Witzgall and Behr, 1986). In the case of chronic overload and disrupted renal function, more potassium is excreted by the colon (up to 30-40% of daily intake) (Brown, 1986; Hayslett and Binder, 1982; Mathialahan and Sandle, 2003; Powell, 1987; Silva et al., 1977). Sudden extremely high enteral or parenteral potassium exposure or parallel kidney damage is caused by an increase in total potassium store and the serum concentration in potassium (hyperkalaemia). Paradoxically, reduced intracellular potassium concentrations can be measured in uraemic patients as a consequence of a defect of Na^+/K^+-ATPase. Frequently, the cause is disturbed glucose tolerance as an expression of increasing insulin resistance and, by extension, reduced intracellular potassium intake in these patients (Bia and DeFronzo, 1981; Mathialahan and Sandle, 2003; Salem et al., 1991; van Ypersele de Strihou, 1977).

Causes of **hyperkalaemia** (>5.5 mmol/l) are:

- elevated intake
  (e.g. excessive oral or parenteral intake, potassium-containing table salt substitutes (Restuccio, 1992; Rimmer et al., 1987; Stühlinger, 2003));
- reduced renal potassium excretion
  (e.g. in the case of acute and chronic renal insufficiency, adrenal insufficiency (Addison's disease), induced by medicinal products (heparin, ACE inhibiters, potassium-saving diuretics, spironolactone, non-steroidal antiphlogistics, cyclosporine A) Gennari

and Segal, 2002; Greenberg, 2000; Hay et al., 2002; Jarman and Mather, 2003; Perazella and Mahnensmith, 1997; Perazella, 2000));

- distribution disturbance between the intracellular space and the extracellular space (e.g. in the case of respiratory and metabolic acidosis, trauma, burns, rhabdomyolysis, acute haemolysis, potassium is released from the tissue (Allison, 1984; Clark and Brown, 1995)).

Acute hyperkalaemia manifests far clearer symptoms and a more severe clinical course than chronic hypercalaemia (habituation effect) on a comparable scale. Acute renal failure is almost always accompanied by hyperkalaemia, particularly in the case of extensive catabolism (operation, stress, steroid treatment) or tissue decomposition (haemolysis, infection, burns). Parallel acidosis also means a disturbed distribution.

The main disorder are neuromuscular changes. The patients complain about general muscle weakness (e.g. "heavy legs") and in extreme cases there may be paralysis. Other symptoms are paraesthesis of the hands and feet, respiratory disorders through muscle weakness and, above all, disruptions of cardiac activity (reduction of contractility as a consequence of disturbed conduction, arrhythmia). Symptoms may already occur at serum concentrations >5.5 mmol/l. In contrast to hypokalaemia, the ECG changes in hyperkalaemia are very typical. The scale of these changes depends on the potassium level in the serum. At a potassium level of 5.5-6.5 mmol/l the typical peak and high T waves occur across the chest wall (30% of all cases). In the case of advancing hyperkalaemia (6.5-7.5 mmol/l), there may also be a slowing down of the PQ interval and a broadening of the QRS complex. In the case of severe hyperkalaemias (>7.5 mmol/l) life-threatening situations (pre-final ventricular tachycardia, ventricular fibrillations and finally diastolic cardiac arrest) are to be expected. Concomitant hypokalcaemia, acidosis and hyponatraemia have an additive effect (BGA, 1991; Clark and Brown, 1995; Gross and Pistrosch, 2003; Mandal, 1997; Stühlinger, 2003).

In healthy adults (70 kg body weight) the maximum excretion ability of the kidneys in the case of acute exposure is 200 mmol (7.8 g) and 2.85 mmol/kg body weight, in the case of chronic exposure 350 mmol (13.7 g) and 5 mmol potassium/kg body weight before hyperkalaemia can occur with severe signs of intoxication. The acute lethal dose of potassium salts is 10-20 g (Hartig, 1994; Mutschler, 1972; NRC, 1989; Preuss, 2001). However, particularly in the case of patients with reduced neurofunction but also with adrenal insufficiency or cirrhosis of the liver, far smaller amounts of 30-50 mmol (1,173-1,954 g) and 0.5 mmol potassium/kg body weight can lead to balance disruptions with potassium retention and intoxication. Patients with chronic renal insufficiency manifest hyperkalaemia in up to 55% of cases (Gennari and Segal, 2002; Mathialahan and Sandle, 2003; Perez et al., 1984). In patients of this kind with disturbances of the potassium status, constant controls of serum potassium level and potassium intake from food are necessary. For that reason it is essential to limit the potassium intake of patients with chronic renal insufficiency and dialysis patients to 1.5-2.8 g/day (Alpers et al., 1983; Clark and Brown, 1995; Großklaus, 1991).

False high potassium values, so-called pseudo hyperkalaemia, are found in conjunction with overly long tourniquet use when taking a blood sample, haemolytic samples (destruction of the red blood cells) or overly long storage of blood. Very strong lipaemic samples can produce false low potassium values in the determination (Clark and Brown, 1995; Preuss, 2001; Tietze, 1995).

6.3.5 Possible risk groups

Infants are more sensitive to excess potassium intake because their kidneys are not mature. The risk group for excess potassium intake includes people with undiagnosed renal function disorders, in particular older people, diabetics with disruptions of the autonomous cardiovas-

cular function, patients with cardiac insufficiency or renal insufficiency and hypoaldostoeonism, as well as people with an inclination to acidosis and alcoholics (Clark and Brown, 1995; Gennari and Segal, 2002; Jarman and Mather, 2003; Perazella and Mahnensmith, 1997; Perez et al., 1984; Swales, 1991).

6.4 Tolerable upper intake level for potassium

SCF has not yet submitted any risk assessment for potassium or set a tolerable upper intake level (UL) (European Commission, 2003). As chronic intakes of more than 150 mmol (5.9 g)/day could be dangerous for individuals with an undiagnosed renal function disorder (Swales, 1991), this level has been proposed up to now by SCF as the upper safe level of intake (SCF, 1993). The UK Expert Group on Vitamins and Minerals (EVM) was unable to establish a safe upper level (UL) because of the lack of data. The observed side effects are obviously dependent on the dose and composition of the supplements. Based on the dose (8 mmol per capsule and 96 mmol per day) used over two years in the intervention study by Grimm et al. (1988; 1990), EVM deems a so-called guidance level of 3700 mg potassium per day for the purposes of supplementation to be adequate for adults (Food Standards Agency, 2002; 2003). In this study side effects like stomach pain, nausea, vomiting, diarrhoea and blood in faeces were observed equally in both groups (potassium supplements and placebo) after 12 weeks. However "stomach pain" occurs significantly more frequently (p 0.25) after the administration of potassium chloride supplements. It is also noted that in around 10% of the test persons the dosage regimen had to be changed during the study because of the side effects that occurred without any more details being provided (Grimm et al., 1990). However, EVM does not rule out either that at this amount (3700 mg per day) endoscopically visible gastro-intestinal damage could occur (Food Standards Agency, 2003).

BfR is of the opinion that the intervention study by Grimm et al. (1988; 1990) mentioned above is not suitable in order to set such a high, so-called guidance level for supplementation as adverse reactions could not be ruled out at all with this high amount of potassium in concentrated form. Both the possible damage to mucosa in the gastro-intestinal tract as well as life-threatening hyperkalaemia must be taken into account as hazard potential when deriving a **Tolerable Upper Intake Level (UL)**. BfR has, therefore derived a UL of 1000 mg (26 mmol) for **additional** intake based on a NOAEL of 1400 mg and an uncertainty factor (UF) of 1.4. This derivation does not apply to potassium which is normally (naturally) contained in foods. A UL for potassium for intake from all sources (foods + drinking water) could not, therefore, be indicated. The use of an UF of 1.4 reflects the uncertainty in data collection (age distribution, state of health of test persons). Given the lack of data for children aged between 1 and 3, the UL applies to children from age 4 upwards, adolescents and adults. As a precautionary measure BfR recommends breaking down the total dose into 2 or 3 doses per day because otherwise possible damage to the gastro-intestinal mucosa cannot be ruled out. For the same reason, potassium-containing compounds should only be used in micro-encapsulated form (Arnold et al., 1980; Fachinformation Novartis Pharma, 2002; Lowance et al., 1982; Senel et al., 1991).

In contrast to potassium-containing food supplements or medicinal products, no high local concentrations and therefore no damage to mucosa are to be expected because of the dilution effect when used in foods. Nor were there any reports of hyperkalaemia following acute or chronic load with potassium from natural foods in healthy individuals without any potassium excretion disorders either. The maximum excretion rate after habituation to high potassium dietary intake was estimated to be 31.3 g (800 mmol) per day in adults, a level that cannot be achieved solely through food. For that reason the Food and Nutrition Board has not set a UL for dietary potassium intake for adults. However, FNB is of the opinion that, given the existing acute toxicity in healthy individuals, potassium-containing supplements should only be administered under medical supervision (FNB, 2004).

6.4.1 Derivation of a maximum level (TL_{NEM}) for potassium in food supplements

6.4.1.1 Possible management options

a) Maintenance of the existing opinion that potassium should not be added for nutritional-physiological purposes to food supplements as several conventional and easily available foods contain significant amounts of potassium. Therefore, the need for additional intake via food supplements is questionable (BgVV, 2001) and the majority of the population is more than adequately supplied with potassium. Independently there is the option of administering potassium-containing medicinal products under medical supervision (FNB, 2004).

   Advantages: For sensitive groups of people, i.e. older people with restricted renal function, there is no risk of hyperkalaemia in conjunction with the uncontrolled taking of potassium-containing food supplements.

   Disadvantages: It cannot be ruled out that some consumers have an inadequate potassium intake.

b) Taking over of the so-called guidance level of 3700 mg for supplements like in the United Kingdom (Food Standards Agency, 2003).

   Advantages: Targeted supplementation via food supplements would be possible.

   Disadvantages: This amount is in the therapeutic dose range of pharmacy-only medicinal products (50-100 mmol (1955-3910 mg) per day) for the treatment of potassium deficiency. If this guidance level is applied, gastro-intestinal side effects, in particular mucosa damage and bleeding, cannot be ruled out as this amount is higher than the maximum tolerable single dose of 20 mmol K^+ (782 mg) in potassium-containing products (Fachinformation Novartis Pharma, 2002; Skoutakis et al., 1984). Because of the risk of hyperkalaemia in individuals with potassium status disorders, particularly in the case of chronic renal insufficiency, a corresponding warning would be required (cf. § 23 of the Ordinance on Foods for Special Dietary Purposes [DiätVO]). The US Food and Drug Administration calls for a warning for potassium-containing OTC (Over The Counter) medicinal products. According to this, people with a renal disorder and individuals with a low potassium diet should first consult their doctor before taking a product containing more than 975 mg potassium in the maximum daily dose (FDA, 2004).

c) Setting of a recommended maximum level (**TL_{FS}**) at 500 mg based on the UL of BfR for **children (>4 years), adolescents and adults**

   If the procedure proposed in Chapter 3.3.2 is used to determine the tolerable intake (**TL_{FS}**) of potassium in individual food supplements, then this leads to the following value with an assumed Multi Exposure Factor (MEF) of 2:

$$\frac{1000\ \text{mg}^{*}\ [\text{UL}] - 0\ \text{mg}^{**}\ [\text{DINF}]}{2\ [\text{MEF}]} = 500\ \text{mg}\ [\mathbf{TL_{FS}}]$$

* UL of BfR
** The value zero is to be used here because the UL does not apply to intake from all sources but only targeted additional intake.

Legend:

UL	=	Tolerable Upper Intake Level (SCF) usually referring to the daily total intake
DINF	=	Dietary Intake by Normal Food (95. or 97.5 percentile)
MEF	=	Estimated Number of Consumed Products
TL	=	Tolerable Level in a single dietary supplement

Advantages: Consumers have the option, in the case of inadequate dietary intake, of supplementing their requirements for potassium with a significant amount (25% of the Reference Labelling Value (RLV)) proposed for the purposes of nutrient labelling (SCF, 2003). It is not to be expected that gastro-intestinal disorders will occur in particularly sensitive consumers at this dose. Nor is there a risk of hyperkalaemia which means that no warnings are needed for individuals with restricted renal function or renal insufficiency. On preventive health protection grounds potassium chloride should be used in microencapsulated form in food supplements in order to facilitate delayed release (Arnold et al., 1980; Lowance et al., 1982; Senel et al., 1991).

Disadvantages: None

6.4.2 Derivation of a maximum level (TL_{FS}) for potassium in fortified foods

Up to now potassium compounds have only been approved as food additives for technological purposes in foods in general or restricted to specific foods with the laying down of maximum levels. When using potassium compounds for nutritional-physiological purposes, minimum and maximum levels were only laid down for specific products for particular nutritional purposes. According to the Ordinance on Foods for Special Dietary Purposes (DiätVO) at least 60 and at most 145 mg potassium/100 kcal may be added to infant formula and a maximum of160 mg potassium/100 kcal to complementary foods. In accordance with the requirements to be met by foods for a low calorie diet for the purposes of weight loss, a daily portion must contain 3100 mg potassium. In the case of foods for special medical purposes which are intended for infants or others, the rule is at least 60 and 80 and at most 145 and 295 mg potassium/100 kcal. According to the Proposal for a Regulation of the European Parliament and Council of 10 November 2003 (KOM (2003) 671 final), potassium compounds may also be added in future to conventional foods for nutritional purposes. This applies to both restoration and fortification.

a) Continuation of existing practice
i.e. that fortification of foods is not necessary as numerous conventional and easily available foods contain significant amounts of potassium. The need for food fortification is, therefore, questionable (BgVV, 2001) and the majority of the population has an adequate supply of potassium.

Advantages: There is no risk of hyperkalaemia for sensitive groups of individuals, e.g. older people with restricted renal function.

Disadvantages: New scientific findings on health-promoting properties of a rich potassium diet advocating a reduction of salt are not taken into account, particularly for

groups of individuals who do not eat enough fruit or vegetables. However, it is not deemed reasonable to adjust potassium intake to high sodium intake as processed foods often contain too much sodium.

b) Setting of a maximum tolerable level per portion of 15-30% of the Reference Labelling Value (RLV of 2000 mg (SCF, 2003) proposed for the purposes of nutrient labelling.

A restriction of the maximum level to 15-30% of the RLV is based on the assumption that it will not be possible in the foreseeable future to estimate the proportion of products fortified with potassium on the market. If only a few products are fortified, it is recommended that the tolerable maximum intake level per portion be set at 30% of the RLV. Were the market share to rise, this should be more restrictive for reasons of preventive health protection and the maximum level should be set at 15% of the RLV. At doses of more than 30 up to 100% of the RLV, i.e. more than 600-2000 mg per person, warnings would have to be required in each case for sensitive groups of individuals.

Advantages: Targeted fortification of processed foods would be possible in order to achieve an optimum sodium/potassium ratio in processed foods. It is not to be expected that gastro-intestinal disorders will occur in particularly sensitive consumers at this level (300-600 mg). Nor is there a risk of hypercalaemia which means that no warnings are necessary for people with limited renal function or renal insufficiency.

Disadvantages: A reduction of the salt content in processed foods should be the precondition for the adding of specific potassium compounds. The extent to which this could lead to sensory or even hygienic disadvantages should be determined in prior examination and testing of foods adapted in the nutrient profile.

c) Addition of potassium compounds for the purposes of restoration

In processed foods the restoration option should be used to a greater degree since considerable amounts of water-soluble potassium compounds can be lost during processing (Irmscher et al., 1988; Kimura and Itokawa, 1990).

Advantages: Compensation of potassium losses improves the nutritional-physiological quality of processed foods. The addition is oriented towards the level of losses and the average natural potassium content of an unprocessed food. There is no need to set maximum levels. There is no risk of hyperkalaemia for possible risk groups.

Disadvantages: None

In the opinion of BfR there is a high health risk of adverse reactions when potassium is used in food supplements. In the case of fortification of food with potassium there is, under certain circumstances, a high risk for individuals with reduced potassium excretion. For reasons of preventive health protection BfR recommends setting the maximum tolerable level for food supplements at 500 mg (Option c) and foregoing any targeted fortification of foods (Option a). Instead, greater use should be made of the restoration option in processed foods as considerable amounts of water-soluble potassium compounds can be lost during processing (Option c). As a preventive measure, if possible this should go hand in hand with a parallel reduction of salt content.

6.5 Gaps in knowledge

- There are no reliable data about actual potassium requirements, particularly taking into account an optimum sodium/potassium ratio in food.
- There are no validated biomarkers to record potassium nutritional status over longer periods.
- There is great uncertainty about the gastro-intestinal tolerance of potassium salts in concentrated form in food supplements.

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7 Risk Assessment of Calcium

7.1 Summary

The data on the calcium intake of the German population indicate a trend towards higher average intake than 20 years ago. New studies, which could confirm this trend, are not available. Nor do we know what proportion of the population increases its calcium intake through supplements or fortified foods.

Besides at least 10% of the population with very low calcium intake (= 60% of recommended intake), there is an equally large proportion with calcium intake far higher than recommended intake or even higher than the UL. Both status situations hold long-term health risks.

BfR is of the opinion that the best way of improving inadequate calcium intake is by taking calcium supplements with a daily maximum level of 500 mg if a change in diet is not possible or not wished. The fortification of foods with calcium should be restricted to a few foods. However, there is no suitable carrier food which could solve the problem of calcium deficiency with any degree of foreseeable reliability. Substitutes for dairy products, which contain the same concentration of calcium, or beverages which are clearly labelled and carry instructions on consumption, are the preferred management options according to BfR.

Recommended intake	1000-1200 mg/day	
Intake [mg/day] (Mensink et al., 2002)	**m**	**f**
Median	950-1400	970-1120
P 10	590-790	580-690
P 90	1560-2550	1670-1790
Tolerable Upper Intake Level (SCF, 2003)	Adults 2500 mg/day does not apply to children or adolescents	
Proposal for **maximum level** in:		
Food supplements	500 mg	
Fortified foods	Substitutes for dairy products or especially labelled beverages (30% NRV/100 g/ml)	

7.2 Nutrient description

7.2.1 Characterisation and identification

Calcium is in Group II of the third period of the periodic system with the atomic number 20. It has an atomic mass of 40.08 and a valence of two. It is the fifth most frequent element which occurs in the human body and is essential for man.

Several calcium compounds may be added to foods for technological and nutritional purposes.

The following are allowed for technological purposes: calcium carbonate and calcium hydrogen carbonate (E 170; CAS No. 471-34-1), the calcium salts of cyclohexane sulphamic acid (E 952) and saccharin (E 954), calcium acetate (E 263; CAS No. 62-54-4), calcium ascorbate (E 302; CAS No. 5743-27-1), calcium lactate (E 327; CAS No. 814-80-2), calcium citrates (mono-, di- and tri-) (E 333; CAS No. 813-94-5), calcium malate and calcium hydrogen ma-

late (E 352; CAS No. 17482-42-7), calcium tartrate (E 354; CAS No. 3164-34-9), calcium alginate (E 404; CAS No. 9005-35-0), calcium salts of edible fatty acids (E 470a), calcium chloride (E 509; CAS No. 10043-52-4), calcium sulphate (E 516; CAS No. 7778-18-9), calcium hydroxide (E 526; CAS No. 1305-62-0), calcium oxide (E 529; CAS No. 1305-78-8), calcium gluconate (E 578; CAS No. 299-28-5), calcium phosphates (mono-, di- and tri-) (E 341, CAS No. 7758-23-8, CAS No. 7757-93-9, CAS No. 7758-87-4), dicalcium diphosphate (E 450), calcium dihydrogen diphosphate (E 450), calcium polyphosphate (E 452), calcium disodium ethylene diamine tetraacetate (E 385; CAS No. 62-33-9), calcium stearoyl-2-lactylate (E 482; CAS No. 5793-94-2), calcium ferrocyanide (E 538; CAS No. 13821-08-4), calcium silicate (E 552; CAS No. 1344-95-2), calcium aluminium silicate (E 556; CAS No. 1327-39-5), calcium diglutamate (E 623; CAS No. 5996-22-5), calcium guanylate (E 629), calcium inosinate (E 633), calcium-5-ribonucleotide (E 634), calcium sorbate (E 203; CAS No. 7492-55-9), calcium benzoate (E 213; CAS No. 2090-05-3), calcium sulphite (E 226; CAS No. 10257-55-3), calcium bisulphite (E 227; CAS No. 13780-03-5), calcium propionate (E 282; CAS No. 4075-81-4), whereby application constraints or maximum levels have been set for individual additives (Additives Approval Ordinance of 29 January 1998, last amended on 20 December 2002).

For nutritional-physiological purposes only carbonate, chloride, citrates, gluconate, lactate, orthophosphate, hydroxide and glycerophosphate (CAS No. 27214-00-2) may be added to foods as a source of calcium along with a few vitamins (pantothenic acid, vitamin C) whose calcium salts may be used (Ordinance on Foods for Special Dietary Purposes, Directive 2002/46/EC on the approximation of the laws of the Member States relating to food supplements).

7.2.2 Metabolism, function, requirements

Metabolism: The calcium content in the human body is 25-30 g at birth (0.8% of body weight) and 900-1300 g in adult men (up to 1.7% of body weight). 99% of calcium is found in bones, mainly in the form of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). It accounts for 39% of the total mineral content of bones (Weaver, 2001). A small proportion is found in the teeth, less than 1% of total calcium is found in other body tissue (~ 7 g) and body fluid (~ 1 g). Together with other minerals, calcium gives bone the strength to maintain the body in an upright position. Calcium in the skeleton also provides a reservoir for maintaining a steady calcium concentration in blood of 2.5 mmol/l (10 mg/dl) (range 2.25-2.75 mmol/l).

Depending on the pH around 50% of blood calcium is ionised, 45% is bound to blood protein and around 10% is available in complexes with citrate, phosphate, sulphate and carbonate. The levels of ionised calcium are homoeostatically controlled by three hormones, parathormone, 1,25-dihydroxycholecalciferol (1,25$(OH)_2$-D) and calcitonin. Calcium-sensitive receptors on the cell surface of various organs produce stimuli which, in turn, trigger cell-specific responses by means of a change in intracellular calcium content; this is tens of thousands of times lower than extracellular calcium content. It normally involves the activation of kinases which phosphorylate one or more proteins. In this way calcium is involved in muscle contraction, hormone secretion, neurotransmitter release, sight, glycogen metabolism, cell differentiation and proliferation.

Furthermore, calcium stabilises or activates certain enzymes without this being mediated by changes to the intracellular calcium content (blood coagulation, intercellular adhesion etc.).

Calcium must be taken up in sufficient amounts from food in order to be available for deposition in bones during growth and during life-long bone remodelling. It must also compensate for calcium losses through the intestines, kidneys and sweat.

Bone modelling through the combined effect of osteoclasts and osteoblasts permits bone growth and changes in bone shape. During growth osteoblast activity prevails. Peak bone mass is normally achieved in adolescence and early adulthood: 90% of total mineral content in the skeleton in girls up to the age of 16.9 ± 1.3 year, 99% up to age 26.2 ± 3.7 years (Teegarden et al., 1995). Maximum bone density is achieved in young women in the greater trochanter (14.2 ± 2.0 years) and femoral neck (18.5 ± 1.6 years) earlier than in the spine (23 ± 1.4 years) (Lin et al., 2003). In men this is around 1.5 years later (Martin et al., 1997). Actual bone density is inadequately characterised in individuals by bone mineral content. Physical activity, muscle mass, frame and size are important co-determining factors (Schönau, 2004). As people grow older bone resorption becomes more predominant than bone formation and there are losses of bone and mineral substance. In women the start of loss in the femoral neck was observed from age 37 and in the spine from age 48 (Hui et al., 1999).

Because of the regulation of blood calcium content, serum calcium content is not a yardstick for calcium nutritional status in man. Bone mineral content and bone (mineral) density and their changes over time can serve as indicators for the calcium status of adults whereas changes in bone mineral content in children may provide information about calcium retention.

Absorption: Already a minor drop in the serum calcium level leads to a counter-regulatory increase in calcium absorption, an increase in renal tubular reabsorption and the release of calcium from bones through the combined effect of parathormone and 1,25$(OH)_2$-D. An increase in intracellular ionised calcium, by contrast, inhibits the secretion of parathormone, the production of 1,25$(OH)_2$-D steered by this and stimulates the secretion of calcitonin by the thyroid gland. The result is reduced calcium absorption in the intestine, elevated renal calcium excretion and reduced release from bones.

Low dietary calcium intake leads to increased calcium absorption in the intestine. However, the increased absorption cannot compensate for chronically low calcium intake. Increased release from bones is necessary in order to maintain the calcium level in the blood.

Calcium is absorbed in the intestine via two mechanisms. Transcellular intake is dependent on parathormone and 1,25$(OH)_2$. It reacts to a lower level of ionised calcium. 1,25$(OH)_2$-D reacts with the vitamin receptor of the enterocytes and, in this way, stimulates the synthesis of a calcium transporter calbindin 9K (Fleet and Wood 1999). At a high calcium intake this transport mechanism is saturated. In addition, there is passive paracellular diffusion independent of parthormone and vitamin D. It follows an electrochemical gradient and is determined by the calcium concentration in the intestine.

We do not know which exact factors determine absorption: the parallel intake of calcium from food, casein phosphopeptides, fructooligosaccharides and possibly of lactose as well as distribution over several single doses seem to promote calcium absorption. Food constituents like oxalate and, more particularly, phytate inhibit calcium uptake by forming poorly soluble complexes (Weaver, 2001).

Fractional dietary calcium absorption is highest in breastfed children (60%) (Abrams et al., 1997). Similarly high values were only observed for calcium absorption from broccoli and kale (Weaver, 2001). Calcium absorption changes with age and, after infancy, it is most efficient in puberty. It then falls to 15-20% in adults (Matkovic, 1991; Miller et al, 1988; Peacock, 1991). The calcium balance in healthy children, adolescents and young adults is positive as long as there is sufficient calcium intake.

Calcium losses: Absorbed calcium, that is not stored in the bones, is excreted in urine, faeces and sweat.

Calcium excretion in urine is normally less than 4 mg/kg/day or less than 300 mg/day in men and less than 250 mg/day in women. It is the result of glomerular filtration and tubular reabsorption (more than 98% of the filtered amount). This occurs passively in the proximal and actively, controlled by parathormone, calcitonin and $1,25(OH)_2$-D, in the distal tubule (Hoenderop et al., 2002).

Calcium excretion in urine increases with increasing dietary calcium intake (Matkovic et al., 1995), with caffeine (Massey and Whiting, 1993), with high protein intake (Whiting et al., 1998) and in the case of chronic acidosis (Bushinsky, 2001). Renal calcium excretion is the mechanism which regulates the calcium content in extracellular fluid.

Individuals with idiopathic (hypocalcaemic) hypercalciuria, which constitutes the largest risk factor for kidney stone formation, show a higher sensitivity to table salt in respect of renal calcium excretion than normocalciuric kidney stone sufferers (Burtis et al., 1994; Massey and Whiting, 1995). They react to table salt and protein restriction with normalisation of renal calcium excretion (Borghi et al., 2002). Idiopathic hypercalciuria is a genetic abnormality of varying causes and of differing forms (absorptive, renal or dietary). It is said to affect 2.3% to 6.4% of all children and adults (Kruse et al., 1984; Moore et al., 1978).

Calcium losses through sweat vary in healthy individuals between 4 and 96 mg/day. The compulsory loss incurred is given as 3-40 mg/day (Charles et al., 1991).

Calcium is secreted in the gastro-intestinal tract. 85% of the secreted amount is available for reabsorption with the same efficiency as that of dietary calcium. The loss of secreted calcium in faeces is estimated to be 80-224 mg/day in healthy individuals.

Calcium is transferred in milk. Independent of the dietary calcium intake of lactating women, the calcium concentration in milk is between 275 and 315 mg/l (Oliveri et al., 2004).

Requirements: Calcium requirements result from the amount which is lost daily through urine, faeces and sweat and the amount which is necessary in order to achieve maximum retention of calcium in the bones. It is corrected by the calcium absorption rate (Matkovic and Heaney, 1992). These calculations were supplemented by studies on the development of bone density and bone mineral content throughout a lifetime (Heaney, 2002).

The population reference intakes of the Scientific Committee on Food (SCF, 1993) are based on a factorial approach to the compensation of losses adjusted for the absorption percentage. Both the Institute of Medicine (FNB, 1997), as well as the German-Austrian-Swiss Nutrition Societies (DGE/ÖGE/SGE/SVE, 2000) calculate their recommended intakes on the basis of the calcium intake required to achieve peak bone mass in childhood, adolescence and adulthood. The D-A-CH recommendations are given in Table 14:

Table 14: Recommended calcium intake

Age	mg/day
Infants	
0 - <4 months*	220
4 - <12 months*	400
Children	
1 - <4 years	600
4 - <7 years	700
7 - <10 years	900
10 - <13 years	1100
13 - <19 years	1200
Adults	
19 - >65 years	1000
Pregnant women**	1000
Lactating women***	1000

* Estimated value
** Pregnant women <19 years 1200 mg
*** Lactating women <19 years 1200 mg

The calcium requirements of the unborn child up to birth are approximately 30 g, 5g in the second trimester, 25 g in the third trimester. This means that in the third trimester 250 mg calcium on average are transferred daily via the placenta to the foetus. These additional requirements of pregnant women are covered by higher calcium absorption in the intestine and through increased calcium release from the bones after the first trimester and are mediated by hormonal changes. In the third trimester there is also an increase in bone turnover with a redistribution of bone mass from the trabecular to the cortical bones. In the case of adequate calcium intake in line with the age-based recommendations, the calcium balance is zero. However this does not apply to lower calcium intake or to pregnant adolescents.

During lactation 250 to 350 mg calcium are transferred via the milk. Breastfeeding for six months means a calcium release of 50-60 g calcium, around 6% of the total calcium body store of the lactating woman. In contrast to pregnancy there is no compensatory increase in calcium absorption in the intestine whereas bone turnover remains high. A six-month lactation period leads to an approximate 5% loss of bone mass, mainly of the spongy bones. However, this is normally restored within 6-12 months of weaning irrespective of the administration of calcium supplements. Only in the case of lactating women with a regularly low calcium intake (<800 mg/day) does calcium supplementation seem to promote an increase in bone density of the spine (Oliveri et al., 2004).

7.2.3 Exposure (dietary and other sources, nutritional status)

Sources:

Food: The calcium content of food varies considerably. The main sources of calcium are milk (120 mg/100 g) and dairy products (up to 1100 mg/100 g), from which on average 32% of calcium is absorbed (Weaver, 2001). Some plants are also good sources of calcium, e.g. some types of cabbage, almonds, dried apricots. Absorption from other high calcium plants like rhubarb or spinach is prevented by the high oxalate content (absorption 5-8%). Some drinking and mineral waters contain easily resorbable calcium. Calcium from calcium fortified fruit juices is as easily absorbable as calcium from milk (32%) and even more so when calcium citrate malate was used (52%) (Weaver, 2001).

Food supplements: Calcium-containing food supplements are widely available. The calcium amounts in the daily portion vary between 100 mg in combined products and between 500 and 1000 mg in monoproducts (Kersting and Alexy, 2000). No exact information is available about the percentage of the German population which takes calcium-containing food supplements.

Fortified food: Calcium is mainly added to fruit juice beverages and beverage powders, dairy products, sweets and ready-to-eat meals for nutritional-physiological purposes (Kersting et al., 1995). Nevertheless, the total daily intake of calcium from fortified foods was at most 5% in the DONALD Study (Sichert-Hellert and Kersting, 2001).

Medicinal products: Calcium-containing medicinal products are available with doses between 100 and 1000 mg per portion.

Nutritional status: The calcium intake in the population varies considerably depending on diet.

In the National Food Consumption Study (NFCS) and its sub-study VERA from 1985 to 1988, the calcium intake of men and women over the age of 18, amongst other things, was determined:

The median intake value was 683 mg/day (n=1134) for women and 753 mg/day (n=854) for men.

- The 2.5 percentile was 273 for women and 340 mg/day for men
- The 25 percentile was 516 for women and 577 mg/day for men
- The 75 percentile was 888 for women and 1009 mg/day for men
- The 97.5 percentile was 1421 for women and 1731 mg/day for men

According to this, three-quarters of women and more than half of men did not achieve the recommended calcium intake (Heseker et al., 1994).

The Nutrition Survey from 1997/1999 with 4030 test persons over the age of 18 determined a lower average calcium intake for the 1268 men and 1540 women who did not take any supplements of 1216 and 1099 mg/day respectively than for those who rarely (255 men, 380 women) or regularly (240 men, 347 women) took food supplements: 1303 (men) and 1148 (women) mg/day and 1334 (men) and 1184 (women) mg/day. 50% and more of the population achieved a calcium intake in line with the recommendations whereby food supplements accounted for maximum 10% of intake (Mensink and Ströbel, 1999). The main source of calcium was dairy products (45-50% of intake) and drinking water (10-20% of intake).

Calcium intake by gender and age is presented in Table 15.

Table 15: Calcium intake (mg/day) of German women and men (n=4030)

Age	Number	Mean value	Median	10 percentile	90 percentile
Women					
18-24	253	1206	1128	691	1789
25-34	471	1190	1118	647	1733
35-44	504	1175	1116	723	1667
45-54	381	1169	1114	672	1709
55-64	391	1122	1065	657	1770
65-79	267	1072	972	586	1722
Men					
18-24	205	1565	1395	790	2548
25-34	340	1370	1318	746	2105
35-44	382	1335	1189	766	2079
45-54	277	1274	1211	702	1871
55-64	346	1153	1117	636	1641
65-79	213	1020	948	590	1567

by age (18-79) according to the data of the Nutrition Survey (1997/1999) (Mensink et al., 2002)

In men calcium intake falls more with increasing age than in women. More than 10% of each age group of women and men has a lower calcium intake than recommended. In young women this deficit of 500 mg is particularly high. On the other hand, in each age group more than 10% take more calcium than is recommended. In young men the 90 percentile of calcium intake is 2500 mg/day (Mensink et al., 2002).

The calcium intake of children and adolescents in Germany is taken from the data of the Dortmund Nutritional and Anthropometrical Longitudinally Designed (DONALD) Study. Since 1985 it has longitudinally recorded data on eating habits in a cohort of infants, children and adolescents aged between 3 months and 18 years on a regular basis.

According to this, intake in the first year is on average and in the 10 percentile in the range of or above recommended intake. In the second and third years of life average calcium intake reaches and exceeds recommended intake; that of girls is just below this. From age 4 the average calcium intake of boys and of girls is below the recommended levels. The 10 percentile intakes of boys are 400 to 600 mg below recommended intake from age 7. This is similar in girls, but the difference between intake and recommendation is up to 800 mg/day. On the other hand, calcium intake in the 90 percentile in 13-18 year-old male adolescents is 500 to 900 mg higher than the recommendation (Alexy and Kersting, 1999). The main sources of calcium are dairy products - more than 50% in all age groups. Foods fortified with calcium contributed less than 5% to total calcium intake (Sichert-Hellert et al., 2001).

The available data on the calcium status of the German population show that, with the exception of the first to third years of life (supply category 4), there is no uniform picture. In some cases 10% and more of an age group has calcium intake which is far lower or far higher than recommended intake. The former is more serious than high intake because of the importance of calcium for bone health (supply category 1/3).

7.3 Risk characterisation

7.3.1 Hazard characterisation (NOAEL, LOAEL)

Theoretically speaking, adverse reactions to high or excessive calcium intake should not occur in healthy individuals because of the dose-related reduction in absorption and control of the calcium level through genetic and hormonal factors. In the case of pathologically elevated bone resorption like bone cancer, hyperthyroidism, hyperparathyroidsm and excessive intake of vitamin D, however, hypercalcaemia (and hypercalciuria) can occur. Adverse reactions to excessive calcium intake are described in conjunction with the so-called milk-alkali syndrome, the pathogenesis of which has not been clarified. The promotion of kidney stone formation in predisposed individuals with hypercalciuria and/or hyperabsorption of calcium and an inhibition of absorption of other minerals are discussed as adverse effects of calcium (Whiting and Wood, 1997).

a) Hypercalcaemia (>11 mg/dl, >2.75 mmol/l) goes hand in hand with lethargy, loss of appetite, nausea, headaches, constipation, thirst, polyuria, confusion and loss of consciousness (>14 mg/dl).

   There are many different causes. In the case of healthy individuals however, excessive intake of calcium is probably not a cause.

   The most frequent causes are primary hyperparathyroidism, through hyperplasia or adenoma or in conjunction with endocrinological disorders (multiple endocrine neoplasias), secondary and tertiary hyperparathyroidism (e.g. as a consequence of renal insufficiency or persistent after a successful kidney transplant), malignant disorders of the parathyroid gland, the lungs and breast and malignant myeloma whereby parathormo-

ne is produced ectopically or there are bone metastases. Excessive intake of vitamin D and intoxications with vitamin A are associated with hypercalcaemia. Genetic causes with disrupted calcium homoeostasis owing to mutations in the calcium-sensitive receptor (hypocalciuric hypercalcaemia, hyperparathyroidism of the newborn) and in the elastine gene (Williams-Beuren Syndrome) are described.

Milk-Alkali Syndrome is the name given to the clinical picture which occurs as a consequence of parallel treatment of stomach ulcer patients with high calcium dairy products and resorbable antacids (normally sodium bicarbonate or calcium carbonate) (McMillan and Freeman, 1965; Sippy, 1915). The therapeutic regime originally envisaged intake of 20 g calcium/day both as milk and carbonate. Changes in the treatment of peptic stomach ulcers has led to a decrease in the frequency of the milk-alkali syndrome. Besides the typical clinical symptoms of hypercalcaemia, patients developed at a later stage or within a few days of commencement of therapy dehydration, renal failure, nephrocalcinosis and kidney stones. In some patients chronic renal insufficiency persisted.

A compilation of the 82 case descriptions published between 1965 and 2001 shows that the patients were aged between 24 and 95, that calcium intake through milk consumption was between 0.9 and 6.8 g calcium per day and through calcium supplements between 1 and 23 g/day whereby 45 patients took both. All calcium supplements consisted of calcium carbonate. Many patients also took sodium bicarbonate. It is not possible to rule out a pre-existing kidney disorder in many of the patients described. Some patients also took thiazides which promote renal reabsorption of calcium (SCF, 2003).

While the milk-alkali syndrome is clinically well defined, calcium alone does not appear to be the cause.

In contrast to FNB of IOM (1997), which took the median value of calcium intake of patients of 4.8 g/day as the LOAEL and used this to derive a UL for calcium intake from all sources, SCF (2003) stated that the list of the published 82 case descriptions contained 11 cases in which calcium intake was less than 2.5 g/day (the UL of the FNB). Furthermore it was of the opinion that the variable quality of available data did not permit the identification of a LOAEL for calcium as the trigger for a milk-alkali syndrome.

b) Kidney stones. Although calcium is a constituent of 80% of all kidney stones, either as oxalate and/or phosphate, excessive dietary calcium intake is not the cause of kidney stones (Goldfarb, 1994).

On the contrary, the results of two large prospective studies involving 45,619 men aged between 40 and 75, who were monitored over five years (The Health Professionals Follow-up Study) and 91,731 women aged between 34 and 59 who were monitored over 12 years (Nurses' Health Study) and who did not have any kidney stones at the start of the study, confirmed that calcium intake of more than 1050 mg/day in men and of more than 1100 mg/day in women reduces the risk of kidney stone formation by 35%. The calcium intake of kidney stone sufferers was significantly lower in both groups than that of individuals who did not form kidney stones even after adjustment for age, body mass index, intake of animal protein, alcohol, sodium, sucrose, fluids and calcium supplements. In both groups a reduced risk of kidney stone formation was observed with increasing intake of dairy products and an increased risk with growing intake of sodium and sucrose (Curhan et al., 1993; 1997).

In a study involving 1309 women aged between 20 and 92, no association was established between the intake of high oxalate foods, vitamin C, protein, fibre, alcohol,

calcium and fluoride content of drinking water in those 44 women who had kidney stones. On average these women had a lower calcium intake (840 mg/day) which was 250 mg/day below that of women with no kidney stones (1070 mg calcium/day). The taking of calcium supplements did not, however, offer any protection against the formation of kidney stones (Sowers et al., 1998). The protective effect of dietary calcium intake at the level of recommended intake is attributed to lower calcium absorption in the small intestine whereby the non-absorbed calcium forms poorly absorbable calcium oxalate with dietary oxalate. Consequently, less oxalate is resorbed and excreted via the kidneys. The taking of calcium supplements without food does not, however, lead to calcium oxalate formation in the intestine and the increased absorption of calcium could increase calcium excretion in urine and, thus, contribute to the formation of kidney stones.

Most patients with kidney stones manifest hypercalciuria (>4 mg calcium/kg body weigh/day). In 50% it is "idiopathic" either on a renal basis or through hyperabsorption in the intestine or as a consequence of primary hyperparathyroidism, malignant disorders, vitamin D intoxication, renal tubular acidosis, immobilisation or bone diseases (Pak et al., 1975; 1998).

Calcium excretion in the urine increases with increasing sodium intake (30-40 mg calcium per two gram dietary sodium) (Matkovic et al., 1995). In 120 men with recurrent calcium oxalate stones and idiopathic hypercalciuria, a diet over five years with a normal calcium content (1200 mg/day), low sodium content (1150 mg/day or 2.9 g salt/day) and a normal protein content (15% of energy intake) led to a 50% reduction in the risk of new kidney stones compared to the same diet with a reduced calcium content (400 mg/day) (Borghi et al., 2002).

The hypercalciuria-promoting effect of calcium and/or sodium intake was tested in 124 hypercalciuric kidney stone patients: at a sodium intake of 2.3 g/day (corresponding to 5.8 g salt/day), hypercalciuria (>300 mg/day in men, >250 mg in women) was predicted if the calcium intake exceeded 2240 mg/day in men and 1420 mg/day in women (Burtis et al., 1994). We do not know whether these associations also apply to healthy individuals or to individuals with hypercalciuria without any stone formation.

In a therapeutic study with postmenopausal women suffering from osteoporosis, hypercalciuria (>350 mg calcium/day) was observed in 44 out of 119 patients, who had taken calcium supplements (1600 mg/day) over a period of four years. It was also observed in 7 out of 117 women who did not take any calcium supplements. One of the supplemented women developed mild hypercalcaemia (Riggs et al., 1996). 3 out of 50 infants, who had been given a high calcium formula from the third month of life (1700-1560 mg calcium/day) developed hypercalciuria (Dalton et al., 1997).

By way of summary, the available data do not permit the identification of a calcium dose which promotes the formation of kidney stones. Calcium intake at the level of recommended intake does not lead to an increased risk of kidney stone formation either in healthy individuals or in kidney stone patients with hypercalciuria. A salt intake in the range of 6 g/day is considered to be "adequate" by the German-speaking nutrition societies.

c) Interaction with the absorption of other minerals
High calcium doses can interfere with the absorption of other essential minerals, iron, zinc, magnesium and phosphorus.

Iron: The absorption of ferrous salts and heme-iron, depending on dose, is inhibited by parallel dietary calcium intake (Hallberg et al., 1991; Minihane and Fairweather-Tait,

1998; Whiting and Wood, 1997). This phenomenon is observed in conjunction with single-dose or short-term additional calcium intake.

Eleven children aged between 3 and 5, who were given a low calcium (502 mg calcium/day) diet or a high calcium (1180 mg calcium/day) diet over five weeks, supplying 9-9.7 mg iron/day, were examined with the help of the stable isotopes ^{44}Ca, ^{58}Fe and ^{46}Ca for iron deposition in erythrocytes, calcium absorption and retention. Whereas the absolute resorbed and retained amount of calcium was significantly larger with the high calcium diet than with the low calcium diet, no difference could be detected in iron integration in erythrocytes (Ames et al., 1999).

In longitudinal studies with calcium supplements, no negative effect on iron status was observed in lactating women, adolescent girls or adult men and women except in cases with prior chronically low calcium intake (Lynch, 2000).

Three month old infants (n=103), who were given either a high calcium and phosphorus (calcium intake after 4 months 1700 mg, after 9 months 1560 mg/day) diet or non-supplemented infant formula (calcium intake after 4 and 9 months 400 mg and 350 mg/day) did not manifest any differences in serum ferritin, in iron binding capacity, in the erythrocyte protoporhyrin or in the haematocrit up to the end of the first year of life. Both infant diets contained the same amount of iron (12.8 mg/l) (Dalton et al., 1997).

Several placebo-controlled studies with calcium supplements (500-1200 mg/day) over 5 months up to 4 years involving girls (8-13 years) and adult women could not detect any negative effect of calcium supplements on serum ferritin, haematocrit or protoporphyrin content of erythrocytes (Ilich-Ernst et al., 1998; Kalkwarf and Harrast, 1998; Minihane and Fairweather-Tait, 1998; Sokoll and Dawson-Hughes, 1992; Yan et al., 1996).

Seven out of nine longitudinal studies examining the influence of the consumption of dairy products on the iron status of adults and infants showed a low negative correlation with a drop in serum ferritin content of 1.6 and 3.3% in girls and women per increased calcium intake of 100 mg/day. A threshold dose for calcium could not be identified (van der Vijver, 1999).

By way of summary, calcium intake in line with recommended intake does not seem to have any negative impact on iron status as long as dietary iron intake is not low.

Zinc: Under certain circumstances calcium can reduce zinc absorption. In a study with 18 postmenopausal, healthy women, intake of 468 mg calcium both as milk or as calcium phosphate in addition to a basal diet containing 890 mg calcium and 17.6 mg zinc, led to a reduction in zinc absorption. It also reduced the zinc balance by 2 mg particularly if calcium was taken at the same time with a meal (Wood and Zheng, 1997). However, other studies in postmenopausal women did not observe any impact on absorption or retention of ^{65}Zn from the additional administration of milk or calcium phosphate (Wood and Zheng, 1990).

Despite a reduction in fractional zinc absorption from 24% to 12% and to minus 3% through the gradual increase of calcium intake from 230 mg over 860 mg to 2000 mg/day in older men, there was no change in zinc excretion or zinc balance (Spencer et al., 1984). In the same way the one-year administration of calcium supplements (1000 mg/day) to lactating women (Yan et al., 1996) and to female adolescents (McKenna et al., 1997) and of 600 and 1200 mg calcium/day to young men did not produce any changes either (Raschke and Jahreis, 2002).

Given the findings that high zinc intake in turn can reduce calcium absorption in the intestine if calcium intake is low (Spencer et al., 1987), it can be concluded that intake of both calcium and zinc at the recommended level is unlikely to produce a negative interaction but that selectively high intake of for instance calcium can have a negative impact on zinc absorption. This effect can be compensated in the long-term by increasing zinc absorption.

Magnesium: Both magnesium absorption and renal magnesium excretion can drop as a consequence of calcium intake of 2000 mg/day which means that a magnesium loss is unlikely (Whiting and Wood, 1997). Abrams et al. (1997) did not observe any drop in the magnesium balance in 25 children (9-14 years-old) related to calcium intake (average 1310 mg/day). Nor was the magnesium status of lactating women affected by calcium supplements (1000 mg/day) over one year (Yan et al., 1996).

Phosphorus: Calcium acetate and calcium carbonate are given to patients suffering from renal insufficiency (up to 2000 mg calcium/day) in order to bind phosphate in the intestinal luman and to reduce phosphate resorption. This effect can also be observed in healthy individuals; however it has no clinical relevance because of customarily high dietary phosphate intake (Whiting and Wood, 1997).

Overall the available examinations show that the short-term impairment of absorption of various minerals through high calcium doses in individual studies cannot be reproduced in longitudinal studies with calcium intakes at the level of recommended intake and with supplementation up to 2000 mg/day. It is only of importance when intake of other minerals is low. A NOAEL and LOAEL for calcium cannot be identified in conjunction with a negative impact on the absorption of other minerals.

7.3.2 Deficiency, possible risk groups

Inadequate calcium supply can be triggered by low intake, low absorption and high losses. As a rule it does not lead to hypocalcaemia if the physiological regulatory mechanisms, which keep the level of ionised calcium steady in the extracellular space, are intact.

Hypocalcaemia (<2.2 mmol/l; <8.8 mg/dl) is linked in its clinical course to neurological disturbances, encephalopathy and cataracts. In the case of severe hypocalcaemia (<1.8 mmol/l; <7.2 mg/dl) or a reduction in ionised calcium without hypocalcaemia through respiratory or metabolic alkalosis, laryngospasm and muscle cramps (tetany) may occur.

Parathormone deficiency, genetic or acquired, for instance after surgery, leads in the kidneys to the reduced formation of $1,25(OH)_2$-D, to increased excretion of calcium and reduced excretion of phosphate. This reduces calcium absorption in the intestine and calcium is lost through the kidneys. A non-response of target organs to parathormone (pseudohypoparathyroidism) leads to the same changes in the calcium and phosphate levels at normal $1,25(OH)_2$-D levels and elevated parathormone levels. A vitamin D deficiency may but need not be linked to hypocalcaemia in the same way as other forms of rickets which are not caused by vitamin D deficiency.

In the first 2 days new-born babies manifest a physiological hypocalcaemia, caused by the abrupt stop of the calcium supply via the umbilical cord blood, coupled with high bone turnover and inadequate dietary intake.

In the case of renal insufficiency $1,25(OH)_2$-D synthesis is reduced directly and through hyperphosphataemia whereby intestinal calcium absorption decreases and hypocalcaemia can occur. A magnesium deficiency of any kind inhibits secretion of the parathormone and can thus lead to hypocalcaemia.

A rare genetic defect in the calcium-sensitive receptor with a downward shift in the threshold for ionised calcium (autosomally dominant hypocalcaemia) produces functional hypoparathyroidism and can also lead to hypocalcaemia (Allgrove, 2003).

A long-term inadequate supply with calcium, particularly during the life phase in which calcium is stored in the bones up to the genetically determined peak bone mass, is one of the preconditions which promote the onset of osteoporosis. Also thereafter it is a major factor which determines the speed at which bone mass is lost.

Since calcium is not fully resorbed in the intestine, despite an adaptive increase in the absorption rate, even in the case of low intake, larger or smaller amounts of calcium depending on intake level remain in the intestine and are excreted in faeces. Non-absorbed calcium binds oxalate, free fatty acids and bile acids. The former has proved its ability to protect against the formation of oxalate kidney stones. The binding of fatty acids and bile acids reduces their carcinogenic potential in the colon (Holt, 1998; 1999). In a multicentric randomised controlled study the administration of 1200 mg calcium/day to patients with a history of colon adenomas did not prevent the proliferation of the rectum mucosa but it did influence the rate of reoccurrence of adenomas (Baron et al., 1999).

Inadequate calcium intake leads, by way of compensation, to the increased formation of $1,25(OH)_2$-D by means of elevated parathormone secretion. $1,25(OH)_2$-D binds to receptors on the membrane of various cell types and results in an increase in intracellular calcium content. This rise in intracellular calcium content leads in smooth muscle cells to hypertonia and in fatty cells to a stimulation of fat synthesis. The consequences were characterised by Fujita and Palmieri (2000) as the "calcium paradox disease". It promotes the onset of high blood pressure, arterial sclerosis, Alzheimer's disease, insulin resistance, malignant tumours (outside the colon too) and of adipositas when other predisposing factors are present at the same time. Epidemiological observations, intervention studies and findings from animal models all point to this mechanism (overviews: Fujita and Palmieri, 2000; Heaney, 2003; Heaney et al., 2002; Teegarden, 2003). It has not been defined at present which amounts of calcium have to be administered – whether these are higher than those derived for bone health – in order to block this mechanism. These reflections do, however, underline the importance for health of calcium intake at least at the level of the recommendations.

7.3.3 Excessive intake, possible risk groups

Toxic effects of high calcium doses have been identified in animals: osteochondrosis, renal failure and death (Whiting and Wood, 1997). High calcium intake, be it from calcium-rich foods or calcium supplements, is mainly "corrected" in human beings by reduced absorption in the intestine and, to a lower degree, through increased excretion in urine. It does not lead to an overload in the body. However, there are no systematic studies available concerning the amounts of calcium which can be tolerated by healthy individuals. Intervention studies and therapeutic studies were conducted in healthy children, adults, pregnant women and patients with colon adenomas with total calcium amounts of up to 3000 mg/day over periods of three weeks up to four years. They examined the question of bone health, the risk of premature birth, the risk of high blood pressure during pregnancy, reoccurrence of colon tumours and interactions with the metabolism of other minerals. They can provide information on tolerated amounts, but given the study design only permit limited statements about the occurrence of adverse reactions (SCF, 2003).

Individuals who take alkalising substances in addition to high calcium doses and/or suffer from renal insufficiency and/or take thiazides, have a non-quantifiable risk of developing milk-alkali syndrome.

Calcium intake at the level of recommended intake does not increase the risk of kidney stone formation in individuals with hypercalcaemia either, as long as there are no other predisposing factors like low fluid intake, high salt intake, high oxalate excretion.

The limited data from the National Food Consumption Study, the Nutrition Survey and the DONALD Study show that in each age group at least 10% of test persons have a calcium intake which is, in some cases, far higher than recommended intake (up to 1500 mg more). There has been an increase in mean calcium intake by men and women in the period between the National Food Consumption Study (1985-1988) and the Nutrition Survey (1997/1998).

In both studies dairy products are responsible for more than half of calcium intake. Although food supplements only account for 10% of total calcium intake and the contribution of fortified foods is not known, a calcium intake of >4 g/day is possible in worse-case-scenario calculations. In a model calculation for an adolescent the mere replacement of fruit juice, water, breakfast cereals with substitutes fortified with calcium and/or calcium-containing mineral water led to a doubling of the possible calcium intake from natural foods including 600 ml milk from 1980 mg to 3850 mg/day (Whiting and Wood, 1997). A Finnish study in which the gradual replacement of non-fortified fruit juices, low fat milk, breakfast cereals and bread of the portions determined in 1992 for a representative section of the Finnish population with calcium fortified variations was calculated with respect to resulting total calcium intake, comes to similar conclusions. The 90 percentile of calcium intake of men and women (median 2150 and 1715 mg/day) would increase to 3280 and 2600 mg for men and women, respectively, in conjunction with 100% consumption of calcium-fortified foods (Suojanen et al., 2002).

These model calculations are not unrealistic for the German situation.

7.4 Tolerable upper intake level for calcium

The Scientific Committee on Food of the European Commission has derived a tolerable upper intake level (UL) of 2500 mg. This amount of calcium was tolerated in placebo-controlled intervention studies with many adult test persons without any adverse effects. It is considered to be the NOAEL. An uncertainty factor was not used. Since many of the test persons were pregnant, the same UL applies to pregnant and lactating women.

It was not possible to derive a UL for children or adolescents because of insufficient data. Furthermore, it was not considered justified to extrapolate from the adult UL on the basis of body surface area, because bone mineral deposition during growth is not proportional to fat-free body mass (SCF, 2003).

By contrast, the Food and Nutrition Board of the Institute of Medicine defined a UL on the same level as that of SCF. The median value (5 g/day) of the amount of calcium which had been taken by patients with the milk-alkali syndrome was considered as the LOAEL and an uncertainty factor of 2 was applied. This UL applies to all age groups over the age of one and to pregnant and lactating women (FNB, 1997).

The available consumption data for Germany (Table 15) show that the calcium intake of 10% of men aged between 18 and 24 is higher than the UL. In the Nutrition Survey food supplements were taken into account but not fortified foods which are, however, increasingly available in Germany. Nothing is known about their contribution to the calcium supply of the adult population. In the case of children and adolescents (2-15 years of age) in the DONALD Study, fortified foods contributed at most 5% of calcium intake between 1986 and 2000.

7.4.1 Derivation of a maximum level for calcium in food supplements

The formula, which is explained in the introduction to this report, calculates the amount of calcium which is available for food supplements and fortified food as difference between the UL and the highest available consumption percentile. It would lead to a calcium amount of zero, i.e. the addition of calcium to food supplements or foods would not be permissible.

Considering that more than 10% of the population have a calcium intake which is far lower than recommended and the resulting health risks, this procedure does not appear appropriate and is not, therefore, applied. For individuals who do not consume dairy products as their main source of calcium, calcium-containing substitutes should be available as well as food supplements with calcium for individuals with a low total calcium intake.

7.4.1.1 Possible management options

a) Up to now a daily level corresponding to the recommended intake, i.e. 1000 mg, has been acepted in food supplements, following a proposal by BgVV in 1998. This practice could be continued.

   Advantages: A food supplement would deliver in a targeted manner the total recommended daily calcium dose and would considerably improve the calcium intake of individuals who take very little or scarcely any dietary calcium. It would also compensate for the consequences of a lengthier deficiency until a change in diet has taken effect.

   Disadvantages: The additional intake of 1000 mg from a food supplement would take the calcium intake of more than 90% of all age groups in the population above recommended intake. For more than 10% of the adult population additional calcium intake of 1000 mg/day would lead to exceeding of the UL of 2500 mg. For all children under the age of 10 calcium intake from one food supplement would already be above the recommended intake for their age. This could be countered by the information that this food supplement is not suitable for children under the age of 10.

b) Reduction of the daily maximum level accepted for calcium in a food supplement up to now by half (500 mg).

   Advantages: The additional intake of 500 mg calcium would improve the calcium supply of population groups with a calcium intake below recommended intake. If one takes the possibly outdated consumption data of the National Food Consumption Study as the basis, calcium intake in the 25 percentile would double and reach recommended intake whereas calcium intake by individuals in the range of the 2.5 percentile would improve considerably but would still be below recommended intake. If we take the consumption data of the Nutrition Survey as the basis, the calcium intake of 40% of the population (50 to 90% percentile) would be above the recommended intake as a consequence of additional intake of 500 mg calcium but, with the exception of 10% of men aged between 18 and 44, it would not exceed the UL of 2500 mg. All age groups whose calcium intake is on the 10 percentile would achieve recommended intake with additional ingestion of 500 mg calcium. Food supplements with 500 mg calcium would be suitable for children from age 4 upwards.

   Disadvantages: 10% of men aged between 18 and 44 would exceed the UL as a consequence of additional intake of 500 mg as would a certain percentage of male adolescents.

c) Further reduction of the previously accepted daily maximum level for calcium in a food supplement to one quarter (250 mg).

Advantages: Individuals, whose calcium intake is at least 75% of recommended intake, would achieve the recommended intake by taking an additional 250 mg calcium. Individuals, whose calcium intake is already high (90 percentile) would, with the exception of young men aged between 18 and 24, not exceed the UL. Food supplements with 250 mg calcium would be suitable for children from age one onwards as well.

Disadvantages: The additional intake of 250 mg calcium would not increase the low calcium intake of around 10% of adult population to the level of recommended intake nor for the at least 10% of boys and girls aged seven and older.

For 10% of men aged between 18 and 24 a supplement of only 250 mg would lead to exceeding of the UL.

7.4.2 Derivation of a maximum level for calcium in fortified foods

Foods fortified with calcium can improve the calcium status of at least 10% of the adult population and children aged 7 upwards whose calcium intake is far below the recommended intake and who do not consume any food supplements. What is problematic, however, is the choice of the suitable carrier food(s). This is confirmed by a model calculation for Canada: based on calcium intake from non-fortified foods with or without taking into account calcium supplements, various fortification scenarios and their effect on total calcium intake were calculated: bread, cereal flakes, rice fortified to 55 or 165 mg calcium per portion; pasta fortified to 130 or 275 mg calcium per portion; fruit and vegetable juices fortified to 55, 165 or 300 mg/portion; other beverages including soya "milk" fortified to 300 mg/portion. It was shown that the results, in particular the percentage of the population whose calcium intake would exceed the UL, was dependent on energy intake, i.e. UL exceedances occurred more frequently amongst men than amongst women. None of the scenarios played out was satisfactory in terms of reaching a calcium intake on the level of "Adequate Intake" (AI) whilst, at the same time, avoiding a high percentage of men whose calcium intake would exceed the UL. The best result was obtained when 300 or 600 mg calcium was added to the calcium intake of all test persons. As dairy products constituted the main source of calcium and a low calcium intake is regularly associated with a low consumption of dairy products, the authors believe that the calcium fortification of foods, which can replace dairy products, is one of the best alternatives. The worst alternative was considered to be calcium fortification of foods which are eaten by individuals with high energy requirements (Johnson-Down et al., 2003).

A comparison of the conclusions of this study with the customary practice of food fortification in Germany clearly shows that this practice is not an appropriate way of reaching the goal of improving the calcium intake of a major proportion of the population, particularly that of older men and women and children aged between 7 and 12. This is because calcium is mainly added to beverages, sweets, dairy products, beverage powders and ready-to-eat meals (Kersting et al., 1995). The median calcium level per portion was less than 10% of the reference value of the Nutrient Labelling Ordinance (800 mg). This is a great amount when it comes to sweets and not so much when it comes to a ready-to-eat meal as the number of portions is probably different.

7.4.2.1 Possible management options

a) No change to current unregulated practice with fortification of different foods

Disadvantages: The consumer who strives to have a high calcium intake has a large choice of fortified foods.

Disadvantages: The goal of a foreseeable improvement in the calcium status of undersupplied consumers is not achieved. Possible misleading of consumers through claims for non-recommended foods that they are "fortified".

b) Restriction of calcium fortification to foods which can replace dairy products. The calcium content should correspond to that of the substituted products: 120 mg/100 g for beverages.

Advantages: Since low calcium intake as a rule is coupled with low or no consumption of dairy products, substitutes should supply the same level of calcium.

Disadvantages: No certainty that consumers who avoid dairy products will consume substitutes.
Extensive intervention in existing fortification practice.

c) Fortification of all types of beverages with calcium on the same level as milk

Advantages: Easily resorbable calcium compounds can be used. Clear nutrient labelling and recommended intake can be useful for consumers when making their choice.

Disadvantages: No certainty that the consumers whose calcium status is deficient will choose these beverages.

d) No restriction of calcium fortification to one category of foods instead a maximum level of 30% of the reference value in the Nutrient Labelling Ordinance (which would correspond at present to 240 mg, in future 300 mg) per 100 g or 100 ml (corresponds to the future advertising claim "high level of")

Advantages: The consumption of two 100 g/ml portions of a food leads to a significantly higher calcium intake (see 7.4.1.1, Option b).

Disadvantages: Fortified foods should not be consumed when people are hungry or thirsty and must be correspondingly labelled. Sweets would have to be excluded from the option of fortification. No certainty that consumers whose calcium status is deficient would choose these foods.

Calcium is consumed by an equally large proportion of the population in amounts that are below or above recommended intake. Inadequate calcium supply brings with it long-term risks for health. Calcium intake above the tolerable daily intake is linked to a poorly quantifiable risk of adverse reactions. Individuals suffering from renal insufficiency who also take resorbable antacids and specific diuretics as well as individuals with inadequate intake of other minerals constitute a risk group. In order to improve inadequate calcium intake, BfR is of the opinion that the simplest option is the taking of calcium supplements with a daily maximum level of 500 mg if a change in diet is not possible or not desired. The fortification of foods with calcium should be restricted to a few foods. However, there is no suitable carrier food which can solve with any foreseeable certainty the problem of inadequate supply. Substitutes for dairy products, which contain a similar concentration of calcium or clearly labelled beverages with corresponding consumption instructions, are the management options preferred by BfR.

7.5 Gaps in knowledge

- There are no exact or up-to-date data on the level of calcium intake from foods, food supplements or fortified foods in Germany.
- There are no up-to-date data on the consumption frequency of food supplements or fortified foods or their contribution to individual calcium intake.

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8 Risk Assessment of Phosphorus

8.1 Summary

The data available for the Federal Republic of Germany on phosphorus intake indicate that otherwise healthy individuals are not likely to have an inadequate supply of the mineral phosphorus. In some cases intake is above the recommendations (supply category 4).

Phosphorus cannot be adequately classified in line with the risk classification of nutrients taken over by BfR. In the opinion of BfR there is overall a moderate risk of the occurrence of adverse effects for this substance taking into account the available data.

BfR observes that given the widespread availability of phosphorus in foods, the frequent use of phosphates as additives for technological purposes and the overall sufficient intake - in some cases higher than requirements - the fortification of conventional foods with phosphorus for nutritional-physiological purposes is not appropriate and should not be undertaken.

The risk assessment did not reveal any signs that supplementation with a maximum of 250 mg phosphorus as phosphate per day in addition to their customary diet would lead to clearly adverse reactions in otherwise healthy adults. There are no indications of the benefits or the suitability of phosphate supplementation for nutritional-physiological reasons.

Recommended intake	From 15 **up** to 19 years: 1250 mg/day from 19 years: 700 mg/day	
Intake [mg/day] (NFCS, 1994)	**m**	**f**
Median	1488	1188
P 2.5	839	592
P 97.5	2517	1988
Tolerable Upper Intake Level	not yet defined (EFSA)	
Proposal for **maximum levels** in:		
Food supplements	250 mg/daily dose (adults)	
Fortified foods	No fortification	

8.2 Nutrient description

8.2.1 Characterisation and identification

Phosphorus, chemical symbol P, CAS No.: 7723-14-0, is an essential mineral for humans. It is a non-metal in the fifth main group of the periodic table with atomic number 15. It has a relative atomic mass of 30.97. The prevalence of this element in the earth's crust is indicated as 0.09%. Given its reactive ability, phosphorus only occurs in bound form in nature, above all as salts of phosphoric acid (phosphates) and in various apatite minerals. Phosphorus is available in its compounds above all in the valence levels -3, +3 and +5; however, all other valence levels between –3 and +5 are possible (Garg and Anderson, 2003).

According to Directive 2002/46/EC of 10 June 2002 phosphorus may be added to food supplements. As an accompanying ion, it may also be added for nutritional purposes of riboflavin-5'-phosphate, pyridoxine-5'phosphate, calcium glycerophosphate, calcium salts of phosphoric acid, magnesium glycerophosphate, magnesium salts of phosphoric acid, ferric sodium diphosphate, ferric diphosphate (ferric pyrophosphate), sodium salts of phosphoric acid, potassium glycerophosphate and potassium salts of phosphoric acid. Binding maximum levels have not been laid down so far in this connection. The same applies to Directive 2001/15/EC of 15 February 2001.

Phosphates, e.g. certain orthophosphates, di-, tri- and polyphosphates, have long been in use as food additives and are approved as such within the EU, e.g. phosphoric acid (E 338) as an acidulant in Cola beverages. Phosphate-containing additives of this kind are used for instance as acid regulators, emulsifiers, acid stabilisers, antioxidants, preservatives, to maintain the flow ability of powdered foods, as smelting salts, separating agents and modified starches.

8.2.2 Metabolism, function, requirements

Metabolism: There are approximately 17 g phosphorus in the body of a newborn baby and approximately 600-700 g in that of an adult. More than 85% of phosphorus is contained in the skeleton and in teeth, approximately 65-80 g in other tissue and only around 2 g in blood (D-A-CH, 2000). The body of the newborn baby contains approximately 0.5% phosphorus, that of the adult 0.65-1.1% (FNB, 1997).

Organophosphate compounds (proteins, nucleic acids, phospholipids, vitamins) are hydrolysed by phosphatases and resorbed in the small intestine as inorganic phosphate. A high concentration of iron, calcium or aluminium reduces whereas 1,25-hydroxycholecalciferol increases bioavailability. Vitamin D raises the gastro-intestinal uptake of phosphate (Marcus, 1995; Martindale, 1999).

In infants, young children and children phosphorus absorption is between 65 and 90%. They have a positive phosphate balance. Adults absorb between 55 and 70% of inorganic phosphate from a mixed diet (FNB, 1997). High calcium intake may lead to complex formation which can inhibit the resorption of phosphorus. Bioavailability from cereal grains is low as phosphorus is mainly found in the bound form of phytic acid (hexaphosphate ester of inositol). Given the lack of phytathydrolasis in the human gastro-intestinal tract, cereals are a relatively poor source of phosphate. However, phytin can be broken down by microbial phytasis (e.g. during the production of bread with sour-dough or special dough handling) (D-A-CH, 2000; Löffler and Petrides, 2003).

The kidneys are the most important organ system for phosphorus homoeostasis. Phosphorous is filtered glomerularly and around 80% is resorbed in the proximal tubule by means of sodium co-transport. The calcium concentration in plasma falls when the glomerular filtration rate sinks whereas the phosphate concentration increases as, in this case, the kidneys do not excrete phosphate nor can calcium be sufficiently reabsorbed. A falling plasma concentration of calcium leads to an increase in parathormone release. One of the consequences of this is elevated calcium and phosphate release from the bones. Therefore, in the case of existing renal insufficiency, phosphate intake should be reduced to 800-1000 mg/day. Depending on the severity of renal insufficiency phosphate binders should also be used (Bowman and Russel, 2001; Lexikon der Ernährung, 2002). The quantative recording of phosphate excretion must be done using the 24-hour urine because of the clear day-night rhythm. Renal phosphate excretion is increased through parathormone, calcitonin, calcium intake, oestrogens, thyroxin and acidosis and reduced by insulin, growth hormone and cortisol (Löffler and Petrides, 2003). The metabolism of inorganic insulin, phosphate is closely linked to that of calcium.

Function: In hydroxylapatite phosphorus helps to strengthen bone structure. In the hydroxylapatite compounds, calcium and phosphorus are in a steady ratio of around 2:1 (Bowman and Russel, 2001). Together with calcium, phosphate is the main component of the inorganic part of the skeleton. Organophosphorus compounds are important building blocks of nucleic acids which occur in all living cells. Phospholipids, like for instance lecithins, are important structural elements of cell membranes. Numerous metabolic processes of the cell are regulated by phosphorylation reactions. As a component of adenosine triphosphate (ATP), phosphorus plays a key role in cellular energy supply and conversion. In muscle tissue crea-

tine phosphate, the phosphorylated form of creatine, is the main source of energy besides ATP. As the dihydrogen phosphate-hydrogen phosphate system, phosphate acts as a buffer in the intracellular space and blood plasma in conjunction with acid-base status (D-A-CH, 2000; Garg and Anderson, 2003; Grimm and Jahreis, 2000; Löffler and Petrides, 2003).

Requirements: The average requirements of adults are given as 580 mg/day (FNB, 1997). On this basis the German Nutrition Society (DGE) derived a recommended intake for adults of 700 mg/day in conjunction with a variation co-efficient of 10% and a mark-up of 20%. In puberty and adolescence phosphorus requirements are elevated because of new net formation of tissue and, more particularly, because of bone growth. This is why the recommended intake for this group of individuals is given as 1250 mg/day. During pregnancy and lactation recommended intakes are higher than for normal adults (D-A-CH, 2000).

Table 16: Recommended daily phosphorus intake

Age	Recommended intake (mg/d)
Infants	
0 up to under 4 months (estimated value)	120
4 up to under 12 months	300
Children	
1 up to under 4 years	500
4 up to under 7 years	600
7 up to under 10 years	800
10 up to under 15 years	1250
Adolescents and **adults**	
15 up to under 19 years	1250
19 up to 65 years and older	700
Pregnant women	800 (<19 years of age 1250)
Lactating women	900 (<19 years of age 1250)

(according to D-A-CH, 2000)

The above recommendations are on the same scale as the phosphate status recommendations issued by the USA and Canada. In the case of infants they refer to the AI (Adequate Intake) and for children, adolescents and adults to the RDA (Recommended Dietary Allowance). According to this the recommended daily intake is: infants (0-6 months old: 100 mg; 6-12 months old: 275 mg), children and adolescents (1-3 years old: 460 mg; 4-8 years old: 500 mg; 9-18 years old: 1250 mg), adults (19->70 years of age: 700 mg), pregnant and lactating women depending on age (FNB, 1997).

Interaction: Phosphate forms non-soluble, non-resorbable compounds with aluminium. This means that in therapeutic terms phosphate resorption can be inhibited by aluminium hydroxide gel (D-A-CH, 2000; Löffler and Petrides, 2003). Calcium and phosphate salts can form non-soluble calcium-phosphate precipitations when mixed together (Martindale, 1999).

8.2.3 Exposure (dietary and other sources, nutritional status)

Sources:

Food: Phosphorus is one of the most widespread nutrients. High protein foods like milk, meat, fish and eggs are very good sources of phosphorus. Considerable amounts are taken up from meat and sausage products (24%), bread (14%) and cheese (9%) and from dairy products (Grimm and Jahreis, 2000; Kasper, 1996). Nuts, pulses, fruit and vegetable also contain larger amounts of phosphorus. By contrast, relatively little phosphorus is to be found in fruit and fresh vegetables. Phosphate is added to many industrially produced foods like, for instance, Cola beverages.

Table 17: Phosphorus content of various foods

Food (consumable portion per 100 g)	Phosphorus (mg)
Cocoa powder	656
Sunflower seeds	618
Gouda (30% fat dry weight)	600
Camembert (30% dry weight)	540
Poultry mortadella	458
Rye crispbread	433
Oil sardines	430
Lentils	411
Wholemeal biscuits	294
Chicken eggs	216
Smoked pork chop	214
Mixed bread	203
Egg pasta	191
Roast pork	180
Curd cheese (20% fat dry weight)	165
Bananas	28
Apples	12

(according to Brockhaus Nutrition, 2001)

Additives: Phosphates, e.g. certain orthophosphates, di-, tri- and polyphosphates, have been used for some time as food additives and are approved as such within the EU for technological purposes, e.g. as acid regulators, emulsifiers, acid stabilisers, antioxidants, preservatives, smelting salts, separating agents, modified starch.

Only provisional estimates are available within the European Union on the expected level of intake from additives. According to them it can be assumed that in the case of adults the estimated intake of phosphate-containing additives E 338, E 339, E 340, E 341, E 343, E 450, E 451 and E 452 does not exceed the MTDI (Maximum Tolerable Daily Intake) of 70 mg total intake phosphorus per kg body weight. In the case of small children the range of estimated intake is given as 53-172%. According to this, it would be possible for this group of individuals to exceed the given maximum level for these additives. The report does, however indicate that the calculations undertaken constitute a conservative estimate of intake based on the assumption that these additives are used in a very wide range of foods up to the admissible maximum level. Further studies are necessary (KOM EU, 2001).

Food supplements and fortified foods: Phosphorus may be contained as an accompanying ion in various vitamins/minerals in food supplements and fortified foods. Actual fortification with phosphorus via food supplements is probably very rare.

Nutritional status:

Intake: Whereas the consumption of phosphorus in the Federal Republic of Germany in 1973/74 was on average 1440 mg per day and person, 1570 mg phosphorus were taken in daily in 1978/79. In 1980/1981 the values were on average 1236 mg for women and 1598 for men (DGE, 1980; 1996; Grimm and Jahreis, 2000).

According to the National Food Consumption Study of the Federal Republic of Germany, average phosphate intake was 1040 mg/day for women and 1326 mg/day for men between 1985-1989 (DGE, 1996; Grimm and Jahreis, 2000). Here the median of phosphorus intake depending on age was between 1208 and 1553 mg/day in the case of male individuals from age 7 upwards whereby the 97.5 percentiles, depending on age group, were between 1946 and 2916 mg/day. For females age 7 and upwards median phosphorus intake, depending on age, was between 1123 and 1232 mg/day. Depending on the age group the 97.5 percentiles were between 1813 and 2075 mg/day (Adolf et al., 1995). In the related sub-random sample with adults and using the special clinical-chemical methods (VERA Study), median phospho-

rus intake for women was 1188 mg/day (97.5 percentile: 1988 mg/day) and for men 1488 mg/day (97.5 percentile: 2517 mg/day) (Heseker et al., 1994).

In conjunction with the Nutrition Survey 1998, one of the modules of the Federal Health Survey conducted between 1997 and 1999, the values in a randomly selected sub-random sample for daily phosphorus intake of individuals who do not take any vitamin/mineral supplements was on average 1712 mg (95% confidence interval: 1694-1730) in men and 1317 mg (95% confidence interval: 1305-1329) in women. In the case of people who took vitamin/mineral supplements at least once a week, the values were on average 1783 mg (95% confidence interval: 1741-1824) in men and 1354 mg (95% confidence interval: 1328-1380) in women (Mensink and Ströbel, 1999).

According to consumption data from the USA the highest mean intake of phosphorus was for men aged between 19 and 30 with a value of 1.7 g/day. The highest 95 percentile of phosphorus intake was 2.5 g/day in the case of male adolescents aged between 14 and 18 (FNB, 1997).

According to consumption data from the United Kingdom the mean phosphorus intake from foods was 1260 mg/day in adults; the 97.5 percentile was given as 2110 mg/day (EVM, 2003).

In principle, phosphorus requirements are closely linked to those of calcium. Hence, reducing phosphorus intake seems to have an advantageous effect on increased calcium intake.

The available consumption data indicate that the intake of the essential nutrient phosphorus generally meets the recommendations and, in some cases, exceeds them. There are no signs for the need for supplementary administration of phosphorus in order to prevent deficiencies.

Plasma concentration: Details of the normal phosphate concentration in plasma (inorganic phosphorus) of adults indicate 0.8-1.4 mmol/l (SCF, 1992) and 1.29-2.26 mmol/l for children (Bowman and Russel, 2001). Total phosphorus in the blood – including phospholipids of the red blood cells and lipoproteins in plasma – is approximately 13 mmol/l; this corresponds to approximately 400 mg/l (FNB, 1997). In order to convert the values from g to mmol, they are multiplied by the factor 32.29, from mg/dl to mmol/l by factor 0.3229. 1 mg phosphorus corresponds to 0.03229 mmol (Bowman and Russel, 2001). Around 30% of phosphorus is present in body fluids in an inorganic form mainly as the divalent HPO_4^{2-}-ion or monovalent $H_2PO_4^-$-ion, at a pH 7.40 in a ratio of 4:1 (Marcus, 1995; Martindale, 1999). Organophosphate compounds like phosphate ester, lipid- and protein-bound phosphate are also present (Garg and Anderson, 2003).

The serum phosphate level is subject to a day-night rhythm (early morning/morning at its lowest, afternoon/evening at its highest). It is determined more particularly by age (decreasing with age) and the excretion capacity of the kidneys but also by dietary phosphorus intake. Kidney excretion (transport maximum phosphate/glomerular filtration rate) is an important regulation parameter for the serum phosphate level and, by extension, for homoeostasis of the phosphorus status (D-A-CH, 2000; Robertson, 1976). If the filtered phosphate amount exceeds the transport maximum of the proximal tubulus, phosphate appears in the urine. This happens at plasma concentrations >1 mmol/l, which can already be exceeded in healthy individuals (Löffler and Petrides, 2003). The phosphate concentration in the plasma does not permit any precise conclusions about total body store of phosphorus; nor is it a meaningful indicator (Bowman and Russel, 2001; Martindale, 1999).

The relatively high serum phosphate level in infants, small children and school children compared to that of adults promotes mineralisation of the skeleton (Marcus, 1995). In adults the

amount of phosphate excreted daily by the kidneys reflects the amount absorbed from food (D-A-CH, 2000; Robertson, 1976). The low phosphorus content of breast milk (Souci et al., 2000) corresponds to the relatively low kidney function capacity which is typical in infants of that age whose excretion ability, more particularly of phosphate, is relatively low (D-A-CH, 2000; Manz, 1992).

The data available for the Federal Republic of Germany on phosphorus intake indicate that an inadequate supply of healthy individuals with the mineral phosphorus is not to be expected. In some cases intake is above recommendations (supply category 4).

8.3 Risk characterisation

8.3.1 Hazard characterisation (NOAEL, LOAEL)

In a clinical study with female osteoporosis patients (age: 50-75) phosphorus was administered orally for 7 days (as phosphate) in an amount of 750 mg per day (19 patients), 1500 mg (19 patients) or 2250 mg (21 patients) in the form of effervescent tablets (mixture of ammonium phosphate, potassium phosphate and glycerol phosphate) compared to placebo (21 patients). In the 750 mg group 2 out of 19 patients manifested gastro-intestinal disorders (like nausea, vomiting, diarrhoea). This was the case in the 1500 mg group for 3 out of 19 patients and in the 2250 mg group for 7 out of 20 patients. The concentrations of phosphate and calcium in the serum did not show any significant change. The concentration of parathormone in serum increased significantly in both groups with 1500 mg and 2250 mg but not, however in the group which had been given 750 mg (Brixen et al., 1992; EVM, 2003).

In a one week cross-over study with 10 healthy male test persons, a daily supplement of 1000 mg phosphorus as phosphate was given in addition to a defined diet with 800 mg calcium and 800 mg phosphorus per day. In a second one-week study with 12 healthy male test persons, increasing phosphate doses were administered from 0 mg, 1000 mg, 1500 mg up to 2000 mg phosphorus per day. The defined diet contains 1000 mg calcium and 1000 mg phosphorus as phosphate per day. In both studies there was an increase in urine phosphate excretion and a drop in urine calcium excretion. An increase in the parathormone concentration in the serum was only observed in the first study but not in the second. Changes in the serum values for phosphate and osteocalcin (specific bone matrix protein, a biochemical parameter of new bone formation) were not observed. One test person receiving 2000 mg phosphate suffered from diarrhoea (Whybro et al., 1998).

8.3.2 Deficiency, possible risk groups

8.3.2.1 Deficiency

Nutritive phosphorus deficiency is scarcely possible as a consequence of high dietary phosphorus intake. Almost all conventional foods contain this nutrient. A low phosphate diet is at the same time low in proteins, calcium and vitamin B (Grimm and Jahreis, 2000). A restriction of phosphate intake temporarily reduces the phosphate serum level and increases the calcium level (Jellin et al., 2002). Severe malabsorption and chronic alcoholism can lead to phosphate deficiency as can cases of inadequate parenteral nutrition. An existing hypophosphataemia is initially asymptomatic. Clinical symptoms are to be expected when the plasma concentration falls below approximately 0.3 mmol/l. The symptoms are, for instance, neuromuscular dysfunction, muscle weakness (D-A-CH, 2000; Marcus, 1995; Martindale 1999). Persistent hypophosphataemia can lead to growth disorders, rickets (children), skeletal deformations, haemolytic anaemia, cardiomyopathy and osteomalacia (adults) (FNB, 1997; Ketz, 1990; Lexikon der Ernährung, 2002; SCF, 1992).

In animal experiments a phosphorus deficiency triggered by a low phosphorus diet led to hypercalcaemia, hypophosphataemia and growth disorders particularly of the bones (Grimm and Jahreis, 2000; Hoshino et al., 1998).

A phosphorus deficiency can occur as a consequence of excessive use of aluminium-containing antacids and in conjunction with specific renal function disorders, hyperparathyroidism or a vitamin D deficiency. The X-chromosomal family hypophosphataemia is an expression of a malfunction of intestinal and/or renal phosphate carriers and goes hand in hand with rickets and dwarfism (Lexikon der Ernährung, 2002; Marcus, 1995; Martindale, 1999).

Distribution disorders (without a cellular phosphorus deficiency) are considered to be another cause of hypophosphataemia, e.g. through accumulation of phosphorus in bones coupled with elevated mineralisation or in the cells for phosphorylation of glucose and fructose and for ATP synthesis. A distribution disorder of this kind is frequently observed after a period of fasting and return to a normal diet or after insulin treatment for metabolic acidosis (Hartig, 1994).

8.3.3 Excessive intake, potential risk groups

The healthy organism excretes excess phosphor following excessive phosphate intake in urine (SCF, 1992). Phosphorus intakes as phosphate of between 1.5 and 2.5 g per day can lead to a drop in the calcium level in serum (hypocalcaemia) and to an increase in the serum concentration of parathormone. It is assumed that the calcium balance is not worsened by this and that the bone destruction processes are not increased (Bizik et al., 1996; Spencer et al., 1988). It should not be necessary to maintain a specific Ca:P ratio in an adult diet (D-A-CH, 2000; FNB, 1997). However, there are differing opinions on this question in the literature (Bowman and Russel, 2001). In children a Ca:P ratio in food of 0.9:1 up to 1.7:1 mmol/mmol is recommended (EVM, 2003; SCF, 1992). In the case of high phosphate intake coupled with overly low calcium intake and the related increase of parathormone (secondary hyperparathyroidism), an elevated rate of bone turnover is to be expected with promotion of osteoporotic processes (Garg and Anderson, 2003).

In the case of restricted kidney function, e.g. in patients with chronic renal insufficiency, excessive phosphorus intake can lead to hyperphosphataemia, nephrocalcinosis and ectopic calcification with loss of calcium from the bones. An underactive thyroid gland (hypoparathyroidism) can also lead to hyperphosphataemia (Martindale, 1999). There are no known cases of phosphorus intoxications in healthy individuals as a consequence of excessive dietary intake. The maximum level for a normal serum phosphate content in adults (19 to 70 years of age) is achieved with a daily intake of 3.5 g phosphorus (113 mmol) (D-A-CH, 2000; FNB, 1997).

Persistent hyperphosphataemia leads to anormal calcification particularly of bradytrophic tissue (bursa, joints). Acute hyperphosphataemia raises calcium binding whereby hypocalcaemia and tetania can occur (Hartig, 1994).

Gastro-intestinal disorders like hyperacidity, flatulence, vomiting and diarrhoea may manifest as symptoms of short-term excessive oral phosphorus intake (Grimm and Jahreis, 2000). In principle, all orally taken phosphate salts can lead to gastro-intestinal irritations and disruptions of the fluid and electrolyte status, including hyperphosphataemia and hypocalcaemia and, depending on the respective accompanying ion, to other disorders (Jellin et al., 2002). Serious electrolyte disorders were also observed in conjunction with the use of phosphate-containing enemas and intestinal lavage (Martindale, 1999).

Diarrhoea was described as an adverse reaction following the oral intake of 750 mg phosphorus (as phosphate per day) and more as a supplement (EVM, 2003).

The postulated impact of excessive phosphorus intake on behavioural disorders in children could not be proven scientifically up to now (Hill, 1998; Manz, 1986; Overmeyer and Ebert, 1999; Robinson and Ferguson, 1992; Stare et al., 1980).

8.4 Tolerable upper intake level for phosphorus

The UL (Tolerable Upper Intake Level) for phosphorus was derived in the USA and Canada in the following way: infants: not determinable; children (1 up to and including 8 years of age): 3 g/day; children aged 9 upwards, adolescents, adults up to 70 years of age: 4 g/day; adults over the age of 70: 3 g/day; pregnant women: 3.5 g/day; lactating women: 4 g/day. Individuals who have an energy consumption of more than 6000 kcal/day may have phosphorus intakes above these limits without any risks being known in this context (FNB, 1997).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) derived an MTDI (Maximum Tolerable Daily Intake) of 70 mg phosphorus per kg body weight in 1982 for phosphates as additives. This applies to the sum of phosphates occurring naturally in foods and to additives. This value of 70 mg/kg body weight was taken over in 1990 by the Scientific Committee on Food of the European Commission as the ADI (Acceptable Daily Intake) for ortho-, di-, tri- and polyphosphates (SCF, 1991). In individuals weighing between 60 kg and 70 kg this would correspond to an upper limit of phosphorus intake of 4.2 g and 4.9 g per day.

SCF has not undertaken a recent evaluation of phosphorus (SCF, 1993).

In the above-mentioned human study Brixen et al., 1992, an increase in the serum concentration of parathormone from supplementation (with phosphate) was observed in patients in the amount of 1500 mg per day. Already supplementation of 750 mg per day led, based on dose, to a growing number of adverse gastro-intestinal effects. In the Whybro et al. 1998 study, test persons were observed to undergo an increase in their serum concentration of parathormone in conjunction with phosphorus (as phosphate) supplementation amounting to 1000 mg per day. Adverse gastro-intestinal disorders like diarrhoea occurred in one test person who was given supplementation of 2000 mg per day.

The Expert Group on Vitamins and Minerals of the United Kingdom (EVM, 2003) comes in its risk assessment for phosphorus to the conclusion that the overall data situation is not sufficient to permit the derivation of a UL (Tolerable Upper Intake Level) for inorganic phosphate. The Expert Group, therefore, adopts a NOAEL of 750 mg phosphate based on the results of the above-mentioned studies. With a view to inter-individual variations it uses an uncertainty factor of 3 and proposes a "guidance level" on the level of supplementation of up to 250 mg phosphorus as phosphate per day under which no adverse effects would be expected. This corresponds to 4.2 mg/kg body weight of an adult person weighing 60 kg. Assuming a maximum phosphate intake from food of 2110 mg daily (consumption data UK, see above) plus supplementation, a UK Expert Group comes to a maximum daily intake of 2400 mg phosphorus as phosphate. This corresponds to 40 mg/kg body weight for a person weighing 60 kg under which no adverse reactions are to be expected (EVM, 2003).

The consumption data available for Germany show that the 97.5 percentile of phosphorus intake, depending on age, is between 1946 and 2916 mg/day in male individuals from age 7 onwards depending on age group. For female individuals from age 7 onwards the 97.5 percentiles, depending on age group, were between 1813 and 2075 mg/day (Adolf et al., 1995). In the relevant sub random sample with adults using special clinical-chemical methods (VERA Study) the 97.5 percentile of phosphorus intake was 1988 mg/day for women and 2517 mg/day for men (Heseker et al., 1994).

If one takes the maximum level for phosphorus from these consumption data available for Germany and the guidance level proposed by EVM, which we consider to be appropriate, of supplementation of maximum 250 mg phosphorus as phosphate per day as the basis for these reflections, then this reveals the following picture: assuming maximum dietary phosphate intake of 2916 mg/day by male individuals and 2075 mg by female individuals, plus supplementation of up to 250 mg, this results in a maximum daily total intake of 3166 mg and 2325 mg phosphorus as phosphate. This corresponds to 53 mg/kg body weight in males and 39 mg/kg body weight in females weighing 60 kg. In individuals weighing 70 kg, this would lead to a maximum daily total intake of 45 mg/kg body weight (males) and 33 mg/kg body weight (females). These total intake levels would correspond to the maximum levels proposed by FNB in 1997 (see above). They are below the range chosen by JECFA 1982 (see above).

8.4.1 Derivation of a maximum level for phosphorus in food supplements

8.4.1.1 Possible management options

A nutritive phosphorus deficiency is scarcely possible given the high intake of phosphorus from a conventional diet. There are no known cases of this in healthy individuals. The data available for the Federal Republic of Germany on phosphorus intake indicate that an inadequate supply of the mineral phosphorus is not to be expected in otherwise healthy individuals; in some cases supply was above the level of requirements.

The risk assessment does not provide any indications that daily supplementation of maximum 250 mg phosphorus as phosphate in otherwise healthy individuals in addition to a conventional diet would lead to obvious undesirable effects. There are no indications of the benefits or the suitability of phosphate supplementation for nutritional-physiological purposes.

8.4.2 Derivation of a maximum level for phosphorus in fortified foods

8.4.2.1 Possible management options

Almost all conventional foods contain the nutrient phosphorus. Furthermore, it is to be found in a series of phosphate compounds used as food additives for technological purposes and approved as such within the EU. There are no indications either that confirm the benefits or suitability of phosphate fortification of conventional foods for nutritional-physiological purposes. The addition of substances like phosphate, which are already sufficiently present in foods, is not considered to be necessary and should not be undertaken.

Phosphorus cannot be adequately classified in line with the risk classification of nutrients taken over by BfR. In the opinion of BfR there is overall a moderate risk of the occurrence of adverse effects for this substance taking into account the available data.

BfR observes that given the widespread availability of phosphorus in foods, the frequent use of phosphates as additives for technological purposes and the overall sufficient intake - in some cases higher than requirements - the fortification of conventional foods with phosphorus for nutritional-physiological purposes is not appropriate and should not be undertaken. The risk assessment did not reveal any signs that supplementation with a maximum of 250 mg phosphorus as phosphate per day in addition to their customary diet would lead to clearly adverse reactions in otherwise healthy adults. There are no indications of the benefits or the suitability of phosphate supplementation for nutritional-physiological reasons.

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9 Risk Assessment of Magnesium

9.1 Summary

The data available for Germany on the nutritional status with magnesium do not indicate inadequate magnesium uptake in healthy adults in the range of recommended intake. Adolescents and young adults aged between 15 and 19 and older people are a risk group. However, there are no validated biomarkers (supply category 2/3).

Magnesium cannot be properly classified using the risk classification of nutrients undertaken by BfR. BfR is, however, of the opinion that there is a moderate risk of adverse effects in conjunction with the use of magnesium in food supplements. Higher doses of magnesium (>250 mg per day as a single dose) can lead to osmotic diarrhoea which is, however, reversible. BfR recommends the setting of a maximum level of 250 mg for food supplements whereby this maximum daily dose should be divided up into at least 2 doses per day. Given the better bioavailability of magnesium there is probably not any risk of diarrhoea from the fortification of foods with magnesium. Hence, these amounts can be ignored or not taken into account. In the case of the extension of fortification to specific calorie-containing food groups, a maximum level of 15-28 mg/100 kcal is recommended and for beverages a maximum level of 22.5 mg/100 ml of the ready-to-eat food. No magnesium sulphate should be added to beverages.

Recommended intake	300-400 mg/day	
Intake [mg/day] (NFCS, 1994)	**m**	**w**
Median	368	300
P 2.5	209	148
P 97.5	633	508
Tolerable Upper Intake Level	250 mg/day (only applies to supplements)	
Proposal for **maximum levels** in:		
Food supplements	250 mg/daily dose (from 125 mg upwards division into at least 2 single rations)	
Fortified foods	15-28 mg/100 kcal and 22.5 mg/100 ml	

9.2 Nutrient description

9.2.1 Characterisation and identification

Magnesium (Mg) is in the second main group of the periodic system and is an alkaline-earth metal (CAS No. 7439-95-4). It has an atomic mass of 24-305; it always occurs in bivalent form in its compounds (as Mg^{2+}). It never occurs in its elementary form in nature but in compounds like magnesite ($MgCO_3$), dolomite ($MgCO_3$ * $CaCO_3$), kieserite ($MgSO_4$ * H_2O), magnesium chloride ($MgCl_2$) and magnesium bromide ($MgBr_2$). Furthermore, there are magnesium compounds in salt water (on average 15% of salt in salt water consists of magnesium compounds). The risk assessment only refers to the ionic form and magnesium compounds mentioned.

In Germany a series of magnesium compounds is permitted in accordance with the Additives Approval Ordinance for technological purposes like magnesium salts of edible fatty acids (E 470b), magnesium carbonates (E 504) and magnesium oxide (E 530), quantum satis. Magnesium carbonate, magnesium oxide and magnesium chloride are authorised for drinking water processing and there is no limit value (TrinkwV, 2001).

With the implementation of Commission Directive 2000/15/EC (of 15 February 2001 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses) the following 11 magnesium compounds may be used in products for special dietary purposes on nutritional-physiological and dietary grounds (Annex 2 to the twelfth Ordinance on the amendment to the Ordinance on Foods for Special Dietary Purposes (DiätVO) (of 31 March 2003):

- Magnesium acetate
- Magnesium salts of orthophosphoric acid
- Magnesium carbonate
- Magnesium lactate
- Magnesium chloride
- Magnesium hydroxide
- Magnesium salts of citric acid
- Magnesium oxide
- Magnesium gluconate
- Magnesium sulphate
- Magnesium glycerophosphate

The same magnesium compounds are included in Commission Directive 2002/46/EC (of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements). They are also envisaged in the "Proposal for a Regulation of the European Parliament and Council on the addition of vitamins and minerals and of certain other substances to foods" of 10 November 2003 (COM (2003) 671 final).

9.2.2 Metabolism, function, requirements

Metabolism: Magnesium is the fourth most abundant cation in the human body. Together with potassium, it is the most important intracellular element. The total body store in newborn babies and adults is approximately 1 and 24 g (approximately 42 and 1000 mmol)[1] respectively. Around 95% of magnesium is to be found in the intracellular space. More than half of this (55%) is in bones, 28% in muscle and the rest in soft tissue. Only 5% is found in extracellular fluid. Less than 1% is in serum and interstitial fluid. The magnesium concentration in serum and plasma varies between 0.8-1.1 mmol/l. Of this 1/3 is bound to protein and 2/3 is freely soluble as magnesium ions. Only free magnesium is biologically active. The serum level depends on magnesium uptake from food, resorption in the small intestine, magnesium distribution in the organism and on losses via the kidneys (normally 3-6 mmol/day) and intestine. The cell membrane is crossed with the help of transport proteins. Depending on the type of cell the intracellular concentration of free magnesium ions is 0.3-1 mmol/l. There is a slow exchange of magnesium between the tissue pools; it has a biological half life of approximately 40 days. In the case of deficiency the big magnesium pool (approximately 250 mmol) is available in bones as more than half of the magnesium in bones is located on the surface of the apatite crystals and is exchangeable (Elin, 1990; Martini and Mayer, 1999).

Magnesium is taken up by means of a carrier-induced process and passive diffusion in the small intestine. New findings on congenital hypomagnesaemia show that magnesium is preferentially taken up via a transporter, the ion channel TRPM6 in the intestinal wall (Walder et al., 2002). Absorption or bioavailability depends on numerous factors like uptake amount (dose), type and solubility of the magnesium compounds used, composition of diet, intestinal motility, passage time, interaction with other elements and the nutritional status of the body. Furthermore, age, physical activity and liquid intake are also important (Benech and Grognet, 1995; Bohmer et al., 1990; Ebel, 1990; Elin, 1990).

[1] 1 mmol magnesium corresponds to 24 mg magnesium

Between 20 and 50% are available from a mixed diet when adults take up on average around 90 mg magnesium per meal. The intestinal absorption rate is higher when magnesium intake is lower or there is a deficiency condition (Rude, 2000; Sabatier et al., 2003). For instance, Fine et al. (1991a) established that 65% of magnesium was absorbed at an intake of 36 mg per day whereas only 11% could be taken up from food with an intake of 973 mg magnesium per day. Magnesium citrate, chloride, lactate and aspartate are more readily available than the poorly absorbable magnesium oxide and magnesium sulphate (Benech and Grognet, 1995; Fine et al., 1991a; Firoz and Graber, 2001; Kuhn et al., 1992; Morris et al., 1987; Mühlbauer et al., 1991). Magnesium from milk is more readily bioavailable than from cereals, pulses or meat (Fairweather-Tait and Hurrell, 1996; Hardwick et al., 1990; Miura et al., 1999; Schaafsma, 1997). Magnesium from mineral water rich in the substance when drunk alone is available to around 50% whereas when taken together with a meal the absorption rate increases significantly by on average 14% (Sabatier et al., 2002; Verhas et al., 2002).

Magnesium is mainly excreted through the kidneys. Around 90% of the glomerularly filtered amount is reabsorbed. Only 3-5% of the glomerularly filtered Mg^{2+} is excreted in urine (5-8.5 mmol magnesium per day). Renal excretion is influenced by calcium, parathormone and calcitonin. In the event of a deficiency, excretion is markedly reduced whereby excretion of less than 4 mmol per day is an indication of a magnesium deficiency. In the case of extensive intake it can be considerably higher. Under physiological conditions the serum Mg^{2+} concentration remains in a very narrow range whereby we do not yet fully understand all the regulatory mechanisms (Fleet and Cashman, 2001; Quamme, 1993; Saris et al., 2000; Weber and Konrad, 2002).

Interactions: Growing calcium intake, chelate formation with phosphate and phytates reduce intestinal absorption in rats. This could not be confirmed in controlled studies in humans (Andon et al., 1996; Fairweather-Tait and Hurrell, 1996; Schaafsma, 1997; Sojka et al., 1997). There does not appear to be any risk of an imbalance of nutrients amongst one another and interactions with food components are unlikely with a normal diet. Certain fermentable substrates like inulin and oligosaccharides and polysaccharides have a stronger affect on magnesium absorption (Coudray et al., 2003). The interactions between magnesium and potassium are of clinical relevance. They not only affect gastro-intestinal resorption and renal excretion but also endogenous distribution between the extracellular and intracellular compartments (Marktl, 2003; Ryan, 1993; Stühlinger, 2003).

Functions: The biological functions of magnesium ions in the organisms are diverse. They include:

- involvement in mineralisation and growth of bones (storage function),
- as a co-factor of most ATP-dependent enzymes, particularly in the case of oxidative phosphorylation, glycolysis, protein and nucleic acid synthesis (Fleet and Cashman, 2001; Laires et al., 2004; Mildvan, 1987; Rude, 2000),
- regulation of cellular signal transfer (second messenger system) of many hormones and neurotransmitters by means of adenylate cyclase through the G protein which requires GTP und Mg2+ (Rude, 2000; Volpe et al., 1990) and
- modulation of the ion channels, e.g. impact on NMDA (N-methyl-D-aspartate) receptor channel by Mg2+, which blocks the channel in an unopened condition. This is important for normal synaptic transfer of action potential in the neurons. Magnesium is also involved in regulating potassium channels in the myocardial cells (Agus and Morad, 1991; Kupper et al., 1996; Laires et al., 2004; Rude, 2000).

Requirements: The exact requirements of magnesium in human beings are not known. More recent balance studies assume a physiological requirement of 3.0-4.5 mg/kg body weight and day. This means that 350 and 280 mg/day respectively are probably adequate for adult men and women. In the case of children aged between 9-14 a positive Mg balance was measured after an intake amount of 6.0 mg/kg body weight and day (Abrams et al., 1997).

Table 18 gives the North American RDA (FNB, 1997) and new DGE recommendations (D-A-CH, 2000). For adults the Scientific Committee on Food (SCF, 1993) had indicated an acceptable range for intake of 150-500 mg/day. The recommendations are based on balance studies and refer to healthy adults with normal physical load (Cashman and Flynn, 1999; Heseker, 1998). The two bodies indicate very different requirements for pregnant and lactating women. In the first trimester of pregnancy the foetus stores 5-7.5 mg magnesium daily. The resulting additional requirements of pregnant women are covered in the opinion of DGE by the intake recommended for (young) women and a conventional mixed diet (D-A-CH, 2000). The arguments put forward by FNB (1997, p. 238) for higher requirements of pregnant women for magnesium are not convincing ("Inconsistent findings of the effect of magnesium supplementation on pregnancy outcome make it difficult to determine whether magnesium intakes greater than those for non-pregnant women are beneficial" (see also 9.3.2.1).

The requirements of athletes were not examined. Recently, the positive impact of magnesium supplementation on the performance of athletes has been questioned (Bohl and Volpe, 2002; Clarkson and Haymes, 1995; Heseker, 1998; Lukaski, 2000; Newhouse and Finstad, 2000).

Table.18: Recommended daily intake (RDA) for magnesium (FNB, 1997) compared with recommended intake (D-A-CH, 2000)

Age (years)	RDA (FNB, 1997) (mg/day) m/f	Recommended intake (D-A-CH, 2000) (mg/day) m/f
Children		
1 up to under 4 years	80	80
4 up to under 7 years	130	120
7 up to under 10 years	200	170
10 up to under 13 years	280	230/250
13 up to under 15 years	410/360	310/310
Adolescents and **adults**		
15 up to under 19 years	410/360	400/310
19 up to under 25 years	420/320	420/320
25 up to under 65 years	400/350	400/310
65 years and over	350/300	350/300
Pregnant women	350 [1]	310 [2]
Lactating women	310	390

[1] Pregnant women <19 years400 mg; [2] and 350 mg

9.2.3 Exposure (dietary and other sources, nutritional status)

Sources:

Food: Magnesium is ubiquitous in food whereby the level may vary considerably. Meat and dairy products contain less (28 mg/100 g) than cereal products, nuts, potatoes and green vegetables (6-270 mg/100 g). Coffee and tea also contribute to covering requirements. The main sources are bread and bakery goods, potatoes, vegetables, beverages, milk and dairy products. Food processing leads to losses which can vary markedly.

Fortified foods: Conventional foods fortified with magnesium in Germany are mainly beverages, sweets and dairy products. As a rule around 15% of the recommended daily dose are

added to 100 g and 100 ml or per serving size (Kersting et al., 1995; Kratochwilla et al., 2002).

Food supplements: The MONICA Longitudinal Study 1994/95 established that women took magnesium preparations significantly more frequently (12.4%) than men (8.7%). The medians (min-max) of intake were 75 mg (1.0 mg-552 mg) for women and 102 mg (1.0 mg-888 mg) for men. For both genders these mineral preparations were taken more frequently in conjunction with self-medication whereby the prescribed intake was more frequent in higher age groups. Hence, only some of the magnesium preparations were food supplements. Up to now BgVV had recommended complying with the 1-fold dose of the DGE recommendation (400 mg/day) as the upper limit for food supplements (BgVV, 1998; Schellhorn et al., 1998). A significantly higher use of supplements was associated with a higher level of education, regular sports activities, a state of health that was subjectively deemed to be unsatisfactory and a change in diet because of health problems (Hahn and Wolters, 2000; Klipstein-Grobusch et al., 1998; Mensink et al., 2002; Mensink and Ströbel, 1999). According to a market analysis by the Research Institute of Child Nutrition in Dortmund, 42% of food supplements are directly sold for children. 31% of them are magnesium-containing food supplements (Kersting and Alexy, 2000).

Drinking water: The magnesium level depends on the region where the water comes from and is between <5 and >30 mg/l. The amendment to the Drinking Water Ordinance no longer contains a limit value (TrinkwV, 2001). In mineral water there are levels of 5 up to >150 mg/l. Mineral waters with a content of 50 mg/l and more may claim to be "magnesium-containing" (MinTafWV, 2002).

Medicinal products: Magnesium-containing products are pharmacy-only medicinal products in doses of 4.5 mg to 9 mg per kg body weight and 121.5 mg up to 600 mg per day. Medicinal products also include healing waters whose magnesium content may be more than 100 mg/l (BGA, 1990; ct-Arzneimittel, 1999; Mohr, 1994; ratiopharm, 2003; Stadapharm, 2002; Wörwag, 1999; 1998).

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

According to the National Food Consumption Study (NFCS) the average magnesium intake of the population in the Federal Republic of Germany in the 1980s (n=1988) was 341 mg/day. In this context the median (2.5-97.5 percentile), given for women (n=1134) and men (n=854) was 300 (148-508) and 368 (209-633) mg/day respectively. Referred to age and gender, median values (2.5.-97.5 percentile) of 285 (150-525) in 19-24 year-olds and 282 (153-495) mg in >65 year-old women were given for daily magnesium intake. In the case of men these intake levels were 367 (190-704) for 19-24 year-olds and 341 (192-559) mg for >65 year-olds (Adolf et al., 1995).

In conjunction with the Environment Survey 1990/91 average magnesium intakes of 319.9 and 275.1 mg per day were determined using the duplicate method in 318 men and women. The level recommended by DGE was undercut by men and women in 62% of cases (Becker et al., 1998). Compared to the results obtained using the market basket analysis or dietary protocols, the duplicate method leads to more exact results as error probability is considerably minimised (Glei and Anke, 1995). A pilot study involving 4-12 year-old children from Greifswald in Mecklenburg-Western Pomerania and the region St. Gallen in Switzerland pro-

duced similar results whereby 23.6% and 5.9% of children had an inadequate supply. However, only a small number of test persons was examined (n=7). Around one-quarter of dietary magnesium intake comes from beverages (Schimatschek et al., 1997).

According to the Nutrition Report 2000 the supply situation with magnesium has improved markedly since the Nutrition Report 1996. Mean daily intake of magnesium was on average 347.2/387.0 mg for the female/male population. In almost all age groups average intake corresponded to the new reference values. Exceptions to this are adolescents and young adults aged between 15 and 19. The highest intake is recommended for this age group (D-A-CH, 2000; DGE, 2000).

In a cohort of the EPIC Study in Germany, average magnesium intake of 371 mg was established using 24-hour dietary protocols. The minimum and maximum intakes were 57 and 1164 mg whereby the 90 percentile was 532 mg (Schulze et al., 2001).

Recent data from the Federal Health Survey show that for daily magnesium intake the medians (10-90 percentile) are 414.5 (265.3-567.4) in the age group of 18-24 year-olds, 362.2 (258.2-539.0) mg in the >65 year-old women, 554.4 (340.5-813.0) in that of the 18-24 year-olds and 402.7 (295.8-583.4) mg in that of the >65 year-old men. Thus, magnesium intake for both men and women is higher than the current reference values in all age groups, i.e. the supply of most of the population with this mineral is guaranteed. The mean values of magnesium intake of regular consumers of food supplements (≥ month/week) vary significantly ($p = 0.001$) from the control group (no intake) (Mensink et al., 2002; Mensink and Ströbel, 1999).

Biomarkers: As shown by the data from the NFCS/VERA Study, large groups in the German population are adequately supplied with magnesium on the basis of the serum concentrations measured (Erdinger and Stelte, 1992). Based on more recent measurements of the serum level of 16,000 non-selected individuals in Germany, hypomagnesaemia (<0.76 mmol Mg/l) was observed in 14.5% of all individuals whereby this generally occurred more frequently in women as they aged and outpatients. Overall, sub-optimal levels were measured in 33.7% of the group studied (Schimatschek and Rempis, 2001).

The measurements of the entire plasma/serum level of magnesium is generally used to record magnesium status. It has not, however, been validated as a reliable indicator of nutritional status (Fawcett et al., 1999; FNB, 1997). The serum concentration of magnesium only reflects acute changes in magnesium status but does not correlate with other tissue pools, with the exception of interstitial fluid. For that reason the Mg serum level can be normal, similar to the potassium level in the case of chronic intracellular magnesium deficiency (like e.g. for diabetes mellitus, alcoholism or malabsorption syndrome). For that reason retention of magnesium after intravenous exposure is also measured to diagnose non-renal magnesium deficiency. Retention of >30% of the dose administered is a sign of a magnesium deficiency. The sensitivity of the method may vary between test persons with and without hypomagnesaemia. More recent tests determine the free (ionised) magnesium in the serum, blood or plasma or after *in vitro* exposure cellular magnesium uptake in lymphocytes and blood platelets. The biologically active form is a better index of magnesium status than measurement of the total magnesium concentration in the serum which requires further validation of this method. This also applies to the new *in vitro* blood load test (Fawcett et al., 1999; Feillet-Coudray et al., 2002; 2003; Fleet and Cashman, 2001; FNB, 1997).

9.3 Risk characterisation

9.3.1 Hazard characterisation (NOAEL, LOAEL)

No disadvantageous effects have been observed in healthy consumers in conjunction with magnesium uptake from conventional foods. This can be explained, amongst other things, by the lower availability, compared to uptake from food supplements, as a consequence of the influence of other food ingredients. Readily soluble magnesium salts, like the ones found in food supplements, medicinal products or water, are fully available in the stomach in the presence of hydrochloric acid. Depending on the individual reaction of the test person and dose level (as a rule between 15 and 40 mmol/day; corresponds to 389-972 mg magnesium per day), symptoms ranging from soft faeces down to diarrhoea are observed (Wörwag, 1999). Magnesium excretion in faeces is the diagnostic criterion as the consequence of the resorption capacity of the small intestine being exceeded (Donowitz, 1991; Fine et al., 1991b; Wörwag, 1999). In a more recent randomised cross-over, placebo controlled study in older roughly 60 year-old test persons (n=73), diarrhoea occurred in 30% of cases at a dose of 300 mg/day when administered as magnesium citrate in a supplement for 6 weeks compared with 17% for the placebo (p=0.1) (Roffe et al., 2002). At doses of 250 mg/day and less, effects of this kind were not observed (SCF, 2001).

Certain sulphate waters (Glauber salts and Bitter salts) are known to have a laxative effect and are, therefore, used pharmacologically as laxatives (Morris et al., 1987). As sulphate (SO_4^{2-}), sulphur stimulates intestinal function and occurs in conjunction with sodium as sodium sulphate (Glauber salt) (Na_2SO_4) or in conjunction with magnesium as magnesium sulphate (Bitter salt) ($MgSO_4$). From 1200 mg sulphate per litre upwards, there will be elevated intestinal secretion. From 3000 mg sulphate per litre, healing waters may have a laxative effect.

Aside from osmotic diarrhoea, other intestinal disturbances observed are nausea and stomach cramp. There is no direct risk to health as these complaints immediately disappear after discontinuation of medication and are reversible (SCF, 2001).

Severe cases of magnesium intoxication are rare. In the case of oral doses of more than 2500 mg, a drop in blood pressure or muscle weakness are observed. At very high doses (30 g/day) there may be metabolic alkalosis and hypocalcaemia. Paralytic ileus (intestinal obstruction) and cardiac arrest may occur when very high individual doses (>400 g) are ingested (Brunton, 1996; Fleet and Cashman, 2001; FNB, 1997; Morris et al., 1987; SCF, 2001; Urakabe et al., 1975).

Healthy test persons are generally speaking more insensitive to magnesium intoxication whereas patients with limited renal function show far stronger systemic effects when they ingest magnesium in the form of supplements or medicinal products (including magnesium-containing antacids or laxatives). In these cases there is reduced excretion of magnesium via the kidneys which may lead to hypermagnesaemia with a fatal course (see 2.3).

SCF (2001) established a **NOAEL** (no observed adverse effect level) of 250 mg/day for the additional intake of readily soluble magnesium salts (e.g. chloride, sulphate, aspartate, lactate) and for compounds like magnesium oxide (MgO) via food supplements, water or other fortified foods and beverages. The natural magnesium content of food was not taken into account there.

FNB (1997) chose a different method which derived a **LOAEL** of 360 mg/day for adults based on the studies by Bashir et al. (1993). They selected the dose which can already trigger osmotic diarrhoea by means of uptake from ("non-food source") supplements. They established that in other studies with various magnesium compounds far higher doses (372, 678 and

1200 mg/day) were also well tolerated for therapeutic purposes without triggering gastrointestinal disorders. Osmotic diarrhoea was not observed after normal dietary magnesium intake. Nor were there any reports of mild cases of diarrhoea of this kind following the intake of magnesium as a food component or food additive even when consumed in larger amounts. The parallel presence of solid foods counteracts the osmotic effect of magnesium salts. Magnesium is also far more readily absorbed from food than at the higher doses used in supplements (Fine et al., 1991a; b; FNB, 1997).

9.3.2 Deficiency, possible risk groups

9.3.2.1 Deficiency

In healthy persons with a conventional diet and food habits no cases of a magnesium deficiency with defined symptoms could be detected. Given the ability of the kidneys for preservation it takes several months until a deficiency condition develops (Shils,1969; Wester, 1987). There are no easily applicable and reliable clinical-chemical parameters or biomarkers to determine magnesium deficiency (see 1.3). Hence, the focus is on symptomatic diagnosis.

A detectable magnesium deficiency or hypomagnesaemia (<0.8 mmol/l) may be caused by the following factors:

- reduced intake, e.g. malnutrition coupled with chronic alcoholism, parenteral nutrition without sufficient magnesium substitution
- intestinal losses and resorption disorders, e.g. loss of gastric juice (vomiting), acute and chronic diarrhoea, malabsorption syndrome, acute pancreatitis (formation of insoluble and poorly resorbable magnesium fatty acid salts), alcoholism, primary hypomagnesaemia (very rare, autosomally recessive and dominantly inherited)
- renal losses, e.g. interstitial kidney diseases, tubule defect, renal tubular acidosis, diabetic ketoacidosis, alcoholism (inhibition of tubular reabsorption), pharmaceutically-induced renal dysfunction (e.g. loop diuretics, also thiazide diuretics, cisplatin, ciclosporine A, gentamicin, aminoglycosides), Gitelman's and Bartter's syndromes
- increased requirements, e.g. lactating women after recovering from kwashiorkor and protein-energy malnutrition and
- endocrine disorders, e.g. primary or secondary hyperaldosteronism, hyperthyroidism, poorly adjusted diabetes mellitus, hyperparathyroidsm

A magnesium deficiency can lead to non-specific symptoms like exhaustion and to symptoms of neuromuscular over-excitability. In the case of manifest magnesium deficiency syndrome, the main symptoms affect the central and peripheral nervous system (concentration problems, depression, psychoses, cramp, fasciculation (isolated muscle twitching), cramp (normocalcaemic tetany), parasthesia (malaise like prickling or numbness), the gastrointestinal tract (nausea, vomiting, colic-like spasms, switch between obstipation and diarrhoea) and the cardiovascular system (ventricular extrasystoles and tachycardia, elevated digitalis sensitivity, angina pectoris, dizziness) (Davies and Fraser, 1993; Deshmukh et al., 2000; Eibl et al., 1995; Galland, 1988; Knoers et al., 2003; Nadler and Rude, 1995; Rude, 2000; Sheehan and White, 1982; Walder et al., 2002; Zumkley, 1987).

Magnesium deficiency is also characterised by secondary electrolyte changes in calcium, sodium and potassium metabolism. This means it is frequently not possible to clearly diagnose the symptoms as being linked to specific, pathophysiological or pathobiochemical organ malfunctions (Classen and Nowitzki, 1990; Leicht et al., 1990).

It is being discussed that an overly low magnesium intake and resulting disturbances of magnesium metabolism could be of etiological importance for a series of chronic diseases like cardiovascular disorders, hypertonia, osteoporosis, preeclampsia and diabetes mellitus (Altura, 1988; Fleet and Cashman, 2001; FNB, 1997; Kao et al., 1999; Laires et al., 2004; Nadler et al., 1993; Roberts, 1995; Rohn, 1991; Saris et al., 2000; Sojka and Weaver, 1995; Stendig-Lindberg et al., 1993; 2004; Tranquilli et al., 1994).
Epidemiological studies indicate that the uptake of "hard" water containing more magnesium and calcium, the consumption of a high magnesium diet or the use of magnesium-containing supplements go hand in hand with reduced morbidity and/or mortality or a reduced risk of suffering a heart attack or having high blood pressure (Ma et al., 1995; Marier, 1990; Rubenowitz et al., 1999; Witteman et al., 1994). No causal relationship has been proven between magnesium deficiency and a higher risk of heart attack. The magnesium losses, that occur in heart attack patients as a consequence of cellular depletion from necrotising tissue, are frequently accompanied by normomagnesaemia and even hypermagnesaemia (ISIS-4 Collaborative Group, 1995; Woods et al., 1992).

In a meta analysis of 20 clinically controlled studies, a low dose-dependent reduction in blood pressure was observed overall after the administration of magnesium supplements (240-480 mg/day). According to the authors, reliable tests with higher doses (480-960 mg/day) are needed in order to confirm this association (Jee et al., 2002).

In a clinically controlled study over 2 years a significant increase in bone density could be measured in 31 postmenopausal women following the ingestion of 250-750 mg magnesium per day. On the other hand, no additional effect of magnesium on bone metabolism could be observed in post menopausal women (Green et al., 2003). More studies are clearly needed in order to clarify the role of magnesium and bone health particularly as there are no reliable biomarkers for magnesium status (Martini and Mayer, 1999; Weaver, 2000).

Preeclampsia (gestoses with higher blood pressure and proteinuria) during pregnancy, lower birth weight and elevated premature birth rate are believed to be consequences of hypomagnesaemia. This means that preventive magnesium supplementation is recommended (Arikan et al., 1997; Kovacs et al., 1988; Spätling et al., 1985; 1993). A systematic Cochrane Review of 7 randomised studies (n=2689 women) did not determine any influence of oral magnesium supplements on foetal growth retardation, the frequency of preeclampsia or birth weight of newborn babies. Nor was any link established between magnesium administration and reduced birth weight in 23 studies with more than 2000 women. Routine supplementation during pregnancy cannot, therefore, be recommended (Crowther et al., 2002; Makrides and Crowther, 2001; Merialdi et al., 2003; Sibai et al., 1989; Villar et al., 2003).

Based on the available epidemiological studies it is unlikely that low magnesium intake or a lower magnesium serum level can be considered a major risk factor in the pathogenesis of type 2 diabetes (Humphries et al., 1999; Kao et al., 1999; Ochard, 1999). In the case of poorly adjusted diabetics there may be increased magnesium excretion via the kidneys as a consequence of gluocosuria leading frequently to a magnesium deficiency which means that magnesium supplements are necessary (Eibl et al., 1995). However there are contradictory findings as to whether insulin sensitivity and empty stomach glucose levels can be improved in diabetics through magnesium supplementation (de Valk, 1999; Eriksson and Kohvakka, 1995; Laires et al., 2004; Paolisso et al., 1990; Rohn, 1991; Wälti et al., 2002).

BfR is of the opinion that it is difficult to prove a clear primary causal relationship between lower magnesium intake and the onset of chronic, multifactoral diseases. On the other hand, most of the clinical trials examine the therapeutic effect of mostly very high, intravenously administered doses of magnesium (see also 2.3). Because of the very different study design of individual studies, it is also difficult to evaluate corresponding positive statements from meta-analyses in order to take information of this kind about the possible preventive effects

of magnesium into account when laying down requirement levels (Shils and Rude, 1996; Tucker, 1996).

9.3.3 Possible risk groups for deficiency

Because of the uncertain data situation, a magnesium deficiency cannot be ruled out at least in the case of adolescents and young adults aged between 15 and 19 as the highest intake is recommended for this age group (DGE, 2000). Older people are also vulnerable since not only reduced dietary intake but also other factors like increasing morbidity and medicine administration (e.g. loop diuretics etc.) can lead to higher losses through the kidneys and, by extension, to deficiencies (Durlach et al., 1998; Laires et al., 2004; Lee and Frongillo, 2001; Rayssiguier et al., 1990; Sheehan and White, 1982; Vaquero, 2002).

The data available for the Federal Republic of Germany on the nutritional status in respect of magnesium do not indicate inadequate magnesium intake in the range of recommended intake in healthy adults. Adolescents and young adults aged between 15 and 19 as well as older people are a risk group. However, there are no validated biomarkers (supply category 2/3).

9.3.4 Excessive intake, possible risk groups

In healthy individuals the increased intake of high magnesium foods does not lead to adverse effects. These were only observed when healthy individuals took magnesium in the form of supplements (Fleet and Cashman, 2001). Higher doses of magnesium (in the form of salts) can lead to osmotic diarrhoea which is, however, reversible after discontinuing the salt and reducing the dose. They are, therefore, safe. In the case of normal renal function only minor direct systemic effects are normally to be expected.

Hypermagnesaemia mainly occurs in conjunction with:

- reduced renal excretion, e.g. as a consequence of oliguria, anuria in conjunction with acute renal failure, chronic renal insufficiency, diuretics (spironolactone, triamterene), lithium therapy
- endocrine disorders, e.g. hypoaldostoronism (in the case of adrenal insufficiency), hypothyroidism
- elevated magnesium intake, e.g. excessive intravenous magnesium therapy, magnesium-containing medicinal products (antacids, laxatives) or
- endogenous magnesium release, e.g. as a consequence of rhabdomyolysis

The main symptoms of hypermagnasaemia (2.5-4.5 mmol/l) are initially nausea, vomiting, lethargy and reduction of cardiac induction. Magnesium intoxication (>5 mmol/l) can lead to so-called magnesium narcosis with muscular paralysis (respiratory paralysis) and diastolic cardiac arrest by blocking neural transmission in the central nervous system. This can be used therapeutically in the case of specific cardiac arrhythmias (e.g. Torsade de pointes, tachycardia), for tocolysis or preeclampsia. In order to achieve "therapeutic hypermagnesaemia" of approximately 2-3 mmol/l, parenteral intake of a high dose (approximately 73 mmol (1750 mg) in 24-hours) is necessary. This level exceeds the normal daily oral intake four-fold (Fawcett et al., 1999; Laban and Charbon, 1986; James, 1999; Mohr, 1994; Saris et al., 2000).

Children are more sensitive than adults when it comes to the sedative effect of magnesium salts. A fatal incident as a consequence of hypermagnesaemia and cardiac arrest was ob-

served in a 28-month-old boy who had been given uncontrolled high doses of 800 to 2400 mg magnesium as a supplement (McGuire et al., 2000).

9.4 Tolerable upper intake level for magnesium

Based on a NOAEL of 250 mg/day with a safety factor of 1, SCF set a **Tolerable Upper Intake Level (UL) of 250 mg/day** for the addition of magnesium compounds to conventional foods including food supplements. This does not apply to foods for special dietary purposes. Nor does it apply to magnesium normally (naturally) contained in foods. It was not, therefore, possible to give a UL for magnesium uptake from all sources. The use of a safety factor 1 is justified by the availability of corresponding data from many human studies in which a large number of test persons of all age groups, including pregnant women and children aged 4 upwards, were examined. Given the fact that there were no corresponding data for children aged 1 to 3, the UL applies generally to children aged 4 upwards and adults. As a precautionary measure, SCF recommends a breakdown of the total dose into 2 or more individual doses per day because frequently the data for the basis of the derivation of the UL stem from studies where the dose was administered several times over a day (SCF, 2001).

In the case of the UL of 350 mg/day indicated by the Food and Nutrition Board (FNB) for adolescents and adults, a LOAEL was taken which only applies to additional uptake from supplements. The addition of magnesium compounds to conventional foods has not, however, been taken into account. A UL of 110 mg and 65 mg per day was set for children aged between 4 and 8 and 1 and 3 (FNB, 1997).

The Expert Group on Vitamins and Minerals of the United Kingdom has given a so-called guidance level of 400 mg/day for supplements using the same database (Food Standards Agency, 2003).

9.4.1 Derivation of a maximum level for magnesium in food supplements

Up to now we were of the opinion that, on the grounds of preventive health protection, supplements should not contain more than one-fold the magnesium intake recommended by DGE and have suggested a maximum level of 400 mg (BgVV, 1998). This corresponds to 133% of the recommended daily dose (300 mg/day) according to the Nutrient Labelling Ordinance. A defined maximum level for magnesium can be derived using the proposed formula based on quantitative risk assessment for children and adults. However, there are derived upper levels of differing quality for additional intake ("Tolerable Upper Intake Level", "Guidance Level"), which means that here there is a certain degree of uncertainty particularly about the risk of osmotic diarrhoea caused by food supplements (FNB, 1997; Food Standards Agency, 2003; SCF, 2001). Because the Tolerable Upper Intake Level of SCF (UL) expressly apply to children aged 4 and upwards only, magnesium-containing food supplements should not be given to children under the age of 4. Hence, products of this kind should carry the warning **"Not for children under the age of 4"**.

9.4.1.1 Possible management options

a) Continuation of existing practice

i.e. the "one-fold rule" with a maximum level of 400 mg magnesium in food supplements per daily portion for **adults**. However, as a precautionary measure, it should be recommended that the total dose be broken down into two or more single doses per day.

Advantages: This level is oriented towards nutritional-physiological requirements and is based on the one-fold dose of the DGE recommendation or D-A-CH reference values (D-A-CH, 2000). It corresponds to the Guidance Level (Food Standards Agency,

2003). There are no reports available to us of negative experience although it must be said that in Germany the side effects of food supplements are not systematically recorded.
Disadvantages: Side effects involving soft faeces and diarrhoea are to be expected for this range in sensitive individuals including children as the risk value is far higher than the set UL. A warning is needed about the laxative effect. The addition to fortified foods is not taken into account.

b) Setting the recommended maximum level (TL_{FS}) for food supplements at 62.5 mg based on the UL of SCF for **children (>4 years of age), adolescents and adults**

If the proposed calculation is used to determine the maximum tolerable level (TL_{FS}) for magnesium in individual food supplements, then this leads to the following value assuming a multiple exposure factor (MEF) of 4:

$$\frac{250\ \text{mg}^{*}\ [\text{UL}] - 0\ \text{mg}^{**}\ [\text{DINF}]}{4\ [\text{MEF}]} = 62.5\ \text{mg}\ [TL_{FS}]$$

* SCF Opinion, 2001
** The value zero is to be used here because the UL does not apply to uptake from all sources but only to targeted additional intake.

Legend:

UL	=	Tolerable Upper Intake Level (SCF) usually referring to the daily total intake
DINF	=	Dietary Intake by Normal Food (95. or 97.5 percentile)
MEF	=	Estimated Number of Consumed Products
TL	=	Tolerable Level in a single dietary supplement or fortified food

As indicated in the report of 18 January 2002 (Part I: Minerals) on pages 15-16, the Multiple Exposure Factor (MEF) is a variable parameter which must be adapted to the current state of knowledge. Therefore, the possibility of adapting the MEF for "well-founded reasons" was explicitly granted (BgVV, 2002). A MEF of 4 from various magnesium intake sources (food supplements, fortified conventional foods and additives for technological purposes) cannot be easily justified according to today's level of knowledge about the differing bioavailability of magnesium in foods and food supplements. Given the better bioavailability of magnesium compounds added to foods and beverages (both for nutritional and for technological purposes) compared to food supplements, no elevated risk of diarrhoea is to be expected from the multiple consumption of conventional foods fortified in this way (FNB, 1997). In future, food supplements should bear the additional wording "do not exceed dose" and consumers are to be clearly informed about the type and amount of ingredients. This protective measure could rule out the possibility of multiple consumption of various similar magnesium-containing food supplements on one day owing to lack of knowledge.

Advantages: The consumption of food supplements (FS) containing this maximum level in the daily portion is not expected to lead to the onset of diarrhoea even when other products fortified with magnesium are consumed that contain this maximum level in the daily ration. There is no need for a warning about a laxative effect. With regard to the lower UL of 110 and 65 mg derived by FNB (1997) for children, there is no risk for this consumer group either.

Disadvantages: These safety considerations are highly restrictive. Measured against recommended intake of 300-400 mg for adolescents and adults (D-A-CH, 2000), food supplements with such a low maximum level no longer meet the supplementary purpose expected by consumers.

c) Setting a maximum safe level (TL_{FS}) at 125 mg based on the UL of SCF for **children (>4 years of age), adolescents and adults**
If the method proposed in Chapter 3.3.2 is used to determine the maximum tolerable level (TL_{FS}) of magnesium in individual food supplements and the residual amount (250 mg) available for supplementation is only allocated to food supplements (FS), and this is based on a Multi Exposure factor (MEF) of 2, then this leads to the following value:

$$\frac{250\ \text{mg}^{*}\ [\text{UL}] - 0\ \text{mg}^{**}\ [\text{DINF}]}{2\ [\text{MEF}]} = 125\ \text{mg}\ [TL_{FS}]$$

Legend: See Option b).

The MEF was set at 2 as multiple consumption of magnesium-containing food supplements is excluded through future compulsory labelling. It does, however, take possible additional intake from other sources into account (fortified conventional foods and beverages).

Advantages: Magnesium supplementation could be extended to fortified foods without there being a higher risk of diarrhoea. There is no need for a warning about the laxative effect.

Disadvantages: None

d) Setting the recommended maximum level (TL_{FS}) at 250 mg based on the UL of SCF for **children (>4 years of age), adolescents and adults**

If the method proposed in Chapter 3.3.2 is used to determine the maximum tolerable level (TL_{FS}) of magnesium in individual food supplements and the residual amount (250 mg) available for supplementation is only allocated to food supplements (FS), and this is based on a Multi Exposure factor (MEF) of 1, then this leads to the following value:

$$\frac{250\ \text{mg}^{*}\ [\text{UL}] - 0\ \text{mg}^{**}\ [\text{DINF}]}{1\ [\text{MEF}]} = 250\ \text{mg}\ [TL_{FS}]$$

Legend: See Option b).

The MEF was set at 1 as additional exposure through other product categories is insignificant with regard to the diarrhoea risk. Where appropriate, on the grounds of preventive health protection, it should be indicated that the admissible daily dose should be broken down into at least two doses per day.

Advantages: This value corresponds to the UL, i.e. to the safe dose indicated by SCF for supplemental intake of magnesium per day. There is no need for a warning about the laxative effect.

Disadvantages: It cannot be completely ruled out that there may still be a certain risk of diarrhoea as a consequence of the consumption of supplemental magnesium compounds from other foods and beverages. This is because magnesium in the form of magnesium carbonate is a generally approved additive in Germany. 50 mg is currently estimated as the normal amount for additional magnesium intake from fortified foods (BMVEL, 2002). Where appropriate, the TL is to be restricted by this amount to 200 mg. On the grounds of preventive health protection, further fortification of conventional foods is not recommended. Reference is made to the deviations in risk assessment

between SCF (2001) and FNB (1997) and the British Expert Group EVM (Food Standards Agency 2002; 2003) (see 9.3.1).

9.4.2 Derivation of a maximum level (TL_{FS}) for magnesium in fortified foods

In Germany some conventional foods, in particular beverages, sweets and dairy products are already fortified with magnesium. In addition, magnesium-containing additives are also admixed to foods for technological purposes. However, the scale of this is not known. Estimates assume that currently approximately 50 mg magnesium is taken up daily from fortified foods (BMVEL, 2002). There are no exact figures for Germany for the proportion of fortified foods in total energy intake compared to non-fortified, processed and also "unprocessed" foods like potatoes, fruit and vegetables (Flynn et al., 2003). Up to now, minimum and maximum levels were only set for specific foods for dietary purposes. According to Directive 1999/21/EC complete foods for special dietary purposes which are not intended for infants, may contain at least 7.5 and at most 25 mg magnesium/100 kcal. The setting of a maximum level is justified as the magnesium content of special food seemingly plays an important role as a cause of osmotic diarrhoea observed in conjunction with an overly high infusion rate of special liquid foods (Kandil et al., 1993). Infant formula must contain at least 5 and at most 15 mg magnesium/100 kcal according to Directive 91/321/EEC.

BgVV was of the opinion that the fortification of conventional foods with minerals should only be permitted as protection against overdose in individual cases if clearly proven preconditions for nutrient deficiency or inadequate supply of the population or groups of the population made this necessary. The formula presented for the derivation of maximum levels for nutrients with a Tolerable Upper Intake Level (UL) in individual food supplements could be applied in the same way if voluntary fortification of conventional foods were to be authorised (BgVV, 2002). Given the inadequate data situation, there are, however difficulties when it comes to setting the so-called MEF ("Multiple Exposure Factor", estimated number of food supplements consumed daily (FS) and fortified foods with the respective nutrient) in a substantiated manner in individual cases. In our opinion a MEF could prove to be a somewhat inflexible instrument. In future, there is likely to be a high growth market for food supplements. It can, therefore, be assumed that the MEF could change considerably over time. Based on the model of energy density by Flynn et al. (2003) consideration should therefore be given to including the energy density of the respective food in addition to the MEF when setting a maximum level or to sensibly linking both principles (energy density and MEF). The linking of the setting of maximum levels to energy density is, however, unsuited for specific beverages and food supplements as they do not contain any or only a low level of energy (AFFSA, 2002).

9.4.2.1 Possible management options

a) Continuation of the risk management proposal of BMVEL (2002) subject to the assumption that at present approximately 50 mg magnesium are taken up daily in addition via fortified foods.

   This management option is based on the quantitative risk assessment of SCF (2001) under the assumption that all added magnesium compounds in food supplements and in other conventional foods including beverages are to be taken into account when setting a tolerable level (TL) for an individual product.

   Advantages: None

   Disadvantages: Depending on the tolerable daily dose to be set for food supplements (e.g. the current proposal is 200 mg), there would be no further possibility for fortification of conventional foods, particularly for risk groups (adolescents, older people).

b) Extension of fortification to specific calorie-containing foods like sweets, dairy products in conjunction with setting a maximum level (TL_{FS}/100 kcal) in a range of 15-28 mg/100 kcal of the ready-to-eat food (Flynn et al., 2003).
This management option assumes that there is only a risk of diarrhoea in conjunction with the taking of high doses of magnesium in the form of tablets, effervescent tablets, capsules etc. whereas the uptake of magnesium compounds from other sources (processed foods and beverages) is not relevant or does not exist because of better bioavailability (FNB, 1997; Food Standards Agency, 2003).

This maximum level is based on the assumption that 50-100% of fortified foods are enriched with magnesium (Flynn et al., 2003). At present, however, only 5-15% of fortified foods are enriched with magnesium (Kersting et al., 1995).

Advantages: There is the option of extending approval without any additional risk. There is no need for warnings about laxative effect.

Disadvantages: Low calorie and calorie-free products are not taken into account.

c) Fortification of beverages with the laying down of a maximum level (TL_{FS}/portion) of 22.5 mg/100 ml of the ready-to-eat food.

This corresponds to an amount of 7.5% of the daily dose recommended in the Nutrient Labelling Ordinance. Mineral waters with a magnesium content of 50 mg and more per litre may be described as containing magnesium. Beverages are mainly intended to quench thirst which means that 225 mg added magnesium are already taken up from 1 litre. As there is some uncertainty in the case of beverages about the possible risk of diarrhoea, BfR recommends setting the maximum level for added magnesium as low as possible in conjunction with fortification. There is only a risk of diarrhoea when larger amounts are ingested, particularly of magnesium sulphate healing waters as the sulphate anion strengthens the osmotic effect (BGA, 1990). For that reason the use of magnesium sulphate should not be authorised in beverages.

Advantages: Beverages fortified with magnesium can make a relevant contribution to magnesium supply as can some magnesium-containing mineral waters.

Disadvantages: None, since there is no risk of diarrhoea at these levels.

Magnesium cannot be properly classified using the risk classification of nutrients taken over by BfR. BfR is, however, of the opinion that there is a moderate risk of adverse effects when magnesium is used in food supplements. A higher dose of magnesium (>250 mg per day as a single dose) can lead to osmotic diarrhoea which is, however, reversible. BfR recommends setting a maximum level of 250 mg for food supplements whereby this admissible daily dose should be broken down into at least two doses per day (Option d). There is probably not any risk of diarrhoea in conjunction with the magnesium fortification of foods because of the better bioavailability of magnesium. Hence, these amounts can be ignored or not taken into account. If fortification is extended to specific calorie-containing food groups, then a maximum level of 15-28 mg/100 kcal (Option b) is recommended and for beverages a maximum level of 22.5 mg/100 ml for the ready-to-eat food. No magnesium sulphate should be added to beverages (Option c).

9.5 Gaps in knowledge

- There are no reliable data on magnesium uptake from all sources (unprocessed, processed and fortified foods including drinking water and beverages, food supplements, magnesium-containing medicinal products) for the healthy population of all age groups.
- Systematic studies on the bioavailability of the magnesium compounds used in food supplements and fortified foods based on single and combined doses.
- Validated biomarkers for recording magnesium nutritional status over longer periods.

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10 Risk Assessment of Iron

10.1 Summary

The calculations available for Germany on iron intake indicate that around half of women do not meet the 50% higher recommended daily intake. The determinations of the serum ferritin level conducted to assess iron supply do, however, indicate that an iron deficiency is relatively rare in pre-menopausal women, too (supply category 1/2).

A series of epidemiological studies indicate that there could be an association between higher iron intake or elevated body iron stores and certain risks of disease. Because of these results it cannot currently be ruled out that uncontrolled and longer-term iron supplementation can increase, amongst other things, the risk of cardiovascular disease or carcinomas. BfR is of the opinion that this experience should be taken into account for precautionary reasons when establishing maximum iron levels even if these findings have not yet been scientifically secured. Various experts already warn against regular iron intake above the recommended level. Furthermore, human beings do not have an efficient excretion mechanism for iron, i.e. they are not able to break down excessive iron or excrete it in a targeted manner. Hence, iron intake is the only way of limiting iron-related damage.

BfR is of the opinion that the use of iron may involve a high risk to health and it should be classified with the nutrients in the highest risk group (in line with Table 2). Against the backdrop of existing gaps in knowledge, the supply situation of the German population, the potential risks linked to uncontrolled iron supplementation and in order to prevent an accumulation of high iron doses from various products, BfR believes that current practice needs to be reexamined. For reasons of preventive health protection it is, therefore, recommended that iron should no longer be used in food supplements. No iron should be added to conventional foods either. Targeted, individual iron substitution, which may be necessary because of specific indications like blood loss or absorption disorders, should only be done under medical supervision.

Recommended intake	10-15 mg/day	
Intake [mg/day] (NFCS, 1994)	**m**	**f**
Median	15.8	13.1
P 2.5	8.5	6.23
P 97.5	27.1	20.6
Tolerable Upper Intake Level	Not yet defined (EFSA)	
Proposal for **maximum levels** in:		
Food supplements	No addition	
Fortified foods	No fortification	

10.2 Nutrient description

10.2.1 Characterisation and identification

Iron is the fourth most common element and the most frequent transition metal on earth and in living organisms. Iron is essential for man and ranks amongst the trace elements. It may be present in two valence rates. Iron(II) compounds are reducing agents whereas the iron(III) compounds are oxidants (DGE/ÖGE/SGE/SVE, 2000; Elmadfa and Leitzmann, 1990; Falbe and Regitz, 1997; Löffler and Petrides, 2003).

In Germany iron or iron compounds may be added to specific foods for special *technological* purposes. Iron oxides and iron hydroxides are authorised as food colours with the E number E 172. The addition of iron(II) gluconate (E 579) and iron(II) lactate (E 585) to olives for "oxidation effect - darkening" is permitted up to a maximum level of 150 mg/kg (calculated as iron). The use of the iron-containing compounds sodium ferrocyanide (E 535), potassium ferrocyanide (E 536) and calcium ferrocyanide (E 538) as agents to maintain flow ability in salt or salt substitutes is permitted up to a maximum level of 20 mg/kg (calculated as water-free potassium ferrocyanide (c. Additives Approval Ordinance).

Iron supplementation for *nutritional-physiological* purposes has only be permitted in Germany up to now for specific products for special dietary purposes but not for conventional foods. The European Commission Directive 2000/15/EC (of 15 February 2001 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses) permits the following 11 iron compounds for nutritional-physiological and dietary purposes in these foods (Annex 2 to the twelfth Ordinance on the Amendment to the Ordinance on Foods for Special Dietary Purposes of 31 March 2003):

- iron(II) citrate
- iron(II) fumarate
- iron(II) gluconate
- iron(II) lactate
- iron(II) sulphate
- iron(III) pyrophosphate (ferric diphosphate)
- iron(III) saccharate
- ferrous carbonate
- ferric ammonium citrate
- ferric sodium diphosphate
- elemental iron (carbonyl + electrolytic + hydrogen reduced)

The same iron compounds are included in the Commission Directive 2002/46/EC (of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements).

Table 19 in the Annex lists the admissible iron compounds, their synonyms and other characteristics. It shows that the compounds ferrous gluconate and ferrous lactate may be used for both technological as well as for nutritional-physiological purposes. The other ones which are permitted solely for technological purposes are merely mentioned for the purposes of completeness but are not examined here.

The above-mentioned iron compounds constitute a heterogeneous group which can be categorised in various classes on the basis of differences in bioavailability (Fairweather-Tait, 1989):

Compounds with good bioavailability: They include water soluble compounds. Frequently, they are the most chemically reactive and may cause unwanted colour and oxidative changes in foods which may limit their use for fortification purposes (Cook and Reusser, 1983; Garcia-Casal et al., 2003; Hurrell et al., 2002).

Iron(II)sulfate is normally used as the standard for comparative measurements of the bioavailability of different compounds. Ferrous sulfate is roughly absorbed on the same scale as intrinsic non-haeme iron which occurs naturally in foods (Hurrell, 1984). According to Brock et al. (1985) moderate to severe side effects occurred in around 50% of people who were given ferrous sulphate in the form of conventional tablets. This corresponds to an amount of 50 mg iron.

Iron(II) fumarate has a similar bioavailability to iron(II) sulfate and around 20% is resorbed in the case of peroral administration. Compared with inorganic iron salts this compound clearly offers the benefit of better local tolerance which is described as good in approximately 75% of patients. Furthermore, the compound is said to be less toxic than iron(II) sulfate (Hartke et al., 2002; Hurrell et al., 1989; Hurrell et al., 2002; von Bruchhausen et al., 1993).

Compared with inorganic iron salts *iron(II) gluconate* is also said to have a better tolerance. In conjunction with peroral iron treatment gastro-intestinal disorders have been described for around 20% of patients (von Bruchhausen et al., 1993).

Iron(II) lactate also ranks amongst the readily water soluble compounds with high bioavailability.

Iron(III) saccharate is obviously not an exactly defined mixture of iron oxide and saccharose (Hurrell, 1984). The working group of Hurrell (1989) observed an availability of 74% in healthy adults compared to ferrous sulphate.

Compounds with moderate bioavailability:
Ferric ammonium citrate, which has not been used very much up to now, is described as having moderate bioavailability (Hurrell, 1984).

Iron(II) citrates were found to have a bioavailability of 50% in animal experiments compared to ferrous sulphate (Shiau and Su, 2003).

Iron from *ferrous carbonates* is less readily absorbable than ferrous sulphate (Ekenved, 1976).

Compounds with low and/or variable bioavailability:
The compounds in this group have poor water and acid solubility (Cook and Reusser, 1983; Garcia-Casal et al., 2003).

The bioavailability of phosphate compounds (like *ferric sodium phosphate or iron(III) pyrophosphate)* is relatively low and varies considerably depending on the product (Cook and Reusser, 1983; Hurrell, 1984). Hurrell et al. (1989) observed a relative bioavailability of 39% for ferrous sodium phosphate compared to ferrous sulphate in their study in healthy adults. The relative bioavailability of the addition of ferric sodium phosphate to cereals is given as being in a range of 14-40% in cereals compared to ferrous sulphate (Hurrell, 1984).

The family of *elemental iron powders* include

- *reduced iron*
- *electrolytic iron* and
- *carbonyl iron*,

which are largely chemically inert. Compared with soluble iron compounds they offer the advantage of good technical properties which do not lead to any unwanted "off flavour" or discolouration. However, bioavailability can vary considerably depending on the production method and physico-chemical properties (e.g. particle size) (Hallberg et al., 1986; Hurrell et al., 2002; Hurrell, 1984).

The details on bioavailability of *reduced iron*, 13-90% of that of ferrous sulphate, show a major range of fluctuation.

For *electrolytic iron* the details on relative bioavailability are on a scale of around 50%.

For *carbonyl iron* this was indicated as between 5 and around 33%. Furthermore, there are signs that bioavailability cannot be increased through the addition of vitamin C. One advantage of carbonyl iron is its comparatively large safety margin. Gordeuk et al. (1987) compared the tolerance and effect of 3 x 600 mg iron/day as carbonyl iron with 3 x 60 mg iron/day as ferrous sulphate in 36 blood donors with mild anaemia. Both therapy regimes had comparable tolerance and an anti-anaemic effect. However, only a 1.5 fold increase in the amount absorbed was observed in conjunction with the 10 times higher iron level in the carbonyl iron.

The SUSTAIN Task Force Report only recommends the use of electrolytic iron powder for fortification. Because of its 50% bioavailability compared with ferrous sulphate, double the amount should be used (Hurrell et al., 2002).

10.2.2 Metabolism, function, requirements

Metabolism:
Basic data: Iron is an important component of numerous oxygen and electron-transferring groups of active substances. Haeme proteins rank amongst the main iron-containing compounds. These are proteins with an iron porphyrin-containing prosthetic group like haemoglobin, myoglobin and cytochromes (DGE/ÖGE/SGE/SVE, 2000; Elmadfa and Leitzmann, 1990; Yip, 2001).

In healthy individuals *total body iron* is 3-5 g or 45 up to 60 mg/kg body weight and is distributed over various fractions (functional, transport and depot iron) (Löffler and Petrides, 2003).

Around 2/3 of iron are available as *functional iron* in the form of *haemoglobin* in the erythrocytes (approximately 5 x 10^6 erythrocytes/mm^3 blood). The molecular weight of haemoglobin is approximately 64 500. As 1 g haemoglobin contains 3.4 mg iron (or 1 mol haemoglobin 4 mol iron), that can bind 1.34 ml O_2 ,1 ml blood with a haemoglobin concentration of 15 g/100 ml (2.3 mmol/l) contains approximately 0.5 mg (9 µmol) iron. This means that the healthy adult has about 2.5 g (45 mmol) haemoglobin iron in his 5 l blood. Of this amount 0.8%, i.e. 20 mg (360 µmol), are used daily in haemoglobin degradation and synthesis. Together with the 5 mg (90 µmol) for the turnover of enzyme iron and storage iron, this means a daily turnover of 25 mg (450 µmol) (Gross and Schölmerich, 1982; Löffler and Petrides, 2003; Yip, 2001).

Iron-containing *enzymes* (catalyses, cytochromes, peroxidases) and *myoglobin*, which is a kind of oxygen store in tissue, account for around 15% of functional iron (Elmadfa and Leitzmann, 1990; Yip, 2001). Around 0.1% of total body iron, corresponding to approximately 3 mg, circulates in blood plasma bound to the iron transport protein *transferrin* (*transport iron*) (Gross and Schölmerich, 1982; Herold, 1987; Schröder, 1994).

Depot iron stored as *ferritin* or *haemosiderin* – depending on gender – accounts for around 15-30%. In healthy adults it amounts to approximately 1.5 g (27 mmol). High tissue concentrations can mainly be found in the liver, spleen and bone marrow (Löffler and Petrides, 2003; Yip, 2001).

Absorption: Iron absorption is dependent on several factors. It is influenced by physiological requirements, the amount and chemical form of ingested iron, individual iron nutritional status, the scale of erythrocyte production and the ratios of various other organic and inorganic food components (Elmadfa and Leitzmann, 1990; Hallberg, 1981; Roughead and Hunt, 2000; Yip, 2001). Depending on availability the absorption of iron is subject to an adaptive control mechanism. Basal iron absorption amounts to around 1 mg/day which falls by up to 50% when iron stores are full. In the case of inadequate supply this can be increased to up to 3-5 mg/day (Cook, 1990). Other authors report that the amount of iron absorbed from foods may

vary between <1% and >50% depending on nutritional status (Yip, 2001). According to other information the absorption of non-haeme iron from a meal containing iron with high bioavailability can vary between the 10-15-fold amount (absorption rate 1-15%), whereas the absorption of haeme iron is only subject to a 2 to 3-fold variation (absorption rate 15-45%) (Hunt and Roughead, 2000).

On average men absorb 6% and women of childbearing age, because of their lower iron stores, around 13% of dietary iron (Yip, 2001). According to Magnusson et al. (1981) the following absorption rates are achieved in conjunction with the administration of a reference dose of 3 mg divalent iron depending on the size of the iron store: 20% of iron storage on a scale of 500 mg (corresponding roughly to serum ferritin of 60 µg/l); 40% in individuals with emptied iron stores who do not suffer from anaemia (serum ferritin approximately 30 µg/l) and roughly 70-80% in individuals who are already suffering from impaired erythropoiesis caused by emptied iron stores (serum ferritin approximately 12 µg/l).

The large proportion of iron in food is complex-bound (porphyrin-bound iron or water soluble Fe^{2+} chelates). Only a small amount is found in ionised form as free Fe^{2+} ions. Sufficient HCl production in digestive juice is an important precondition for optimum exploitation of dietary iron. In the acid milieu of the stomach the compounds are cleaved into free iron ions and loosely bound organic iron. Besides the digestive juices the organic acids to be found in food and digestive juices are also important for cleavage. Reducing substances in foods like sulfhydryl-containing aminoacids (cysteine in proteins) or ascorbic acid as well as a mucosa-associated ferrireductase convert trivalent iron into bivalent iron which is more readily soluble and absorbable (Forth and Rummel, 1987; Greiling and Gressner, 1989; Löffler and Petrides, 2003).

The main sites for reabsorption of iron are the duodenum and the upper jejunum. However, the resorptive activity in the case of iron deficiency can be considerably extended towards the distal region. In the lower sections of the small intestine, for instance in the ileum, the lower resorption rate can be compensated to a certain degree by the longer retention time of digesta (Forth and Rummel, 1987; Löffler and Petrides, 2003). Iron resorption is a complex, multi-stage process in which various proteins are involved.

Uptake into the mucosa cell is done via the transporter for bivalent metals; besides iron it also transports other bivalent metals like manganese, copper, cobalt, cadmium or lead. In the mucosa cell iron has two potential fates: it can be stored as ferritin, an iron storage protein or transported with the shuttle protein mobilferrin via the basolateral membrane to plasma. Haeme iron taken up into the cell is probably released through haemoxygenase from the porphyrin skeleton and imported into the mobilferrin shuttle (Löffler and Petrides, 2003).

The iron is then transferred to the iron transport protein in plasma, *transferrin*. This is a polypeptide with a mean molecular weight of 90,000. It is mainly synthetised in hepatocytes and, to a lesser degree, in bone marrow, spleen and lymph nodes. Protein binding is necessary because trivalent iron only has limited solubility in the aqueous medium and inclines towards polymerisation when there is a physiological pH. Each transferrin molecule binds two atoms of trivalent iron. Transferrin also binds and transports other trace elements whereby a distinction must be made between the following binding affinities: $Fe^{3+}>Cr^{3+}>Cu^{2+}>Mn^{2+}>Co^{2+}>Cd^{2+}>Zn^{2+}>Ni^{2+}$. A transferrin concentration in the plasma between 220-370 mg/100 ml (26-42 µmol/l) is considered to be the normal range. The total amount of 7 to 15 g transferrin in an adult is distributed evenly between plasma and the interstitial space. Transferrin bound iron has a short half-life, 70-140 minutes as the total amount in the blood is approximately 3-4 mg and 25-30 mg iron are required daily for haemoglobin synthesis. The maximum binding capacity of transferrin is normally only exploited to around 30%. But even in the case of full saturation total plasma transferrin can only take

up a small amount of maximum 12 mg iron (Forth and Rummel, 1987; Greiling and Gressner, 1989; Hartke et al., 2002; Löffler and Petrides, 2003).

From plasma iron reaches bone marrow where it is available for haemoglobin binding which takes place there. Around 70-90% of iron bound to transferrin are used by the erythrocyte precursors in bone marrow for *haemoglobin biosynthesis*; the rest is used for the biosynthesis of enzymes and coenzymes or migrates to the iron stores (Gross and Schölmerich, 1982; Löffler and Petrides, 2003).

Erythropoesis is responsible for the main share of *iron turnover*. Erythrocytes contain around 2/3 of total body iron and are phagocytised by macrophages in the reticuloendothelial system (RES) after their average life span of 120 days. The RES iron is the main source of plasma iron. The daily iron turnover in plasma is around 30 mg in healthy individuals. This means that serum iron is renewed approximately 10 times a day. Anaemia occurs when no depot iron is available any more (Greiling and Gressner, 1989; Gross and Schölmerich, 1982; Yip, 2001).

The iron which is not used for the biosynthesis of haemoglobin or other proteins is first stored as *ferritin* (25 percent by weight iron) and – if the ferritin store is full – as *haemosiderin* (35 percent by weight iron) (Löffler and Petrides, 2003).

The most important physiological role of *ferritin* is the storage, transport and detoxication of iron. In structural terms this is a high molecular protein with a molecular weight of 450,000. In line with requirements iron can be quickly mobilised from ferritin and used for haemoglobin synthesis. An apoferritin molecule can take in up to 450,000 iron atoms. Here it is oxidised into Fe^{3+}. In this storage form the toxicity of iron is neutralised and water solubility guaranteed. A reduction to Fe^{2+} is necessary in order to release iron from ferritin. This is probably done by NADH-dependent ferrireductase. The intracellular iron content has a regulatory impact on both ferritin synthesis as well as probably on the active secretion of apoferritin into blood (Greiling and Gressner, 1989; Gross and Schölmerich, 1982).

In healthy adults the ferritin concentration in plasma correlates directly with the total amount of mobilisible storage iron in the organism. 1 µg/l serum ferritin corresponds in adults to a storage iron amount of approximately 8 mg (Walters et al., 1973; Yip, 2001) and in small children to approximately 14 mg (Hambidge, 2003). Lower serum ferritin values are only known in conjunction with low iron stores. A plasma ferritin value reduced to below 30 µg/l is an indicator of an exhaustion of total body iron reserves available for haemoglobin biosynthesis. In general ferritin values of <12-15 µg/l are assumed to be the limit values. On the other hand iron overloads can be diagnosed in conjunction with elevated ferritin. Ferritin values >200 µg/l in women of childbearing age and >300-400 µg/l in men are an indication of high iron stores which should be clarified using differential diagnosis (Heath and Fairweather-Tait, 2003; Löffler and Petrides, 2003; Yip, 2001).

Haemosiderin is also an iron protein complex which is scarcely water soluble compared with ferritin. Iron is stored permanently in this substance iron in a form that is not available for metabolism. It is probably formed from ferritin after prolonged intracellular iron storage, e.g. in the case of chronic haemolytic anaemias or after frequent blood transfusions (Greiling and Gressner, 1989; Schröder, 1994).

Regulation – correlation – bioavailability: Intestinal iron resorption is regulated by various *regulators* about which very little is known up to now. Evidently the precursors of the intestinal mucosa cells are able to register body iron level by changes in transferrin receptor and ferritin expression. The transferrin receptor in the precursor cells is associated with the HFE protein which is involved in regulation by an unknown means. Mutations in the gene can lead

to chronic iron overload of the organism (Greiling and Gressner, 1989; Löffler and Petrides, 2003).

It is known that a multi-day iron intake can block further iron uptake (dietary regulator) which has been described in the past as the mucosa block theory. Another regulatory mechanism reacts to total body iron (storage regulator). This means that the amount of resorbed iron can be increased in the case of a lower depot iron. Another regulatory principle, the erythropoietic regulator, regulates iron resorption in line with the needs of erythropoiesis (Greiling and Gressner, 1989; Löffler and Petrides, 2003).

If the organism needs more iron, the metal can be mobilised from the mucosal ferritin store. If the organism's iron requirements are met, mucosa ferritin is lost after 2 to 3 days by means of physiological desquamation of the intestinal epithelia. The scale of iron resorption increases with declining total body iron store; this can be indirectly determined through the concentration of ferritin detectable in plasma too. The increasing drop in the plasma ferritin level leads to a higher percentage of a constant amount of orally ingested iron being resorbed (Löffler and Petrides, 2003).

Because of the various adaptive control mechanisms accompanying iron absorption, it has been assumed up to now that there can be no iron overload in healthy individuals (Hallberg, 2002). Hallberg et al. (1997) concluded from their studies that haeme and non-haeme iron absorption in healthy individuals was down-regulated in the case of a ferritin concentration of 60 µg/l. However, more recent study results contradict the experimental findings of Hallberg et al. (1997). They indicate an inverse association between iron stores and iron absorption. Fleming et al. (2002) noted that 70% of a study population encompassing 614 individuals aged between 68 and 93 had serum ferritin levels of more than 60 µg/l. Certain dietary factors were linked to an elevated risk of high iron stores: >3 portions fruit/fruit juice per day, >4 portions red meat/week and the use of iron-containing supplements (>12 and <30 mg/d). By contrast, a 77% lower risk for high iron stores was identified in conjunction with the consumption of 7 portions wholegrain products/week (corresponding to a mean dietary fibre intake of around 23 g/day).

Roughead and Hunt (2000) described incomplete adaptation in conjunction with supplementation with ferrous sulphate. In individuals with adequate to high iron stores they noted that iron supplementation led to a further increase in the serum ferritin concentrations even after completion of supplementation. Furthermore, supplementation with 50 mg iron/day in the form of ferrous sulphate merely led to a reduction in absorption of non-haeme but not of haeme iron. The working group (Hunt and Roughead, 2000) produced similar findings in another study involving a switch from a diet with high bioavailable iron to a diet with low bioavailable iron. This led to an adaptive process only for the absorption of non-haeme but not of haeme iron. The authors did not rule out that the differences in the bioavailability of iron in the various diets had not been adequately recorded when absorption is only measured over a short period.

Bergström et al. (1995) conducted studies on iron supply in 867 healthy Swedish adolescents aged between 14 and 17. The mean iron intake of the boys was 1.6 times higher than recommendations and for girls it was in the 0.9-fold recommendation range. In 15% of the girls and 5% of the boys low serum ferritin values (<12 µg/l) were determined. No association could be established between low iron intake and an elevated risk for low serum ferritin levels. The authors suspect that gender-dependent differences of perhaps a hormonal nature could affect the formation of iron stores during and after puberty. However, they did not identify any influence of menstrual bleeding or inadequate iron intake.

Numerous other studies did not establish any association between iron intake and iron status. Soustre et al. (1986) observed that the ferritin level does not correlate with daily iron in-

take. However, a significant association was established between the consumption of meat, the main source of iron with easily bioavailable haeme iron and the serum ferritin concentration. Osler et al. (1998) also observed within the framework of the MONICA Survey in 238 Danish individuals aged between 35 and 65 years over a period of 6 years that, with the exception of alcoholic beverages, there was no association between diet and ferritin levels. Although iron intake was below the recommendations, the mean ferritin concentrations were in the normal range.

Hence, it can be observed that there is neither a correlation between daily iron intake and serum iron nor with serum ferritin. This can be attributed to a large number of different factors (Lilienthal Heitmann et al., 1996; Soustre et al., 1986):

- Inter-individual fluctuations in the bioavailability of dietary iron (different intestinal absorption, dependence on iron status)
- Differences in the bioavailability of dietary iron
- Interaction between dietary iron and the factors that promote and inhibit absorption
- Fluctuations in physiological (menstruation) and non-physiological (blood donations) iron losses
- Lack of reliable data on the intake of iron-containing supplements/medicinal products
- Uncertainties in nutrient tables (discrepancies between calculated and chemically measured iron levels in food)
- Mistakes in diet history (discrepancy between reported and actual iron intake).

It is assumed that the composition of overall diet is more important for the level of absorption than the form in which iron occurs in a specific food (Elmadfa and Leitzmann, 1990). This would mean that indications of iron contents in individual foods would not offer any reliable lead for choosing foods in conjunction with elevated iron requirements.

Furthermore, based on different regulatory mechanisms there seem to be differences in the bioavailability of iron depending on the available form (normal diet versus tablets). There are signs that individual iron status exerts a lower influence on the absorption of iron from supplements than from normal diet (Hallberg, 2002). This means that extensive absorption also takes place when there is no inadequate supply or no deficiency and this can lead to overload. Linakis et al. (1992) found indications that iron is better absorbed from multivitamin products than from mono-iron products.

Interactions: Iron absorption is subject to numerous factors and interactions. This applies in particular to non-haeme iron.

Inhibition of absorption: The absorption of non-haeme iron can be inhibited by absorption-inhibiting ligands (e.g. *lignines, oxalic acids, phytates and phosphates*), which are to be found in plant foods like cereals, unpolished rice, corn, peas, beans and lentils. Iron absorption from cereals could be increased through phytate destruction. Iron-binding *polyphenols* like, for instance *tannins* are to be found in numerous foods and beverages like coffee, black tea or red wine (DGE/ÖGE/SGE/SVE, 2000; Hallberg and Hulthén, 2000; Hallberg, 2002; Hurrell et al., 2003; Yip, 2001).

Furthermore, the absorption of non-haeme iron through *calcium, soya proteins* and *eggs* is decreased. A high calcium content in a meal can also reduce the absorption of haeme-iron (DGE/ÖGE/SGE/SVE, 2000; Hallberg and Hulthén, 2000; Hallberg, 2002).

Various experimental studies supplied evidence that iron absorption can be competitively inhibited through high intakes of *zinc, cobalt, cadmium, copper* and *manganese* (Monsen, 1988).

Rossander-Hultén et al. (1991) reported a decrease in iron absorption by 56% in conjunction with a zinc overload in a ratio of 5:1 (15 mg zinc – 3 mg iron). However, this could only be determined in the absence of meals which means that intraluminal interaction is suspected between the two trace elements. Inversely, it is known that high iron amounts depending on dose can have a disadvantageous effect on *zinc* absorption (Whittaker, 1998). The interaction is attributed to the competitive inhibition of zinc absorption through iron overload when the molar relationship is greater than 2:1 for a total iron amount of >25 mg (Solomons, 1986).

The strong inhibitory influence of manganese on iron absorption is attributed to the use of joint transport systems through the intestinal mucosa. A ratio of manganese: iron of 2.5 : 1 (7.5 mg manganese – 3 mg iron) or of 5 : 1 (15 mg manganese – 3 mg iron) led to a decrease in iron absorption of 22% and 34-40% respectively (Rossander-Hultén et al., 1991). Inversely, there are signs that the level of the iron store can influence manganese status. Finley (1999) described the fact that individuals with low ferritin levels absorbed 3-5 times more manganese than individuals with high ferritin levels.

Promotion of absorption: By contrast, the absorption of non-haeme iron can be encouraged by absorption-promoting ligands like *citric acid* or *ascorbic acid* (e.g. in fruit). *Meat, poultry, fish and seafood, soya sauce* and some *fermented types of vegetables* as well as *alcohol* can promote absorption (DGE/ÖGE/SGE/SVE, 2000; Hallberg and Hulthén, 2000; Hallberg, 1981; Hallberg, 2002; Yip, 2001).

Mechanisms of interaction: In many cases it is not clear which components play a concrete role or to which mechanisms the interactions can be exactly attributed.

- A dose-dependency was described between *calcium* and inhibition of non-haeme iron absorption. Whereas no effect was observed with a calcium content in the meal of <50 mg, a maximum inhibitory effect was observed for a level of 300-600 mg. The effect on iron absorption was independent of the calcium source and was observed in the form of calcium salts, milk or cheese for the same calcium amounts. Haeme iron absorption was influenced by calcium in a similar way (Hallberg and Hulthén, 2000; Hallberg et al., 1992). The underlying mechanism is not yet known; an intraluminal interaction is suspected (Lynch, 1997).
- In the case of *soya proteins* it has long been suspected that the absorption-inhibiting influence could be due to a high phytate level. On the other hand, technological reduction of the phytate content could not completely overcome inhibition (Hallberg and Hulthén, 2000).
- Polyphenols are clearly able to remove iron from absorption through complex formation (Lynch, 1997).
- The reduction in non-haeme iron absorption observed during the consumption of eggs is attributed to the yolk; however the underlying mechanism has not yet been identified (Benito and Miller, 1998; Hallberg, 1981).
- Studies in man have shown that alcohol can increase the absorption of trivalent but not divalent iron. This absorption-enhancing effect is attributed to an increase in gastric acid secretion (Hallberg and Hulthén, 2000).
- The promotion of non-haeme iron absorption observed in conjunction with ascorbic acid is attributed to iron reduction and, by extension, to inhibition of the formation of the poorly soluble iron(III) compounds. A significant increase in absorption was already ob-

served at low levels of only 25 mg vitamin C; 1 glass orange juice with 70 mg vitamin C led to a 2.5-fold increase in iron absorption (Hallberg and Hulthén, 2000; Hallberg, 1981).

- It is suspected that *vitamin A* can promote iron absorption by masking the effect of certain absorption-inhibiting substances. Studies by Layrisse et al. (1997) indicate that vitamin A can bind iron during the digestion process. In this way it can remove iron from the absorption-inhibiting influences of phytates and polyphenols thereby increasing the bioavailability of iron. The working group of Garcia-Casal (2003) reported on a 3.6-fold increase in iron absorption when coupled with parallel administration of *vitamins A* and *C*. *In vitro* tests provided indications that the vitamins play an import role in increasing the solubility of ferrous chloride and elemental iron on a scale comparable with a shift in the pH from 6 to 2.

Interactions with drugs: There are several known interactions with drugs (Campbell and Hasinoff, 1991). By means of complex formation with iron the efficacy of the numerous medicinal products can be reduced. Examples:

- *Antibiotics*: tetracyclines, gyrase inhibiters *(ciprofloxacin),* penicillin *(ampicillin*), tuberculostatics (*rifampicin*)
- *Antihypertensives*: methyldopa, captopril, minoxidil
- *Parkinson medicinal products*: levidopa
- *Hormones*: thyroxine
- *Vitamins*: folic acid
- *Analgesics*: paracetamol, salicylic acid
- *Antirheumatic agents*: indomethacin

Aluminium, magnesium and calcium-containing *antacids* and *lipid-lowering agents* (*cholestyramine)* can prevent iron resorption by binding up to 70% of poorly soluble compounds (Hartke et al., 2002; Schröder, 1994).

Non-haeme iron absorption can also be inhibited by *chelating agents* like *penicillamin*, *ethylene diamine tetraacetic acid (EDTA)* or *deferoxamine* which is used for iron detoxication or mobilisation and expulsion of abnormal iron deposits (Forth and Rummel, 1987). The calcium-disodium-salt of EDTA (calcium disodium methylene diamine tetraacetate) is also used as a food additive (E number 385). In this capacity it may be added for instance to fish, vegetables and shellfish up to a certain maximum level (c. Annex 2 List B Ordinance on Requirements to be met by Food Additives and Marketing of Food Additives authorised for technological purposes (ZVerkV) and Annex 4 Additives Approval Ordinance (ZZulV)).

Excretion/loss: One specificity of iron metabolism is that iron status is exclusively controlled by resorption and there is no regulated excretion of iron (Löffler and Petrides, 2003; Schröder, 1994; Schümann et al., 1997).

Physiological iron loss is extremely low. Men and women after menopause excrete approximately 1-2 mg (19-36 µmol/l). This means that there is balanced resorption and excretion. Iron in the organism is lost through desquamation of intestinal epithelial cells (500 µg = 9 µmol/day) and skin cells (200-300 µg = 3.6-5.4 µmol/day), urine (100 µg = 1.8 µmol/day), bile and sweat (100 µg = 1.8 µmol/day) (Löffler and Petrides, 2003).

Larger iron losses only occur in conjunction with bleeding by means of the related haemoglobin loss. Approximately 25-60 ml blood is lost during menstruation whereby 12.5-30 mg (225-540 µmol) iron is excreted monthly. These losses can normally be compensated through a 2-2.5-fold higher absorption rate than in men. The iron loss of approximately 300 mg (5.4 mmol) during pregnancy is also of importance. The largest share of this loss is the

iron supplied to the foetus via the placenta. There is also blood loss during birth and lactation 0.5 mg (9 µmol/day). This iron loss is almost fully compensated by the fact that after pregnancy women do not normally menstruate for a few months (Bergström et al., 1995; Löffler and Petrides, 2003).

Parameters for the assessment of iron status: There are various parameters available to assess iron status or diagnose anaemia. The most important are transferrin, ferritin, iron and blood count from which other parameters like transferrin-iron binding capacity and transferrin saturation can be calculated (Greiling and Gressner, 1989). By means of the various parameters it is possible to record iron metabolism disorders in the stages sub-given in Table 20 in the Annex.

- *Ferritin* is currently described as the best marker for iron status. Its clinical importance stems from the fact that the amount of ferritin in serum correlates positively with total body iron pool. The reference range depends on method and there are various opinions about which lower limit value should be applied to ferritin. As a rule values <12 µg/l are seen as the indicator for emptied iron stores (Gaßmann, 2001; Hambidge, 2003; Milman et al., 1998). Serum ferritin is dependent on age and gender. Furthermore, there is a positive correlation with the Body Mass Index (BMI) (Heath and Fairweather-Tait, 2003).

  However, normal ferritin concentrations do not reliably rule out low iron stores. In the case of certain diseases the correlation may not apply and ferritin may be reactively elevated. False-positive elevated plasma ferritin values can, for instance, occur in liver disease as a consequence of elevated ferritin release by the hepatic cells, chronic inflammation and infections or carcinomas as a consequence of elevated ferritin biosynthesis through tumour cells (Löffler and Petrides, 2003; Yip, 2001). Elevated ferritin concentrations may also be found in conjunction with alcohol consumption and hyperglycaemia (Hambidge, 2003).

  The level of the serum *transferrin* correlates inversely with the size of the iron pool, i.e. it is higher in the case of an iron deficiency and lower in the case of iron overload. The transferrin level is also lowered by impairment of synthesis because of protein deficiency, protein losses or liver diseases as well as in conjunction with acute inflammations, trauma and malignant tumours. This means that where there is, for instance, parallel inflammation the transferrin value does not provide any information about iron status (Greiling and Gressner, 1989).

  Transferrin saturation provides information about iron transport to the tissues and is determined from serum iron and iron-binding capacity. Low transferrin saturation (<16%) generally goes hand in hand with an iron deficiency. Very high saturations (>50% in women and >60% in men) are seen as suitable indicators for haemochromatosis screening (Yip, 2001).

- Measurement of the *transferrin-bound* or *serum iron* can be done photometrically. However, the biological scattering range of iron concentrations is very large which can be attributed to physiological factors. Firstly, there is a circadian rhythm of iron concentration in serum with the highest values in the morning and the lowest in the evening. Furthermore, the serum concentration varies in women in conjunction with the oestrogen level (pregnancy, ovulation inhibitors) and during the menstrual cycle. For these reasons, the diagnostic importance of a one-off determination of the serum concentration is considered to be minor. The reference range given for men is 71-201 µg/dl and for women 62-173 µg/dl. A lowering of serum iron occurs in conjunction with manifest iron deficiency anaemia but also in conjunction with infectious anaemia or tumour anaemia (Greiling and Gressner, 1989).

An increase in *erythrocyte-protoporphyrin* in conjunction with inadequate iron intake or lead intoxication is described as a haemoglobin precursor. Because of its earlier reaction compared to haemoglobin, this parameter is classified as a suitable screening method for inadequate iron supply and early iron deficiency. However, other conditions like inflammatory reactions or conditions that go hand in hand with elevated erythrocyte turnover, may be accompanied by elevated erythrocyte-protoporphyrin concentrations (Yip, 2001).

If the iron intake is not sufficient to permit adequate haemoglobin synthesis, then an increase in the *transferrin receptors* can be observed on the erythrocyte precursors and in plasma. For these reasons elevated receptor concentrations can be used as an iron deficiency in tissue and can be considered as markers for early functional iron deficiency. However, not enough experience is yet available and a receptor elevation was also observed in other conditions. The threshold value is >8 µg/l for healthy adults. This market is not suitable for screening for haemochromatosis as no reduction in the receptor is observed in conjunction with iron overload (Hambidge, 2003; Yip, 2001).

A typical indication of anaemia is a lower *haemoglobin* concentration. The limit values, which can indicate anaemia, are <12 g/l in women and <13 g/l in men for adults. It should be borne in mind that these values are dependent not only on age or gender but also on race. Significantly lower haemoglobin levels were measured in black adult US Americans (approximately 8 g/l) (Yip, 2001).

- Furthermore, a series of *further haematological tests* are available which can contribute to differential diagnostic distinction between other forms of anaemia not attributable to iron deficiency, e.g. erythrocyte count, mean cell volume etc. (Yip, 2001).

Function: Iron porphyrin derivatives are involved in various ways in the utilisation of oxygen in biological oxidation processes. Furthermore, iron plays a role in cellular energy supply, non-specific infection defence and DNA synthesis. It is a component of enzymes (Elmadfa and Leitzmann, 1990).

In living organisms the potentially dangerous reactivity and the oxidative potential of iron are modulated by binding iron to carrier proteins or through the presence of molecules with antioxidative properties. Free iron catalyses the fenton reaction, one of the most well-known processes for the conversion of superoxide and hydrogen peroxide to free, reactive radicals which are linked to elevated oxidative stress and premature cell aging (Yip, 2001).

More recent studies indicate that iron and glucose metabolism are linked and that iron can influence both insulin metabolism in healthy individuals and in diabetics (Fernández-Real et al., 2002).

Requirements: Iron requirements result from iron losses via the intestines, kidneys and skin (approximately 1 mg per day). In women there are also losses during menstruation of approximately 15 mg per month. Growth and pregnancy increase requirements (DGE/ÖGE/SGE/SVE, 2000). Recommendations for iron intake must take into account bioavailability. This may fluctuate depending on the composition of food by the 10-fold amount (DGE/ÖGE/SGE/SVE, 2000). An intake of 15 mg per day would lead to an iron intake of 1.5 and 2.2 mg taking into account an absorption rate of 10-15% and cover the requirements of all women with normal menstrual bleeding. After menopause women do not have higher iron requirements than men. 10 mg/day is the recommended intake. During pregnancy a total intake of 30 mg per day is recommended (DGE/ÖGE/SGE/SVE, 2000).

In their latest report from 2001 FAO and WHO made recommendations, in response to the varying food habits around the world, which are based on different bioavailability levels (5, 10, 12 and 15%) (FAO/WHO, 2001). For western countries depending on meat consumption the application of levels 12-15% is proposed, for developing countries the levels 5-10%.

Table 21 gives the recommended intakes of DGE/ÖGE/SGE (2000), FNB (2002) and SCF (1992). The recommended intakes of FAO/WHO (2001) are given in Table 22.

10.2.3 Exposure (dietary and other sources, nutritional status)

Sources: Almost all foods contain iron, however, normally only in low amounts. Iron in food can be in the form of *non-haeme iron* and haeme iron (Monsen, 1988). In western countries the proportion of non-haeme iron which is normally found in plants and dairy products is estimated to be >85% of iron intake (Hallberg, 1981; Soustre et al., 1986; Yip, 2001).

A mixed diet contains 5-15 mg non-haeme iron and 1-5 mg haeme iron per day. The absorption rate of non-haeme iron, which is dependent on individual storage iron reserves and other dietary factors, is relatively low and relatively variable with a fluctuation range of around 1-15% (Hunt and Roughead, 2000).

Haeme iron primarily comes from haemoglobin and myoglobin in meat, poultry and fish (Benito and Miller, 1998; Monsen, 1988; Yip, 2001). Although it only accounts for the lower proportion, it is 2-3 times more readily absorbable than non-haeme iron since it is less influenced by other dietary components (Yip, 2001). The resorption rate is estimated to be 25% (Falbe and Regitz, 1997). Meat is the best source of iron (Löffler and Petrides, 2003). Other good sources are some types of vegetable (like spinach, beetroot) and cereal products (like wholegrain flour and sesame).

In line with the results of the Nutrition Survey (Mensink et al., 2002) conducted as a supplement to the Federal Health Survey 1998, bread is the main uptake source for iron, followed by meat and vegetables. Table 23 gives the iron contents of some foods (Souci-Fachmann-Kraut, 2000).

Food fortification: Current practice in Germany Up to now in Germany fortification of conventional foods with iron was only permitted after the prior issuing of an exemption or general disposition. Approvals of this kind have been issued for the food group *breakfast cereals*. Examples:

Iron compound used	Iron/100 g	Source
Ferrum reductum (elemental iron)	14 mg/100 g	Announcement of a general disposition in accordance with § 47a of the Foods and other Commodities Act concerning the import and the placing on the market of commercially available breakfast cereals (with iron fortification and with the colour capsanthin E 160c) of 8 July 1993
Iron(II) sulphate	9 mg/100 g	Announcement of a general disposition in accordance with § 47a of the Foods and other Commodities Act concerning the import and the placing on the market of breakfast cereals with iron and vitamin D supplementation of 16 November 1997
Iron(III) diphosphate	8 mg/100 g	Exemption in accordance with § 37 paras 1 and 2 No. 1 Foods and other Commodities Act for the production and placing on the market of various breakfast cereals with iron(III) disphosphate supplementation as fortified foods of 8 August 2002 (GMBl No. 40, p. 806 (2002))

Experience from countries in which more extensive fortification is undertaken: Given the sparse data situation, it seems appropriate to draw on experience from other countries when examining the question of food fortification. One good example is Denmark where flour was compulsorily fortified with 30 mg elemental iron/kg between 1954 and 1987. After withdrawal of the national iron fortification programme regular studies were conducted on iron nutritional status in the population.

Milman et al. (2002) compared the iron status of 40-70 year-old men during the period of compulsory fortification (1983-1984; n=1324) and again 6-7 years after the abolishing of this programme (1993-1994; n=1288). Although withdrawal of compulsory flour fortification reduced average iron intake from 17 to 12 mg/day, a significant increase was observed in the prevalence of high ferritin levels (ferritin >300 µg/l) from 11.3% to 18.9%, which indicate iron overload. This development was understood by the authors as an argument against the reintroduction of the fortification programme. It was attributed to changes in food habits. The lower iron intake was possibly compensated by the consumption of products with more readily bioavailable iron.

In other studies in Danish women (n=1319, age: 40-70 years) (Milman et al., 2000) and men (n=1332, age: 40-70 years) (Milman et al., 1999) from 1994, it was observed that – compared with studies from 1984 and despite cessation of the national food fortification programme – the prevalences of iron deficiency and iron deficiency anaemia had remained unchanged in both genders but the prevalence of iron overload had increased. From the results it was concluded that no significant effects on iron nutritional status could be achieved through supplementation with iron in healthy women or men with adequate iron stores.

Food supplements: BgVV has been of the opinion up to now that the maximum intake of iron in a food supplement should not exceed 5 mg per day (BgVV, 1998). In a renewed assessment in 2002 (BgVV, 2002), it was again deemed acceptable, until the final assessment by SCF, to tolerate the use of iron in individual products up to a provisional maximum level of 5 mg/daily ration food supplement.

Based on these estimates, numerous exemptions and general dispositions have been issued for iron-containing food supplements.

Medicinal products: A monograph of the Federal Institute for Medicinal Products on peroral iron products is not available as far as we know. The therapeutic dose range is between approximately 36 and 200 mg iron/day (BPI, 2003). For peroral treatment of iron deficiencies with and without anaemia, mainly bivalent iron compounds are used because of their better bioavailability like iron(II) sulphate, iron(II) lactate, iron(II) fumarate, iron(II) gluconate or glycinate. Stabilisers like ascorbic acid are frequently used to avoid oxidation. In order to ensure improved use, administration is normally recommended on an empty stomach. However, for reasons of tolerance, the dose can be taken during or after a meal whereby single doses should not exceed 50 mg iron (Forth and Rummel, 1987).

Nutritional status:
Intake: In its revised version the *National Food Consumption Study* (NFCS) (DGE, 1996) gave as mean average intakes for men, dependant on age, 13.2-14.1 mg iron and 10.7-11.8 mg iron/day for women. In males of all age groups and for females aged 50 upwards mean intake was in the range of the DGE recommendations. In females aged between 10 and 50 years mean iron intake remains, by contrast, below recommended intake. 75% of 19 to 25 year-old women only achieved 85% or less of the recommendation. The highest intake values, measured at the 97.5 percentile, were observed in 15-18 year-old males of 27.7 mg (VERA-Schriftenreihe, 1995b). Table 24 in the Annex contains the results of the NFCS in percentiles broken down for age and gender.

The Nutrition Survey (Mensink et al., 1999) conducted as a supplement to the *Federal Health Survey 1998* produced the following results: on average the recommended daily intake was clearly exceeded by men of all ages (median approximately 160%, 25. percentile approximately 130%, 75. percentile approximately 195%) (Mensink et al., 2002). By contrast, around half of women did not reach the 50% higher daily recommended intake (median approximately 100%, 25. percentile approximately 80%, 75. percentile approximately 130%). As a precautionary measure, the authors also point out, at the same time, that the failure to reach the recommended intakes does not mean that there is necessarily a deficiency (Mensink et al., 1999). In principle, higher iron intake was observed amongst younger than amongst older women. As in the NFCS study the highest intake values, measured at the 90. percentile, were found in 18-24 year-old men of 27.4 mg (Mensink et al., 2002). With the exception of the age group of the over 65s, the median and mean values from the Federal Health Survey for both men and women were higher than those in the NFCS. Table 25 gives the results of the Federal Health Survey in percentiles broken down for age and gender.

In the *EPIC Study* (Schulze et al., 2001) conducted in Heidelberg and Potsdam in 1996-1998, the average iron intake in the middle age group for men was 14.6-15.1 mg and 11.6-12.3 mg/day for women. The 10. and 90. percentiles determined for men were 8.4/8.7 and 21.6/22.1 mg and for women 6.9/7.2 and 17.2/18.0 mg/day. The highest intakes measured at the 90. percentile of 21.6 and 22.1 mg were found in men (see Table 26).

No reliable information is available on the proportion or level of iron intake from fortified foods and food supplements. Nor are any data available at all on the level of iron intake from iron-containing compounds used for technological purposes (cf. Table 19).

Iron status: It has already been mentioned that various clinical-chemical parameters are available to assess iron status. As the ferritin concentration in blood serum has the largest power because of the direct association with the level of mobilisable iron store in the body, reference should only be made to ferritin for the purposes of estimating iron supply.

In the VERA Study the ferritin concentrations in blood serum were determined using enzyme immunoassay in a representative random sample of over 18 year-olds. 15-400 µg/l was defined as the reference range for men and 12-200 µg/l for women (VERA-Schriftenreihe, 1995a). Only 6.3% of all participants (9.1% women and 2.7% men) showed emptied iron stores at ferritin values below 12 µg/l. In contrast, ferritin values of more than 200 µg/l were observed in almost 10% (3.2% women, 17.9% men). This was interpreted by the authors as a sign of an elevated risk of cardiovascular diseases or cancer (see Table 27).

If one takes the serum ferritin values from the VERA Study as the basis, then critical iron supply is relatively rare even in pre-menopausal women.

10.3 Risk characterisation

10.3.1 Hazard characterisation (LOAEL, NOAEL)

Non-bound, free iron is toxic (Forth and Rummel, 1987). Iron is also discussed as a prooxidant in conjunction with the onset of cardiovascular and neurodegenerative diseases and as a promoter of cancer. The underlying mechanism is thought to be iron by means of its catalytic key function in the formation of cytotoxic hydrogen radicals and hydroxyradicals which promote oxidative stress, for instance in conjunction with the Fenton reaction and the Haber-Weiss-reaction (Nelson, 2001; Schröder, 1994).

What is new is the hypothesis based on these findings, that elevated iron stores can also increase the risk of disease (Schröder, 1994). At present, there is no generally accepted model for assessing the extent to which body iron stores could contribute to a higher cardiovas-

cular risk. It is suspected that iron can indirectly promote arterial sclerosis by means of the catalysation of LDL cholesterol oxidation (Sempos und Looker, 2001). In this context the role of vitamins A, C and E is also discussed; as prooxidants they have a direct impact on reduction to Fe^{2+} for the Fenton reaction. Here supplementation with these vitamins could lead to serious complications involving additional oxidative damage (Crawford, 1995; Fraga and Oteiza, 2002). In principle, these associations have not been sufficiently researched.

FNB (2002) derived a **LOAEL** (Lowest observed adverse effect level) of 60 mg/day and a LOAEL of 70 mg/day for total iron intake from human studies for adolescents and adults aged 14 upwards for non-haeme iron in the form of supplements. For children up to age 13 FNB established an **NOAEL** (No observed adverse effect level) of 40 mg non-haeme iron in the form of supplements. Gastro-intestinal effects were used as the end point.

The controlled, double blind study by Frykman et al. (1994) in 97 blood donors (46 men and 51 women aged between 34 and 52 years) to re-examine tolerance was used as the basis for this derivation. Over 3 periods of 1 month they were either given 60 mg Fe^{2+} (as ferrous fumarate), 16 mg Fe^{2+} (as ferrous fumarate) plus 2.4 mg haeme iron or placebo. It was demonstrated that the gastro-intestinal side effect rate of 25% was significantly higher for the non-haeme iron product than for the combination product. With a side effect rate of 14% respectively no difference was established between the combination product and placebo. Although the combination product had a lower dose, a comparable therapeutic effect on haemoglobin and ferritin concentrations was observed.

10.3.2 Iron overload and risks linked to high intakes and higher iron stores

Elevated intake may be the cause of iron overload in the organism as the excretion of this element is very limited. There are various diseases and adverse reactions which can be attributed to elevated intake or iron absorption. The following risks are currently under discussion:

Acute iron intoxication: There were mainly reports of *acute* iron intoxication in children as a consequence of the inadvertent ingestion of iron supplements intended for adults. This led in 1977 to provisions being introduced for child-resistant packages. Acute toxic effects were observed at doses between 20 and 60 mg iron/kg body weight. Amounts of 180 mg/kg body weight upwards are considered to be lethal for children. Although acute iron intoxications are rare in adults, a scale of around 100 g (approximately 1400 mg/kg body weight) is assumed as the lethal dose based on case studies (Anderson, 1994; FNB, 2002; Forth and Rummel, 1987; FSA, 2003).

Approximately 30 to 120 minutes after ingestion, symptoms may occur as a consequence of haemorrhagic-necrotising gastroenteritis, like blood-tinged vomit, diarrhoea, hypotonia and finally coma with liver and kidney failure. After a seeming improvement there may be renewed symptoms ranging from a drop in blood pressure, cramp to coma and respiratory paralysis after 20 hours (Anderson, 1994; Hartke et al., 2002).

According to Anderson (1994) acute iron intoxication in the USA in 1992 was the most frequent cause of fatal intoxication events in children under the age of 6. Kroeker and Minuk (1994) examined the frequency of intoxication cases in a large Canadian hospital and observed an increase in acute iron intoxications over the period from 1979 to 1991. 80% of patients were female, mean age 19.8 years (range 9-48 years). In one-third of the cases an association was observed with excessive alcohol abuse. Levels of between 38 and 108 mg iron/kg body weight were determined as the mean dose range for these cases. Although the preponderance of female individuals could not be explained, it is not ruled out that young women may possibly react more sensitively to the acute toxic effects of iron. There are indications of gender-specific differences from animal experiments, too (Berkovitch et al., 1997).

After iron administration significantly higher iron levels were observed in pubescent female rats than in male animals. This means that the influence of the female sexual hormone cannot be ruled out on iron absorption. Furthermore, higher iron resorption rates and a higher mortality rate were found in prepubescent female rats than in male animals. There is uncertainty as to the relevance of these findings for humans.

Chronic iron overload conditions: In certain cases chronic iron overload of the body may occur. A distinction is made between 3 types (Bassett, 2001; Yip, 2001):

1. primary iron overload or hereditary haemochromatosis due to excessive, uncontrolled gastro-intestinal resorption;
2. secondary iron overload conditions or haemosideroses which are due either to haematologic disorders, which regularly require blood transfusions, or chronically elevated dietary iron intake (e.g. chronic alcoholism);
3. *others (African iron overload, Porphyria cutanea tarda etc.):*

A distinction is made between 3 degrees of iron overload (Bassett, 2001):

- Mild form with 1.5-2 g storage iron
- Moderate form with 2-5 g storage iron
- Severe form with >5 g storage iron

Chemical laboratory tests established elevated ferritin concentrations, elevated transferrin saturation and a low iron-binding capacity (see Table 20).

on 1) *Primary iron overload (haemochromatosis):* Haemochromatosis (synonyms: bronze diabetes, siderophilia, iron storage disease) is an autosomal recessive hereditary disease. Because of a mutation in the HFE gene (frequently also described as HLA-H gene discovered in 1996) more iron is resorbed through the mucosa cells (Löffler and Petrides, 2003; Whittington and Kowdley, 2002). There are reports of various mutations. More than 80% of mutations concern the substitution of cysteine at position 282 by tyrosine on chromosome 6 (abbreviated C282Y). In the Caucasian population the frequency of the homozygotic gene carriers is estimated to be 1:250 and the heterozygotic frequency as approximately 1:10 (Milman and Kirchhoff, 1996; Milman et al., 2000). There are reports of higher homozygote prevalence from the United Kingdom: 1:138 (East England), 1:148 (Wales), 1:102 (Northern Ireland). A second, more frequent mutation, which affects around 20% of the Caucacian population, is described as His63Asp or abbreviated H63D. It is assumed that around 30% of C282Y homozygotes do not develop haemochromatosis. On the other hand, there are also known cases of a form of haemochromatosis which is not linked to a HFE-mutation, for instance in Italy (Bassett, 2001; Bulaj et al., 2000).

Over the years the body iron store can increase to more than 50 g. Here, iron is mainly deposited in the parenchymal cells of the organs and leads to functional disorders (in particular the liver, pancreas, heart, gonads). The main clinical symptoms, which manifest mostly at a more advanced age, are weakness, weight loss, brown-grey skin pigmentation, arthritis and at a later stage cirrhosis of the liver, diabetes mellitus and myocardial lesions (Bassett, 2001; Gross and Schölmerich, 1982; Schröder, 1994; Yip, 2001).

Persons suffering from haemochromatosis, have a higher risk of tumour. The risk of developing a primary liver carcinoma is approximately 200 times higher in men >55 years who already suffer from cirrhosis of the liver (Whittington and Kowdley, 2002). It was observed that other carcinomas, too, like mammary or colorectal carcinomas fre-

quently occur (Nelson, 2001). More than 50% of haemochromatosis patients develop diabetes mellitus.

These are the reasons that prompted the recommendation of examining the possibility of a genetic predisposition before administering or prescribing any iron-containing supplements (Milman et al., 2000). The favoured screening method is determination of transferrin saturation. In the case of pathological values diagnosis should be supplemented by gene typing. Since, however, it is known that even the presence of a C282Y-homozygosity may not necessarily lead to the development of haemochromatosis, the benefits of screening are not generally accepted (Bassett, 2001; Whittington and Kowdley, 2002).

on 2) *Secondary iron overload:* Secondary iron overload can occur as a consequence of frequent blood transfusions or in conjunction with specific, more rare haematologic diseases with ineffective erythropoiesis (e.g. thalasaemia major, sideroblastic anaemias).

In the case of thalassaemia major or "Cooley anaemia" (Greiling and Gressner, 1989; Gross and Schölmerich, 1982; Hallberg, 2002) we are dealing with a homozygotic form of a hereditary disruption of haemoglobin synthesis. Clinically speaking this is a case of severe haemolytic anaemia, hepatosplenomegalia and frequently also diabetes mellitus. The prognosis is bad and patients normally die young from coronary heart disease, infections or cancer.

Sideroblastic anaemia also involves defect haeme synthesis as a consequence of congenital or acquired enzyme defect which prevents either the formation of individual porphyrin compounds or the coupling of iron and protoporphyrin. One typical symptom for this disease is anaemia with ringsideroblasts in bone marrow and elevated bone deposits in tissue (Gross and Schölmerich, 1982; Herold, 1987).

Another cause may also be increased absorption in conjunction with *alcoholism*. Increased iron deposition in the liver can be detected in around one-third of all cases of cirrhosis of the liver, particularly those caused by toxic alcohol effects (DGE/ÖGE/SGE/SVE, 2000; Löffler and Petrides, 2003).

It is still unclear whether sole, ongoing, excessive oral intake can lead to iron overload. As the organism does not have any regulated excretion mechanism for iron and iron absorption cannot be down regulated to zero even in the case of high ferritin stores, an association of this kind cannot be ruled out (Heath and Fairweather-Tait, 2003).

on 3) *Other forms:* The disease described as "*Bantu siderosis"* which occurs in some regions of Africa is based on a genetic defect in iron metabolism in addition to elevated intake. Typical symptoms are damage to the liver and pancreas due to exogenous iron intake of >50 mg iron/day from home-brewed beer with a mean iron content of 80 mg iron/litre (N.N., 1992; Schümann et al., 2002).

Porphyria cutanea tarda (PCT) is the most frequent form of porphyria. It does not normally manifest until after age 40 and affects men three times more frequently than women. No concrete figures are available on the frequency of the disease. Prevalence is estimated at 1 : 5,000-25,000 (Bulaj et al., 2000). The defect concerns uroporphyrinogen decarboxylase, whose activity is reduced. There is always damage to the liver with porphyrin deposits and frequently iron overload can be observed (Gross and Schölmerich, 1982; Herold, 1987). The noxae which trigger manifestation mainly include alcohol (70%) and oestrogens. However, there were also reports of the provocation of PCT-typical symptoms in conjunction with iron therapy (Forth and Rummel, 1987; Ginsburg et al., 1990). Here it seems that iron overload is

the new trigger factor for PCT. More recent studies indicate an increased incidence of HFE-mutations in PCT patients (Bulaj et al., 2000; Skowron et al., 2001).

Gastro-intestinal side effects: As, depending on the concentration, iron ions can irritate the stomach, reversible gastro-intestinal disorders rank amongst the typical and most frequent side effects described in conjunction with oral pharmaceutical iron preparations. There seems to be a clear causal relationship between the level of iron intake and the onset of gastro-intestinal side effects. Higher iron doses are frequently associated with the side effects obstipation, epigastric disorders, bloatedness, nausea, diarrhoea and vomiting (FNB, 2002; Forth and Rummel, 1987; FSA, 2003; Hartke et al., 2002; Schröder, 1994; Schümann et al., 2002).

In the study by Frykman et al. (1994) mentioned above, gastro-intestinal disorders attributable to iron ingestion were observed in 34% of study participants. Brock et al. (1985) reported moderate to severe side effects in 50% of 272 individuals given 50 mg iron in the form of conventional iron(II) sulfate. Liguori (1993) compared the tolerance of iron protein succinylate (120 mg iron/day) with ferrous sulphate (105 mg iron/day) in a prospective double blind placebo controlled multi-centre study. The side effect rate was 11.5% for the first and 26.5% for the second product. In addition to the typical gastro-intestinal symptoms skin rashes were observed. Hallberg et al. (1996) examined the side effects of various oral iron compounds compared to placebo. At iron levels of 180-222 mg, broken down into 3 doses, no significant differences in terms of tolerance were observed between ferrous sulphate, ferrous fumarate, ferrous glycin sulphate and ferrous gluconate.

Other typical side effects are harmless black colouring of faeces and reversible dental discolouration as a consequence of iron depots following the administration of iron as drops. Furthermore, false-positive benzidine samples and guaiac tests must be expected (BPI, 2003). This may be of relevance in conjunction with cancer screening examinations. According to some authors (Laine et al., 1988) tests involving occult blood in faeces do not produce positive results following oral administration of ferrous sulphate.

High iron stores as a potential risk factor: Higher iron stores are associated with an elevated risk of the onset of various diseases.

Cardiovascular risk: The "iron hypothesis" already advanced in 1981 by Sullivan (1981) claims that women are better protected than men against atherosclerotic changes because of their lower iron stores as a consequence of their periodic menstrual bleedings up to menopause. This hypothesis is supported by the higher life expectancy of regular blood donors and lower frequency of heart attacks in developing countries (Kieffer, 1993). It has already been assumed for some time now that the formation of oxygen radicals and oxidative stress encourage the onset of cardiovascular diseases. A series of studies indicate that elevated iron depots can increase the cardiovascular risk (Ascherio et al., 1994; Salonen et al., 1992).

Salonen et al. (1992) established a statistical link between the level of serum ferritin and heart attack incidence. In this context the cardiovascular risk was comparable to that for cigarette smokers. The level of iron ingested daily was also positively associated with an elevated risk of heart attack; an increased risk of 5% was concluded per mg iron ingested daily. Men with ferritin levels >200 µg/l had a 2.2-fold higher risk than men with lower ferritin levels. Ascherio et al. (1994) described a positive correlation between cardiovascular risks and haeme iron intake but no such risk for non-haeme iron or total iron intake.

In their overview from 1996 Sempos et al. (1996) compiled the epidemiological studies available up to then and came to the conclusion that the majority of studies could not support the observation of Salonen et al. (1992) in 1992. The meta-analysis by Danesh and Appleby

(1999), which covered prospective longitudinal studies published before 1998, did not produce any evidence of an association between coronary heart disease and iron status.

In the meantime a whole series of other studies have been published which would seem rather to support the iron hypothesis. Kiechl and Mitarbeiter (1997) observed in their 5-year prospective study ("Bruneck Study") involving 826 men and women aged between 40-79 an association between ferritin levels and the progression of arteriosclerosis. Furthermore, serum ferritin was one of the clearest indicators for the presence and progression of arteriosclerosis of the carotid artery. The Finnish working group of Tuomainen reported (Tuomainen et al., 1997a) for the first time a reduced cardiovascular risk in male blood donors through a reduction of body iron stores. It observed (Tuomainen et al., 1998) a 2 to 3-fold higher risk of myocardial infarction in men with high body iron stores. Tzonou et al. (1998) presented findings from Greece which point to an association between excessive iron intake and cardiovascular risk particularly amongst older people (in particular women). In 1999 Milman and Kirchhoff (1999) reported an association between serum ferritin and cardiovascular risk factors in both men and women. This was based on their epidemiological study which was conducted in conjunction with the MONICA Study (Monitoring of Trends and Determinants in Cardiovascular Disease) in Denmark between 1982-1984 involving 2235 healthy people aged between 30 and 60 years.

In 1999 findings from the Netherlands were published which showed that the risk of myocardial infarction is elevated in older people as a consequence of high ferritin concentrations in the presence of other risk factors (Klipstein-Grobusch et al., 1999a; b). Furthermore, a positive correlation was shown between high haeme iron intake and an elevated risk of myocardial infarction. A similar correlation had already been identified by Ascherio et al. (1994).

The working group of Tuomainen (1999) described in 1999 a two-fold higher risk of myocardial infarction in heterozygotic carriers of the gene mutation HFE Cys282Tyr typical for haemochromatosis based on a prospective study with an observation period of 9 years.

Meyers et al. (1997) conformed the iron hypothesis by noting a lower cardial risk in a perspective cohort study involving blood donors. The results were differentiated in another retrospective cohort study from 2002 (Meyers et al., 2002) by showing that the frequent, regular giving of blood compared with the sporadic giving of blood is associated with a lower cardiovascular risk. Ascherio et al. (2001) determined, by contrast, in their study results published in 2001 involving male blood donors that they could not confirm the hypothesis that low body iron stores could reduce the risk of cardiovascular disease.

Ramakrishnan et al. (2002) described a positive association between ferritin and cardiovascular risk even in young women of childbearing age. Facchini and Saylor (2002) examined 31 patients with pathological glucose tolerance or manifest non-insulin dependent diabetes mellitus over a period of 6 months. They noted that these risk patients can benefit both metabolically and haemodynamically from a reduction of body iron reserves in a range which is frequently found in pre-menopausal women.

The review by Salonen et al. (1992) and the meta-analysis by Danesh and Appleby (1999), which sum up the positions in the works published up to then, constituted the main basis for the FNB (2002) assessment. In the meantime a whole series of other studies have been published. The majority support the iron hypothesis. This means there is increasing likelihood of a causal relationship between cardiovascular diseases and the level of iron stores. Table 28 gives a brief chronological overview of the studies presented.

Tumour risk: Various large-scale epidemiological studies (Heath and Fairweather-Tait, 2003; Knekt et al., 1994; Stevens et al., 1988; Stevens et al., 1994) have produced indications that iron intakes and high iron stores are associated with an elevated tumour risk.

One possible mechanism in this context is iron which can catalyse the formation of reactive radicals. They can develop a carcinogenic effect by means of elevated oxidative stress and damage DNA. Furthermore, iron probably plays a role as a limiting nutrient for growth and replication of tumour cells (Stevens et al., 1994). It is also known that the tumour risk is elevated in conjunction with haemochromatosis.

In his review Nelson (2001) compiled 33 human studies from 26 publications on the relationship between iron and the risk of colorectal tumour. He came to the conclusion that this is supported by the majority (around 75%) of the studies. According to them, increasing iron intake correlates with an elevated colorectal tumour risk.

As around 90-95% of dietary iron is not absorbed because of the low iron absorption rate, a roughly 10-fold higher concentration of iron in free form is to be found in faeces than in other tissues. This means that the amount needed for the Fenton reaction described above is considerably exceeded (Babbs, 1990). Lund et al. (1999) noted a significant increase in the iron content in faeces in healthy test persons given a supplement of 19 mg iron/day. This was also accompanied by a significant 40% increase in the formation of free radicals.

Of the risks discussed, which examined the role of iron as a potential risk factor, the association between increasing iron intake and an elevated colorectal tumour risk is currently the most important one. Further studies are needed in order to confirm this (Heath and Fairweather-Tait, 2003). The evidence is not yet satisfactory when it comes to other tumours.

Diabetes mellitus: Initial signs that an iron overload could play a role in type II diabetes mellitus result from the observation of an elevated haemochromatosis prevalence in these patients. A 2.4% or 1.34% higher haemochromatosis risk is assumed for the diabetic population in Australia and Italy respectively. In recent years there were increasing signs of an elevated risk of developing type II diabetes mellitus in conjunction with higher iron stores whereas emptied stores have been shown to offer protection (Fernández-Real et al., 2002).

Hua et al. (2001) noted that lacto-ovo-vegetarians with lower iron stores (35 µg ferritin/l) had a higher sensitivity to insulin than meat eaters with higher ferritin values (72 µg/l). They also noted that insulin sensitivity could be increased by reducing iron stores. Indications of this kind were provided from the following, larger "cross-sectional, population based studies":

- Tuomainen et al. (1997b) noted a positive association between specific markers of carbohydrate metabolism (elevated blood sugar, fructosamine and serum insulin concentrations) and already only moderately elevated serum ferritin concentrations (mean value: 148 µg/l), which are not yet considered to be an "iron overload" in 1013 men of average age.
- Salonen et al. (1998) examined 1038 men in Finland aged between 42-60 over a period of 4 years. They observed an association between iron stores and the incidence of diabetes mellitus. Here iron stores on a scale which was not linked to haemochromatosis were already associated with an elevated risk of developing non-insulin dependent diabetes mellitus.
- Ford and Cogswell (1999) observed in their study involving 9486 adults (age: >20) a positive association between high ferritin concentrations and the risk of diabetes.

There is a need for further research on this possible association as well. One fundamental problem is that serum ferritin can also be influenced by other factors like inflammation which would have to be definitely ruled out.

Neurodegenerative disorders (in this case Parkinson's disease): Elevated iron contents in the brain have been observed in various neurodegenerative diseases like Parkinson's or Alzhei-

mer's. It is suspected that iron could play a role in the pathogenesis of these diseases (Logroscino et al., 1998; Sipe et al., 2002; Wolozin and Golts, 2002). Elevated iron concentrations in the substantial nigra are typical for Parkinson's disease. In pathophysiological terms, the aggregation of the protein a-synuclein, which has been identified as a typical pathological characteristic of Parkinson's disease, is also under discussion in addition to the pro-oxidative properties of iron ions (Wolozin and Golts, 2002).

Powers et al. (2003) compared the eating habits of 250 patients who had been diagnosed with Parkinson's disease between 1992 and 2002 with those of a control group of 388 persons. The authors found signs for a statistical association between a high iron diet and an elevated risk of developing Parkinson's disease. The elevated risk was associated with a dietary iron intake above the median and the ingestion of more than 1 multivitamin- or iron supplement/day. Isolated consideration of the haeme iron did not identify any elevated risk in statistical terms. The authors also noted that the risk could be doubled through additional high manganese intake.

By contrast, in their case-control study Logroscino et al. (1998) (104 Parkinson's patients, 352 control persons) did not find any association between dietary iron intake and the risk of disease. A 2-fold elevated risk of disease may be relevant, in conjunction with high transferrin saturation, for a possible association between Parkinson's disease and iron metabolism.

10.3.2.1 Other adverse effects

Cutaneous reactions: There are case reports about skin reactions following the oral administration of pharmaceutical iron products. Ito et al. (1996) reported the onset of a generalised pustulous exanthema after taking ferrous fumarate. Ortega et al. (2000) observed a generalised pruritis and erythamatous, maculopapulous skin rashes following the administration of various iron compounds in one patient. These symptoms were provoked in conjunction with ferrous sulphate and with iron protein succinilate. In effort tests milder symptoms occurred one hour after administration of 30 mg Fe^{3+} whereas no symptoms were described in conjunction with 5 or 10 mg.

Mucosa lesions in the gastro-intestinal tract. After 7-day oral treatment with ferrous sulphate (corresponding to 300 mg Fe^{2+}/day), endoscopically diffuse mucosa skin lesions and an ulcer in the ileocaecal valve were diagnosed in one patient (Stolte and Hulskat, 1999). Another case report described mucosa skin lesions in the oesophagus after 9-months oral treatment with 400 mg ferrous sulphate which were also determined endoscopically (Zhang et al., 2003).

10.3.3 Deficiency, possible risk groups

10.3.3.1 Deficiency

Iron deficiency or anaemia caused by this is still described in the literature as the most widespread deficiency condition. According to WHO estimates approximately 600-700 million people suffer from iron deficiency anaemia around the world (FAO/WHO, 2001). However, in contrast to developing countries, dietary iron deficiency no longer plays a major role in our latitudes. WHO estimates the prevalence of iron deficiency anaemia in industrial countries as being 2-8%. DGE (2000) also notes that a diet-driven iron deficiency is far more rare than in the past.

The development of manifest iron deficiency takes place over a longer period which can be broken down into several stages on the basis of biochemical and haematological parameters (Yip, 2001). Table 20 assigns the available biochemical/haematological test results to the

individual stages of iron deficiency. For more information on the standard ranges please refer to Chapter 10.2.2.

Stage I is characterised by exhausted iron stores and can be diagnosed on the basis of lower serum ferritin concentrations. No disease value is attributed to this stage nor is any physiological impairment described. Frequently, progression to Stage II can be avoided through a compensatory increase in iron resorption.

Stage II, also frequently described as a latent iron deficiency, is already characterised by typical biochemical changes which point to the inadequate provision of iron for haemoglobin synthesis.

In *Stage III* there is a manifest iron deficiency with hypochromic, microcytic iron deficiency anaemia and a reduction in the haemoglobin concentration.

An iron deficiency can be caused firstly by inadequate intake and secondly by elevated losses (Gross and Schölmerich, 1982):

on 1: Inadequate intake may arise for instance in conjunction with malnutrition or a one-sided, low iron diet. In this context the bioavailability of iron also plays an important role (Benito and Miller, 1998). Other causes may be inadequate resorption (villus atrophy of the small intestine, e.g. in the case of sprue) or inadequate exploitation (e.g. after partial gastrectomy). During pregnancy (iron supply of the foetus) and during growth periods elevated needs must be met (DGE/ÖGE/SGE/SVE, 2000).

on 2: Elevated losses as a consequence of chronic bleeding are the most frequent cause (80%). Around 70% of cases are attributed to gastro-intestinal bleeding (ulcers, haemorrhoids, carcinomas etc.). 10-15% of cases are attributed to genital bleeding in women (hypermenorrhoeas, childbirth) (Gross and Schölmerich, 1982; Herold, 1987; Yip, 2001).

The average loss of blood during *menstruation* of 30 to 60 ml roughly corresponds to a loss of between 15 and 30 mg iron. These losses can be compensated by an optimum diet and an increased resorption rate in the case of iron deficiency. However, this is not possible when the individual has a one-sided diet or when high blood losses occur like, for instance, with hypermonorrhoea (up to 800 ml) or uterine polyps (up to 1200 ml) (Forth and Rummel, 1987).

The typical symptoms of disorders, which do however depend on the degree of iron deficiency, include (Gross and Schölmerich, 1982; Herold, 1987): general symptoms like adynamia, effort dyspnoea, headaches, loss of appetite or impaired psychomotoric performance, paleness of skin and mucosa and "epithelial symptoms" (angular cheilosis, glossitis, dysphagia, hair loss, brittle finger nails). Furthermore, thermoregulation may be abnormal and host defense mechanisms against infections may be impaired (DGE/ÖGE/SGE/SVE, 2000; Yip, 2001).

Given the iron requirements of the brain during growth periods, sufficient supply is of major importance in childhood. Inadequate supply can bring on concentration and learning difficulties and lead to irreversible disruptions of mental development (Sipe et al., 2002).

10.3.4 Possible risk groups for deficiency

An iron deficiency mainly occurs as a consequence of elevated losses and/or reduced resorption and exploitation as a consequence of an underlying disease. The following risk groups are discussed in conjunction with a diet-driven deficiency:

- Individuals with a long-term one-sided diet (e.g. vegans)
  No representative data are available on the basis of which the size of this group in the German population could be determined. Frequently, it is suspected that a drop in the consumption of beef as a consequence of the *BSE* (Bovine Spongiform Encephalopathy) crisis has led to inadequate iron intake. An analysis of the UK Women's Cohort Study, involving 35-69 year-old women, did not, however, reveal any differences in iron intake between those who ate beef and those who ate meat but no beef. The mean iron intake in both groups is 18 mg/day, the median was 17 mg/day (Cade et al., 1998).

- Individuals who have higher growth-related requirements
  DGE/ÖGE/SGE/SVE (2000) commented that in the first two years of life and during puberty iron intake was often not enough for rapid growth and a latent iron deficiency and anaemia would, therefore, occur most frequently at ages 1 to 2 and in boys during pubescent growth spurts. Taking into account the results of the NFCS (VERA-Schriftenreihe, 1995b) the mean intake of boys in puberty is in the range of recommendations. Information on the ferritin concentration is not available for this age group from the VERA Study. Olsson et al. (1995) conducted studies in Sweden on iron supply amongst 3975 male adolescents aged 18 in order to re-examine the opinion that had prevailed for many years that an iron deficiency was frequently to be found amongst male adolescents because of growth spurts. With mean ferritin levels of 36.8 µg/l the authors established that the prevalences of iron overload and iron deficiency were equally high (0.4%). The prior assumption of a high prevalence in this group of the population was not confirmed. The authors further concluded that with a prevalence of primary haemochromatosis of 0.4%, 12.6% of this population could, in fact, be carriers of the HFE mutation. Based on these results it was concluded that an extension of food fortification with iron was neither meaningful nor necessary but could in fact be dangerous.

- Women of childbearing age who have a 50% higher recommended intake than men
  From the diet surveys available (Mensink et al., 1999; Schulze et al., 2001; VERA-Schriftenreihe, 1995b) it can be seen that around half of women of childbearing age do not meet the higher recommended intake. If one takes, by contrast, the ferritin values from the VERA Study (VERA-Schriftenreihe, 1995a) then a critical iron supply is also rare amongst pre-menopausal women.

  Choice of contraceptive seems to play a decisive role when it comes to iron requirements and the nutritional status of pre-menopausal women. Guillebaud et al. (1976) observed a 2-fold increase in menstruation-related iron losses as a consequence of the use of intrauterine devices. By contrast, a better nutritional status was described in conjunction with oral hormonal contraceptives (Galan et al., 1998; Milman et al., 1998).

  Milman et al. (1998) examined iron status in relation to menstruation, form of contraception and iron supplements in 268 Danish women aged between 18-30 during the period from 1992-1993. The authors did not identify an iron deficiency in any of the women with lighter menstrual bleeding; in the case of mean or stronger bleeding an iron deficiency was determined in 12 and 21% of women respectively. The following risk factors were derived for the development of an iron deficiency: length of menstruation: >5 days, more intense bleeding, use of intrauterine devices (IUDs) with no gestagen, blood donors. From the results the authors concluded that general iron fortification or supplementation is not justified for this group as it would involve an unnecessary treatment of 50-60% who have no emptied iron stores.

The calculations available for Germany on iron intake indicate that around half of women do not meet the 50% higher recommended daily intake. The determinations of the serum ferritin level undertaken to estimate iron supply do, however, indicate that an iron deficiency is relatively rare even amongst pre-menopausal women (supply category 1/2).

10.3.5 Excessive intake, possible risk groups

10.3.5.1 Excessive intake

Apparently it is not clear whether and, if so, to what extent high oral intake in healthy individuals can lead to iron overload and to an abnormally high ferritin level. Based on more recent findings, which refute a strictly inverse relationship between iron store and iron absorption, this possibility cannot, however, be ruled out.

The highest intake levels were measured in the NFCS at the 97.5 percentile in which 15-18 year-old males were found with 27.7 mg. In the Federal Health Survey the highest levels were observed at the 90. percentile of 27.4 mg in 18-24 year-old males.

There was a completely different picture for ferritin concentrations. In almost 10% of the participants, ferritin levels were measured of more than 200 µg/l. The highest ferritin concentrations of 580 µg/l were measured at the 97.5 percentile in women over the age of 65.

10.3.6 Possible risk groups in conjunction with growing iron supplementation

In principle, all patients with chronic iron overload are a potential risk group in conjunction with the growing use of iron in foods (see Chapter 10.3.1).

Even if scientists cannot give a definitive answer to the question whether iron does in fact play a role as a potential risk factor for specific diseases, the uncontrolled long-term prophylactic intake of iron-containing supplements or fortified foods by the population at large does seem to be worrying. There could be an additional risk in particular for men and postmenopausal women on the basis of the existing supply situation.

An additional risk would also have to be considered for individuals who regularly take vitamin-containing food supplements as increased absorption of iron was described in conjunction with vitamins C and A. The current data situation does not, however, permit any estimates about the possible size of this potential risk group.

10.4 Tolerable upper intake level for iron

In the EU the UL deliberations have not yet been concluded. In 1992 the Scientific Committee on Food (SCF, 1992) stated that side effects in adults could already occur at levels of only 30 mg elemental iron; as a rule, however, single doses of 100 mg were well tolerated.

FNB (2002) established a **Tolerable Upper Intake Level (UL)**♦ of 40 mg up to age 13 and from 14 years upwards a UL **of 45 mg**. The latter level also applies to pregnant and lactating women. The onset of gastro-intestinal disorders was chosen as the critical endpoint. This means that the derivation was undertaken on the basis of side effects described in conjunction with orally administered pharmaceutic iron preparations (see also Chapter 10.3.1). The associations between high iron intake and/or high iron stores and an elevated risk of coronary vascular and carcinoma diseases described in epidemiological studies were not included in the derivation as the results were not considered to be convincing. All the same, a series of other studies have since been published which back the "iron hypothesis".

The UL derived by FNB has been criticised. Schümann et al. (2002) are of the opinion that the extensive indications of an elevated risk of cardiovascular disease must be taken into account and lead to a re-evaluation of the ULs derived from the reversible local effects after

♦ The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals.

taking iron tablets. There are also doubts about the transferability of symptoms after single administration of an iron salt on an empty stomach to dietary iron intake. The authors believe it is more appropriate to distance themselves to the setting of a numeric UL and are in favour of serious statements which advise against exceeding recommended intake. Iron supplementation in non-anaemic individuals would not be defensible on these grounds.

Already for these reasons the application of a formula, in which the UL laid down by FNB is used, is not appropriate when it comes to deriving a safe and tolerable maximum level of iron in a food supplement.

It has also been shown that the recommendations made so far from the various bodies on a tolerable upper intake level vary considerably. The Nordic Council (2001) indicated a **Upper Safe Intake Level** of **60 mg** for iron. A French body (CSHPF, 1995) did not derive a concrete value in 1995 but had already indicated that iron overloads constituted just as big a health problem as iron deficiencies. This meant that any iron fortification should be viewed with great caution.

The Expert Group on Vitamins and Minerals of the United Kingdom (EVM) (FSA, 2003) did not feel that it could set a "safe upper level" for iron based on the inadequate data. For *bivalent* iron only a **Guidance Level of 17 mg/day** (corresponding to 0.28 mg/kg body weight/day of 60 kg) was derived by extrapolating the LOAEL to NOAEL using an uncertainty factor of 3. It was explicitly stated that this level which was based on the guidance value referring to supplemented intake did not apply to groups in the population who have an elevated risk of iron overload. The study situation was considered to be critical since side effects had not been taken into account in many of the available studies and the long-term effects of iron supplementation on iron status and store were not known.

For reasons of completeness reference should also be made to the Expert Committee of FAO/WHO for food additives (JECFA) (FAO/WHO, 1983a; 1983b) which derived a "**Provisional maximum tolerable daily intake for man**" of **0.8 mg/kg** body weight for iron. For an adult weighing 60 kg this leads to a maximum value of 48 mg iron per day. Taking into account the reference weight of 68.5 kg for adults taken as the basis by FNB this leads to a value of just under 55 mg/day. The Committee admits that this evaluation referred to iron from all sources but that it neither encompassed iron oxide as a colour or iron supplements for pregnancy and lactation or any special clinical requirements. Furthermore, it is stressed that this value is not to be used as a guidance value for the fortification of food.

In the opinion of BfR (nutritional-)psychological aspects and other specificities of iron metabolism should be taken into account when deriving maximum levels. The following points are of relevance for iron:

- Human beings do not have an efficient excretion mechanism for iron, i.e. they do not have any way of breaking down excess iron or excreting it in a targeted manner. Hence, iron intake is the only significant parameter in order to limit iron-induced damage.
- In healthy individuals the iron status is controlled by changes in the absorption rate and cannot be determined by the level of dietary intake.
- The individual variability of iron absorption is high.
- The use of iron would have to be undertaken in conjunction with bioavailability which can clearly vary greatly.
- There is no correlation between dietary and serum iron.
- There is no correlation between dietary iron and biochemical markers of iron status.

- Low serum ferritin levels are an indicator of depleted iron stores. They cannot be equated with iron deficiency. There is no gold standard or definition for iron deficiency without anaemia.
- There are no indications that high or high normal iron stores could offer a health benefit or advantage. However, there are indications that high iron stores could be linked with a health risk.
- Iron absorption from tablets and conventional foods are clearly not governed by the same regulatory mechanism.

BfR is of the opinion that the use of iron brings with it a high risk to health and that it should be classified with the nutrients in the highest risk group.

10.4.1 Derivation of a maximum level for iron in food supplements

The comments show that there are different recommendations and assessments for the upper safe intake level. It can be noted that there are still considerable gaps in knowledge about iron. Furthermore, iron metabolism is extremely complex and influenced by numerous factors.

Based on the available date from the VERA Study it can be assumed that high iron stores (around 10% of participants) constitute a greater problem than low ones (around 6% of participants) in the German population – measured against the ferritin values.

In other Chapters of our report the following formula was used to calculate maximum levels for some micronutrients for use in food supplements:

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

Legend:

UL	=	Tolerable Upper Intake Level (SCF) usually referring to the daily total intake
DINF	=	Dietary Intake by Normal Food (95. or 97.5. percentile)
MEF	=	Estimated Number of Consumed Products
TL	=	Tolerable Level in a single dietary supplement or fortified food

It has already been mentioned that the EU deliberations on iron have not yet been completed and the UL set by FNB has provoked criticism. It should not, therefore, be used in the formula for the derivation of a maximum tolerable level in food supplements.

A series of epidemiological studies provides indications that there could be an association between high iron intake and/or an increase in iron depot and specific disease risks. Based on the available findings it cannot be ruled out at present that uncontrolled and long-term supplementation with iron can increase, for instance, the risk of cardiovascular diseases or carcinomas. BfR is of the opinion that this experience should be taken into account when setting maximum levels for iron as a precautionary principle even if these findings have yet to be scientifically validated. Various experts are already advising against regular iron intake above the recommended level (Schümann and Golly, 1996; Schümann, 2001). Supplementation with iron without a diagnosed condition like anaemia would have to be rejected in this context.

Up to now BgVV has proposed a maximum level of **5 mg**, corresponding to around 50% of the PRI value (BgVV, 1998; 2002) proposed by SCF (1992) for the daily intake of iron from food supplements.

10.4.1.1 Possible management options

Bearing in mind the current data situation and the above comments, the following management options are proposed:

a) Continuation of existing practice with the maximum level of 5 mg iron in food supplements per daily dose
   There are no reports of any side effects in conjunction with existing practice. Nevertheless, it is unclear whether a health risk for consumers can in principle be ruled out given the inadequate data available. Nor is it possible to predict the actual contribution of this amount to iron supply given the numerous factors that influence iron metabolism. Based on more recent findings various experts advise against regular iron intake above the recommended level. In arithmetic terms the group of women, who have not met their recommended higher daily intake up to now, would already be above the recommendations with an additional intake of 5 mg iron.

b) Change in existing practice by reducing the existing maximum level
   From the available food consumption studies it can be concluded that most people reach the recommended intake. Bearing in mind that the recommendation should not be exceeded, iron should no longer be contained in food supplements. In principle the question seems to be justified whether, against the backdrop of the supply situation and the potential risks, uncontrolled iron supplementation can still be justified in industrial countries. Within the framework of preventive consumer health protection it, therefore, seems appropriate to rethink current practice. Targeted, individual iron substitution, which may be necessary because of specific indications like blood loss or absorption disorders, should only be undertaken under medical supervision.

10.4.2 Derivation of a maximum level for food in fortified foods

BgVV has been of the opinion up to now that conventional foods should not be fortified with iron (BgVV, 2002). Hence only few exemptions or general dispositions for the addition of iron to breakfast cereals have been issued so far.

Because of the gaps in knowledge, the supply situation of the German population, the potential risks linked to high iron intake and for the purposes of preventing an accumulation of high iron doses from various products, BfR does not see any need to extend current practice.

10.4.2.1 Possible management options

Taking into account all these comments there is only one management option:

- Continuation of existing practice with no addition of iron to conventional foods.

  Experience from Scandinavian countries, in which more comprehensive iron fortification has been undertaken, supports this recommendation.

BfR is of the opinion that the use of iron brings with it a high risk of adverse effects. There is not, therefore, any justification for extending the current practice of using iron in food supplements or to fortify conventional foods.

More recent findings on potential risks, which could be linked to iron intake above recommended intake, do however advocate a change in current practice of adding iron to food supplements along the lines of Option b. BfR, therefore, recommends for reasons of preventive health protection that iron should no longer be used in food supplements.

As in the past, with a few exceptions, there should be no addition of iron to conventional foods.

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Table 19: Admissible iron compounds, their synonyms and other characteristics

Iron compound	Synonym(s)	CAS Number	EINECS	Molecular formula	E No. (List of references 1998, ZZulV)	Directives (2003/46/EC and 2001/15/EC)
Ferrous citrate	Iron(II) citrate	23383-11-1	245-625-1	C6-H8-O7.x-Fe		++
Ferrous fumarate	Iron(II) fumarate	141-01-5	205-447-7	C4-H4-O4.Fe		++
Ferrous gluconate	Iron(II) gluconate, ferrous digluconate	12389-15-0	206-076-03	C12-H22-Fe-O14	E 579	++
Ferrous lactate	Iron(II) lactate	5905-52-2	227-608-0	C3-H6-O3.1/2 Fe	E 585	++
Ferrous sulphate	Iron(II) sulphate	7720-78-7	231-753-5	Fe.H2-O4-S		++
Ferric diphosphate (ferric pyrophosphate)	Iron(II) pyrophosphate	10058-44-3	233-190-0	Fe.3/4H4-O7-P2		++
Ferric saccharate	Iron(III) saccharate; saccharated ferric oxide	8047-67-4	232-464-7	unknown		++
Ferrous carbonate	Iron(II) carbonate	563-71-3	209-259-6	C-H2-O3.Fe		++
Ferric ammonium citrate	Iron(III) ammonium citrate	1185-57-5		C6-H8-O7.x-Fe.x-H3-N		++
Ferric sodium diphosphate	Iron(III) sodium pyrophosphate	10045-87-1	233-150-2	Fe.H4-O7-P2.Na		++
Elemental iron (carbonyl + elektrolytic + hydrogen reduced)		7439-89-6	231-096-4	Fe		++
Iron oxides and iron hydroxides: a) Iron oxides, yellow b) Iron oxides, red c) Iron oxides, black	b) Iron(III) oxide	b) 1309-37-1	a) 257-098-5 b) 215-168-2 c) 235-442-5	a) $FeO(OH) \times H_2O$ b) Fe2-O3 c) $FeO.Fe_2O_3$	E 172	
Sodium ferrocyanide	Sodium hexacyanoferrate, yellow soda prussiate		237-081-9	$Na_4Fe(CN)_6 \times 10 H_2O$	E 535	
Potassium ferrocyanide	Potassium hexacyanoferrate, yellow potash prussiate		237-722-2	$K_4Fe(CN)_6 \times 3 H_20$	E 536	
Calicum ferrocyanide	Calcium hexacyanoferrate, yellow prussiate of lime		215-476-7	$Ca_2Fe(CN)_6 \times 12 H_20$	E 538	

Table 20: Iron metabolism disorders and parameters to assess iron status

Iron status	Indicator	Diagnostic area
Iron deficiency – broken down into stages 1-3		
1. Emptied stores	➢ Stainable bone marrow iron ➢ Total iron binding capacity (TIBC) ➢ Serum ferritin saturation	➢ Not available ➢ >400 µg/dl ➢ <12 µg/l
2. Early functional iron deficiency	➢ Transferrin saturation ➢ Erythrocyte protophorphyrin ➢ Serum-transferrin receptor	➢ <16% ➢ >70 µg/dl erythrocytes ➢ >8.5 mg/l
3. Iron deficiency anaemia	➢ Haemoglobin concentration ➢ Mean cell volume	➢ Men: <130 g/l Women: <120 g/l ➢ <80 fL
Iron overload	➢ Serum ferritin concentration ➢ Transferrin saturation ➢ Total iron binding capacity	➢ Men: >300 and 400 µg/l Women: >200 µg/l ➢ Men and postmenopausal women: >55-60% premenopausal women: >50% ➢ <250 µg/dl

(according to Greiling and Gressner, 1989; Heath and Fairweather-Tait, 2003; Solomons, 1986; Whittaker, 1998; Yip, 2001)

Table 21: Iron intake recommended by DGE/ÖGE/SGE/SVE (2000), FNB (2002) and SCF (1992)

Age (years)	Dose recommended by DGE (mg/day) (m/f)		RDA of FNB (mg/day) (m/f)		PRI of SCF (mg/day) (m/f)	
Children	1 to up to under 4	**8/8**	1-3 years	**7/7**	1-3 years	**4**
	4 to up to under 7	**8/8**	4-8 years	**10/10**	4-6 years	**4**
	7 to up to under 10	**10/10**	9-13 years	**8/8**	7-10 years	**6**
	10 to up to under 13	**12/15**			11-14 years	**10/22**
	13 to up to under 15	**12/15**	14-18 years	**11/15**	15-17 years	**13/21**
Adolescents and	15 to up to under 19	**12/15**			from 18 years	**9/20**
Adults	19 to up to under 51	**10/15**		**8/18**		
	51 and older	**10/10**				
Pregnant women		**-/30**		**-/27**	**Supplements**	
Lactating women		**-/20**		**-/9**		**10**

Table 22: Intake recommendations of FAO/WHO (2001) for iron depending on bioavailability

Age (years)	Recommended intake (mg/day)			
Bioavailability (%)	15	12	10	5
Children				
1 up to 3	3.9	4.8	5.8	11.6
4 up to 6	4.2	5.3	6.3	12.6
7 up to 10	5.9	7.4	8.9	17.8
Boys and **men**				
11 up to 14	9.7	12.2	14.6	29.2
15 up to 17	12.5	15.7	18.8	37.6
18+	9.1	11.4	13.7	27.4
Girls and **women**				
11 up to 14 (non-menstruating)	9.3	11.7	14	28
11 up to 14	21.8	27.7	32.7	65.4
15 up to 17	20.7	25.8	31	62
18+	19.6	24.5	29.4	58.8
Postmenopausal	7.5	9.4	11.3	22.6
Lactating	10	12.5	15	30

Table 23: Iron contents of some foods

Food	Mean iron content/100 g
Pig liver	18 mg
Liver sausage	5.3 mg
Spinach	3.8 mg
Black salsify	3.3 mg
Beef	2.4 mg
Lambs lettuce	2.0 mg
Rye wholegrain bread	2.0 mg
Hens egg	2.0 mg
Mixed wheat bread	1.7 mg
Mackerel	1.2 mg
Turkey breast	1.0 mg
Pork	1.0 mg
Potatoes, boiled	930 µg
Beetroot	908 µg
Broccoli	857 µg
Egg pasta, cooked	800 µg
Wheat bread (white bread)	738 µg
Apples	248 µg
Cows milk	59 µg

(according to Souci-Fachmann-Kraut, 2000)

Table 24: Daily iron intake (in mg) by gender (F = Female, M = Male) and age

Age (years)		4-6	7-9	10-12	13-14	15-18	19-24	25-50	51-64	>/= 65
Recommended intakes (mg; f/m) (DGE/ÖGE/SGE/SVE, 2000)		8	10	15/12	15/12	15/12	15/10	15/10	10	10
P 2.5	F	4.9	6.5	6.5	6.2	6.2	6.3	6.3	7.6	6.6
	M	5.6	6.7	6.5	7.6	8.0	8.4	8.3	8.7	8.0
P 25	F	7.7	9.5	10.0	10.1	9.7	9.9	10.3	10.7	10.6
	M	8.4	10.0	11.3	11.9	12.6	12.7	12.8	13.0	12.5
Median	F	9.3	11.5	11.9	12.7	12.0	12.2	12.6	13.0	12.7
	M	10.0	11.8	13.4	14.9	15.5	15.4	15.5	15.8	15.1
P 75	F	11.1	13.3	14.3	15.1	14.8	14.6	15.3	15.5	15.3
	M	12.2	14.1	15.6	18.0	19.0	18.6	18.8	18.9	18.0
P 97.5	F	15.8	19.3	21.3	22.1	22.9	22.9	21.8	22.2	22.4
	M	17.8	19.5	26.0	25.7	27.7	27.5	27.4	27.5	25.2

(from: Nationale Verzehrsstudie Band XI, VERA-Schriftenreihe 1995 (VERA-Schriftenreihe, 1995b))

Table 25: Daily iron intake (in mg) by gender (F = Female, M = Male) and age

Age groups (years)		18-24	25-34	35-44	45-54	55-64	65-79
Recommended intakes (mg; f/m) (DGE/ÖGE/SGE/SVE, 2000)		15/10-12	15/10	15/10	10-15/10	10	10
Mean value	F	14.1	14.8	14.6	14.2	13.7	12.0
	M	19.2	18.0	17.5	16.6	15.5	14.8
Standard deviation	F	4.0	8.1	6.2	4.0	5.1	3.9
	M	5.7	6.1	5.2	5.2	4.2	4.6
P 10	F	8.9	9.1	10.0	9.4	9.1	8.8
	M	11.7	11.5	11.8	11.1	10.8	10.2
Median	F	13.8	13.4	13.8	13.7	13.0	11.3
	M	19.0	17.3	17.2	15.9	15.1	14.2
P 90	F	19.2	20.1	19.0	19.4	18.1	16.0
	M	27.4	24.1	24.0	23.0	21.3	20.6

From: Beiträge zur Gesundheitsberichterstattung des Bundes. Was essen wir heute? Ernährungsverhalten in Deutschland. Robert Koch-Institute, Berlin 2002 (Mensink et al., 2002)

Table 26: Daily iron intake (in mg) by gender (F = Female, M = Male) and region (Potsdam/Heidelberg)

Gender (F/M)	F	M
Age groups (minimum/maximum years)	35-64	40-64
Recommended intakes (mg) (DGE/ÖGE/SGE/SVE, 2000)	10-15	10
Mean value	11.6/12.3	14.6/15.1
Standard deviation	4.3/4.7	5.7/6.9
P 10	6.9/7.2	8.7/8.4
P 25	8.5/9.0	10.9/10.8
Median	11.0/11.6	13.4/14.1
P 75	13.7/14.6	17.0/17.8
P 90	17.2/18.0	21.6/22.1

From: Nutrient intakes in EPIC – Germany, 2001 (Schulze et al., 2001)

Table 27: Serum ferritin concentration (in µg/l) by gender (F = Female, M = male) and age

Age groups (years)		18-24	25-34	35-44	45-54	55-64	>65
Reference ranges (µg/l)	F						12-200
	M						15-400
P 2.5	F	4.0	6.0	3.0	2.0	12.0	16.0
	M	6.0	8.0	8.0	10.0	26.0	11.0
Median	F	25.0	29.0	34.0	48.5	75.0	88.0
	M	67.5	79.0	116.0	131.0	156.5	146.0
P 97.5	F	91.0	110.0	195.0	311.0	282.0	580.0
	M	221.0	228.0	349.0	428.0	525.0	462.0

From: VERA-Schriftenreihe, Band V: Versorgung Erwachsener mit Mineralstoffen und Spurenelementen in der Bundesrepublik Deutschland, 1995 (VERA-Schriftenreihe, 1995a)

Table 28: Overview of studies on the association between iron and the risk of cardiovascular disease

Year	Author/country	Type of study	Length of study	Study cohorts	Study goal	Study result Association -*Indicator*	
						Association or elevated risk	*No or inverse association or no elevated risk*
1992	Salonen et al. (1992) Finland	"Prospective observational study" participants in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) (1984-1989)	5 years	n=1931 men with no coronary heart disease Age: 42-60 years	Association between high serum ferritin level and high iron intake and myocardial infraction risk	*- Serum ferritin* *- Iron intake*	
1994	Sempos et al. (1994) USA	NHANES I (First National Health and Nutrition Examination Survey (1971-1974 with follow-up to 1987)	13-16 years	n=4518 men and women Age: 45-74 years	Association between transferrin saturation and coronary heart disease risk Myocardial infarction risk Total mortality Cardiovascular mortality		Coronary heart disease and myocardial infarction risks - *Transferrin saturation* Total mortality and cardiovascular mortality – *Transferrin saturation*: signs of inverse association
1994	Ascherio et al. (1994) USA	"Prospective observational study" (Health Professionals Follow-up Study) (1986-1990)	4 years	n=44933 men with no coronary heart disease Age: 40-75 years	Association between iron intake and coronary heart disease incidence	*- Haeme-iron intake*	*- Total iron intake* *- Nonhaeme-iron intake*
1995	Reunanen et al. (1995) Finland	"Prospective population study"(1966-1972 with follow-up up to 1986)	∅: 14 years	n=6086 men and n=6102 women Age: 45-64 years	Association between high body iron store (here: transferrin saturation/iron binding capacity) and high iron intake and cardiovascular mortality		Coronary heart disease mortality *- Meat intake* *- Iron intake* *- Transferrin saturation: S*igns of inverse association
1996	Sempos et al. (1996)	Review (studies up to and including 1995)			Association between high body iron store and coronary heart disease risk		+
1999	Danesh & Appleby (1999)	Meta-analysis ("long-term prospective studies" prior to 1998)			Association between iron status and coronary heart disease		+
1997	Kiechl et al. (1997) Italy	"Prospective survey" (1990-1995)	5 years	n=826 men and women Age: 40-79 years		+	

Continuation Table 28: Overview of studies on the association between iron and the risk of cardiovascular diseas

Year	Author/country	Type of study	Length of study	Study cohorts	Study goal	Study result Association –*Indicator*	
						Association or elevated risk	*No or inverse association or no elevated risk*
1997	Tuomainen et al. (1997a) Finland	"Prospective observational study" Participants in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) (1984-1989 with follow-up to 1992)	∅: 5.5 years	n=2682 male blood donors 42-60 years	Examination of iron hypothesis: association between blood donation (= lower body iron store) and myocardial infarction risk	Association: lower iron store – lower risk of infarction	
1997	Meyers et al. (1997) USA	"Prospective cohort study" Sample der Nebraska Diet Heart Survey (DHS) (1985-1987 with follow-up to)	5-8 years	n=655 blood donors n=3200 non-donors (Men and Women) Age: >40 years (∅: 56.8 years)	Examination of the iron hypothesis: comparison of incidence of cardiovascular events in blood donors (= lower body iron store) and non-donors	Association: blood donation (= lower iron stores) lower incidence of cardiovascular events	
2001	Ascherio et al. (2001)	"Prospective observational study" Health Professionals Follow-up Study (1992-1996)	4 years	n=38244 male blood donors Age: 40-75 years	Examination of iron hypothesis: association between blood donation (= lower body iron store) and coronary heart disease risk		No association: lower iron store – lower risk of infarction
2002	Meyers et al. (2002) USA	"Retrospective cohort study" (1988-1990)	3 years	Blood donors (Male and Female) n=1508 regular donors n=1508 sporadic donors Age: (∅: 58 years)	Examination of iron hypothesis: comparison risk of cardiovascular events depending on frequency of blood donation (regular/sporadic = lower/higher body iron stores)	Association: frequent blood donation (= lower iron store) – lower risk of cardiovascular events	
1998	Tozonou et al. (1998) Greece	"Case control study" (1990-1991)	1.3 years	n=329 with condition after myocardial infarction n=570 control group (Women and Men) Age <49 years up to >70 years	Association between iron intake and coronary heart disease risk	+	

Continuation Table 28: Overview of studies on the association between iron and the risk of cardiovascular diseas

Year	Author/country	Type of study	Length of study	Study cohorts	Study goal	Study result Association -*Indicator*	
						Association or elevated risk	*No or inverse association or no elevated risk*
1998	Toumainen et al. (1998) Finland	"Prospective case-control study" participants in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) (1984-1992 with follow-up between 1-8.8 years)	∅: 6.4 years	n=99 men with condition after myocardial infarction n=98 control group	Association between high body iron store (here: serum-transferrin receptor/serum ferritin) and myocardial infarction risk	+	
1999	Tuomainen et al. (1999) Finland	"Prospective observational study" participants in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) (1982-1992 with follow-up to 1996)	∅: 9 years	n=1150 men Age: 42-60 years	Association between myocardial infarction risk and presence of HFE Cys282Tyr gene mutation	+	
1999	Klipstein-Grobusch et al. (1999b) Netherlands	"Case control study" (Participants in the Rotterdam study; 1990-1996)	∅: 4 years	n=60 with condition after infarction n=112 control group (Women and Men) Age: >55 years	Association between indicators of iron status (ferritin) and myocardial infarction incidence	*- Haeme-iron intake* *- Serum ferritin*	
1999	Klipstein-Grobusch et al. (1999a) Netherlands	"Prospective cohort study (Rotterdam study 1990-1996)	∅: 4 years	n=4802 men and women Age: >55 years	Association between iron intake and myocardial infarction incidence	*- Haeme-iron intake*	*- Total iron intake* *- Serum iron* *- Serum transferrin*
1999	Milman and Kirchhoff (1999) Denmark	"Epidemiological population survey" (MONICA study (Monitoring of Trends and Determinants in Cardiovascular Disease) (1982-1984)	2 years	n=2235 healthy individuals (1044 men, 1191 women) Age: 30-60 years	Associtation between serum ferritin and coronary heart disease risk factors	+	*- Total iron intake*
2002	Facchini and Saylor (2002) USA	"Prospective study"	6 months	n=31 overweight men and women, no control group, glucose tolerance disruption Age: ∅: 51 years	Association between arterial sclerosis risk factors (plasma glucose, insulin sensitivity) and body iron store (=ferritin amongst others)	+	
2002	Ramakrishnan et al. (2002) USA	"Cross-sectional study" NHANES III (Third National Health and Nutrition Ex-amination Survey (1988-1994)	6 years	n=4579 women Age: 20-49 years	Association between body iron store (= ferritin) and cardiovascular risk factors	+	

11 Risk Assessment of Iodine

11.1 Summary

The data available for the Federal Republic of Germany on the iodine nutritional status indicate that there is a risk of a clinically manifest deficiency or store depletion in around 30% of the population. Women are affected five times more frequently than men. According to the WHO criteria there is a mild iodine deficiency. Heavy smokers, pregnant and lactating women, infants and small children are particularly at risk. A vegetarian diet also increases the risk particularly when no iodised salt or other iodine-containing products are consumed (supply category 1).

BfR is of the opinion that there is, by way of definition, a high risk of adverse effects bearing in mind the most sensitive consumers with an undiagnosed functional autonomy of the thyroid gland when iodine is used in food supplements or for food fortification. BfR, therefore, recommends that the current maximum level for food supplements (100 µg/day) be maintained and that only iodised salt be used as the suitable carrier food. This will ensure that foreseeable amounts of iodine can be ingested by the general population and the tolerable upper intake level of 500 µg iodine will not be exceeded. The iodisation of feedstuffs makes an indirect but significant contribution to iodine supply. Control measures are necessary in order to reach and maintain an optimum iodine supply.

Recommended intake	180-200 µg/day	
Intake [µg/day] (Manz et al., 1998)	**m**	**f**
Median	116	106
P 5	66.4	59.8
P 95	209.6	185.8
Tolerable Upper Intake Level	600 µg/day	
in Germany:	500 µg/day	
Proposal for **maximum levels** in:		
Food supplements	100 µg/daily dose	
Fortified foods	No fortification	

11.2 Nutrient description

11.2.1 Characterisation and identification

Iodine (CAS No. 7553-56-2) is a natural element which is essential for the health of animals and man. It is one of the halogens in the seventh main group in the periodic system. It has an atomic mass of 126.90. Given its size and its lower electron negativity (2.2) iodine occurs in a cationic bound form. Elemental iodine does not, therefore, occur in nature in a free form but in a mineralised form as iodide or iodate or organically bound. Inorganic iodine compounds are sodium iodate ($NaJO_3$) (CAS No. 7681-55-2), sodium iodide (NaJ) (CAS No. 7681-82-5), potassium iodate (KJO_3) (CAS No. 7758-05-6) or potassium iodide (KJ) (CAS No. 7681-11-0). The risk assessment refers to iodide (J^-) and to the above-mentioned inorganic iodine compounds.

According to Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, only the iodine compounds listed there like sodium iodide, sodium iodate, potassium iodide and potassium iodate may be used for nutritional purposes. With the entry into force of Euro-

pean Commission Directive 2000/15/EC (of 15 February 2001 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses) potassium iodide, potassium iodate, sodium iodide and sodium iodate may be used in dietetic foods for nutritional-physiological and specific dietary purposes (Annex 2 to the twelfth Ordinance on the Amendment to the Ordinance on Foods for Special Dietary Purposes of 31 March 2003). According to the Proposal for a Regulation of the European Parliament and the Council of 10 November 2003 (COM (2003) 671 final) these compounds may also be added to foods. According to the Additives Marketing Ordinance of 10 July 1984 only iodates (sodium and potassium iodate) are approved for the manufacture of iodised table salt.

11.2.2 Metabolism, function, requirements

Metabolism: Dietary organic and inorganic iodide is quickly absorbed in the small intestine. Iodate is quantitatively reduced by non-enzymatic reactions to iodide which means that it is available to the organism as iodide. Organic iodine compounds have a lower bioavailability (Aquaron et al., 2002; Bürgi et al., 2001). The intake mechanism via the mucosa cells is not known. It may happen, similar to chloride transport, via the Cl^- channels (Katayama and Widdicombe, 1991). The serum level of inorganic iodine is normally between 0.1 and 0.5 µg/dl. In the organism iodide accumulates in the thyroid and in other tissue like the salivary gland, mammary gland and stomach. This is due to a specific sodium-dependant iodide transporter in the basolateral membrane of the thyroid follicular cells, the so-called sodium-iodide symporter (NIS). It consumes energy and thereby transports two Na^+ ions together with one I^- ion against a concentration gradient in the same direction (symporter). The thyroid-stimulating hormone (TSH) formed by the pituitary gland stimulates iodide transport (Spitzweg and Heufelder, 1999). In the thyroid gland iodide is rapidly oxidised by peroxydase and bound to tyrosine whereby 3-monoiodotyrosine (MIT) and 3,5-diiodotyrosine (DIT) are created (iodisation). In the case of an iodine deficiency more monoiodotyrosine is created. During the coupling reaction L-thyroxine (T_4) is formed from two molecules of DIT; triiodothyronine (T_3) is formed from DIT and MIT. All T_4 and T_3 molecules are bound to thyroglobulin (TG) and are released into the colloid of the thyroid follicles. An accumulation of TG suppresses NIS-dependant iodide intake and NIS gene expression. This can, therefore, halt once again TSH stimulation of the follicular cell (Suzuki et al., 1999). Selenium-containing thyroxine-5'-deiodases catalyse the conversion and degradation of T_4 to biologically active T_3 (Arthur et al., 1999). The iodide store of healthy adults with optimum long-term iodine supply is estimated to be 10-20 mg. 70-80% of this is in the thyroid gland. In the enlarged thyroid caused by iodine deficiency, the iodine content in the thyroid may be reduced to 1 mg and less (Heseker, 1999). Around 80 µg are released daily in the form of T_4 and T_3 (90:10) and are metabolised by the liver and other tissues. More than 99% of both hormones are bound to transport proteins in blood and only a very small proportion is available as free, i.e. unbound hormone. This is described as free T_3 (fT_3) and free T_4 (fT_4). Only the free hormones play an active role in metabolism. The half life of T_3 is 20 hours, that of T_4 is approximately 8 days. Some of the iodide is again released through deiodases from the thyroid gland and other tissue into the extracellular space. Some hormone derivatives are excreted by the gall bladder. This means that some of the iodine is again available via the enterohepatic circulation whereas around 20 µg iodine are lost daily through faeces (11%). Iodine is mainly excreted in urine (89%) (Anke et al., 1998; 2001; Heseker, 1999; Jahreis et al., WHO, 1996).

Functions: Iodine is an essential nutrient which serves the endogenous formation of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). These hormones control many metabolic processes in the body like growth, bone formation, brain development and energy metabolism. By means of various receptors (thyroid hormone receptors, a-, ß-TRs) T_4, mediated through T_3, influences the cells of the periphery tissue by modulating gene expression (Freake, 2000; Jepsen and Rosenfeld, 2002; Viguerie and Langin, 2003; Zhang and Lazer, 2000).

Interactions: Interactions of various dietary components (in particular selenium, zinc and iron), environmental pollution (smoke, nitrate, humic acids, glucosinolates, thiocyanates and other goitrogenic substances) and medicinal products with iodine influence their bioavailability and thyroid hormone metabolism (Arthur et al., 1999; Bartalena et al., 1995; Delange and Ermans, 1976; Fairweather-Tait and Hurrell, 1996; Gaitan, 1990; Höring, 1992; Kramer et al., 1998; Rayman, 2000; Seffner, 1995; Unger et al., 1993; Zimmermann and Kohrle, 2002). Most of the naturally occurring goitrogenic (antithyroidal) substances have only been tested in animal experiments and/or have only shown antithyroidal effects *in vitro* (Gaitan et al., 1993). However, interactions of this kind only occur when iodine intake is limited and/or the goitrogenic substance are ingested over a longer period. Via various mechanisms of action goitrogens lead to a drop in iodine reserve and, by extension, to an increase in iodine requirements. The negative effects on goitre prevalence are all the more critical, the poorer the iodine supply. On the other hand, elevated iodine intake compensates for the additional requirements and reduces goitre prevalence (Bartalena et al., 1995; Gaitan, 1990; Hampel et al., 1999; 2003; Höring, 1992; Knudsen et al., 2002; Kramer et al., 1998; Müller et al. 1995). Within the framework of risk assessment only those interactions are listed which are of clinical relevance for man.

Selenium: Selenocysteine is a component of *deiodases* that catalyse the deiodination of the prohormone thyroxine (T_4) to the active thyroid hormone 3,3' 5-triiodothyronine (T_3) and catalyse the deiodination of T_3 and inverse T_3 to inactive 3,3'diiodothyronine (T_2) (deiodase type 1). In the case of inadequate selenium supply the ratio of T_4 to T_3 increases in serum which can be used as a functional marker for selenium status (Brown and Arthur, 2001). Through type 2 deiodase, T_4 is converted intracellularly from plasma to T_3 and inverse T_3 to T_2 (tissue-specific regulation). The inactivation of the thyroid hormone by deiodisation from T_4 to inverse T_3 and from T_3 to T_2 is catalysed by type 3 5-deiodase (also a selenoprotein). The latter regulates maternal supply of the foetus during pregnancy with T_4 and T_3 and protects it from excessive amounts of T_3 (Anke et al., 2000). Selenium-containing enzymes are not just the three deiodases but also the four glutathione peroxidases and thioredoxin reductase whereby the latter play a role as antioxidants in the thyroid gland. As a consequence of a reduction in glutathione peroxidase activity in conjunction with a selenium deficiency, there is also greater oxidative damage when there is a parallel iodine deficiency through H_2O_2. The latter is produced in a greater volume in thyroid hormone synthesis as a consequence of TSH stimulation (Bouvier and Millart, 1997; Corvilain et al., 1993; Hotz et al. 1997). This means that regulation of tissue T_3 level and protection of the thyroid gland against H_2O_2 are the most important interactions (Arthur et al., 1999; Levin et al., 2002).

A selenium deficiency exacerbates an existing hypothyrosis already caused by iodine deficiency (Vanderpas et al., 1993). In older people (n=36) with a low selenium status (serum selenium concentration, activity of glutathione peroxidase in the erythrocytes) it could be shown in a double blind, placebo-controlled study that, after administration of selenium, not only was the selenium status significantly improved but the T_4 level also fell as an indication of the increased conversion of T_4 to T_3 (Olivieri et al., 1995; 1996). In a study involving lactating women a reduced fT_3 concentration in the serum was observed in conjunction with a marginal selenium offering of <20 µg/day as a consequence of reduced activity of thyroxine-5'-deiodase-1. The administration of 50 µg selenium per day significantly normalised the fT_3 level of the lactating woman (Anke et al., 2000). In contrast, in the case of sufficient selenium status no decrease in the T_4 level could be achieved through the additional daily administration of 100-200 µg selenium in the form of selenium methionine or selenium yeast as the activity of the deiodases was already optiman (Thompson, 2003).

Selenium intake beyond requirements can lead to changes in the metabolism of the thyroid hormone. For instance in the case of lactating mothers from selenium-rich regions in Venezuela, a significant inverse association was observed between the fT_3 concentration in the serum and dietary selenium intake. It is assumed that the activity of type 1 deiodase in the

liver is increasingly suppressed where there is a growing selenium intake already in a range of 350-450 µg/day (Brätter and Negretti de Brätter, 1996; Eder et al., 1995).

Zinc: Zinc is possibly a co-factor in type 1 iodothyronine deiodase and is, therefore, involved in thyroid gland metabolism. There were also signs of increased thyroid growth and a lowering of the circulating thyroid hormones in conjunction with zinc deficiency in animal experiments and clinical observations (Anke et al., 1982; 2000; Licastro et al., 1992, Nishiyama et al. 1994). In Germany, at least, a zinc deficiency does not play any role at all in the emergence of iodine deficiency diseases (Hampel et al., 1997).

Iron: The most recent studies confirm that iron deficiency anaemia has a negative effect on iodine and thyroid hormone metabolism. This reduces the efficacy of iodine prophylaxis in iodine deficiency regions. In one study in Morocco the parallel fortification of salt with iron and iodine significantly reduced the prevalence of endemic goitres in children with iron deficiency anaemia (Zimmermann et al., 2003). One point of attack is thyroid peroxidase since an iron deficiency reduces its activity (Hess et al., 2002).

Smoking (thiocyanate): Smoking, above all through thiocyanate (SCN^-) a degradation product of cyanide (CN^-) in smoke and other noxae, leads to competitive inhibition of iodide intake and impairment of hormone synthesis in the thyroid gland. This means that smokers are more at risk of developing a goitre (Barrère et al., 2000; Hampel et al., 1999; Kramer et al., 1998). In this case SCN^- serum levels are measured in the range of 8-12 mg/l. Women with a sub-clinical hypothyrosis are particularly vulnerable. Thiocyanate crosses the placenta and can, therefore, effect the foetus's thyroid gland. In iodine deficiency areas smokers are also more at risk of developing nodular changes in the thyroid gland (Bartalena et al., 1995; Chanoine et al., 1991; Christensen et al., 1984; Knudsen et al., 2002; Müller et al., 1995; Utiger, 1995;).

Nitrate: Nitrate (NO_3^-) inhibits active iodide transport both in the thyroid gland and in the gastro-intestinal tract by forcing the iodine molecule from its bond at the sodium-iodide symporter (Eskandari et al., 1997; Szokeova et al., 2001). High nitrate exposure from food (e.g. spinach, large white radish, radishes, chard) and drinking water (>50 mg/l) can lead in themselves or in conjunction with an existing iodine deficiency to an increase in goitre prevalence (Höring et al., 1991; Höring, 1992; Van Maanen et al., 1994). In order to avoid these negative effects on health, care should be taken not only to ensure sufficient iodine supply but also to ensure an, if possible, low nitrate content in drinking water besides other dietary nitrate exposure. A recent nationwide random sampling of 3,059 clinically healthy individuals aged between 18 and 70 years of both sexes demonstrated that the goitrogenic potency of nitrate is of individual but not of epidemiological importance. The median of nitraturia of 55.2 mg NO_3^-/g creatinine (men 61.5; women 51.5; $p < 0.03$) as the yardstick for nitrate exposure was far lower than the WHO limit values. Only in 71 individuals with inadequate iodine supply (ioduria <50 µg I-/g creatinine) did nitraturia correlate with thyroid volume ($r = 0.18$; $p < 0.05$). Furthermore, individuals with higher sodium exposure (n = 1166) (nitraturia >60 mg NO_3^-/g creatinine) showed a correlation with thyroid volume ($r = 0.18$; $p < 0.01$) (Hampel et al., 2003).

Other antithyroidal (goitrogenic) substances: Various types of cabbage, cassave, beans and peanuts contain cyanogenic glycosides, whose degradation product thiocyanate (rhodanide) competitively inhibits iodine intake (Gaitan, 1990). Furthermore, there are also thyreostatic goitrogens which inhibit the iodisation of tyrosine (iodisation inhibiter). Their effect cannot be compensated through iodine but only through the administration of a hormone (thyroxine) (Manz, 1990). Relatively large amounts (so-called nodular goitres) were found in swedes. However, as this vegetable is not generally eaten raw but cooked, the direct uptake of thiooxazolidones is not relevant. As a consequence of enzyme activation these substances are no longer formed. The situation is different when the plants are given as raw feed to cows as these substances can migrate into milk. At the same time, the iodine content of milk is redu-

ced which can be balanced through iodine supplements for the animals (Arstila et al., 1969; Großklaus, 1986; 1993; Laurberg et al., 2002; Papas et al., 1979). A one-sided diet with foods of this kind, e.g. when cassava is the main component of diet, as well as low iodine and selenium intake can be shown to influence goitre prevalence (Erdogan et al., 2001; Konde et al., 1994; Peterson et al., 1995; Thilly et al. 1992; 1993; Ubom, 1991).

Medicinal products: Numerous medicinal products (e.g. amiodarone, lithium and many more) interfere with iodine metabolism which means that iatrogenic disruptions of thyroid function, particularly in conjunction with long-term medication have to be taken into account. Iodine-containing oral bile contrast media (ipodate, iopanoate) contain organically bound but no freely available iodide. The latter is contained as a contaminant or degredation product and can indeed lead to interactions (Barsano, 1991; Clark and Hutton, 1985; Heufelder and Wiersinga, 1999; Rendl and Saller, 2001; Saller et al., 1998; Unger et al., 1993).

Requirements: The minimum iodine requirements of adults are given as 1 µg/kg body weight and 60-120 µg/day subject to sufficient iodine accumulation in the thyroid (Delange, 1985; Levander and Whanger, 1996). Iodine requirements are dependant on various factors. They include age, environmental exposure and a high consumption of foods of plant origin containing goitrogenic substances (*see Interactions*).

Table 29 compares the recommended intakes for Germany, Austria and Switzerland (D-A-CH, 2000) and the population reference intakes (PRI) of the Scientific Committee on Food (SCF) (SCF, 1993):

Table 29: Recommended iodine intake

Age	Iodine Germany Austria µg/day	Iodine WHO Switzerland µg/day	Population Reference Intakes (PRI) µg/day
Infants			
0 up to under 4 months *	40	50	
4 up to under 12 months	80	50	50
Children			
1 up to under 4 years	100	90	70
4 up to under 7 years	120	90	90
7 up to under 10 years	140	120	100
10 up to under 13 years	180	120	120
13 up to under 15 years	200	150	120
Adolescents and **adults**			
15 up to under 19 years	200	150	130
19 up to under 25 years	200	150	130
25 up to under 51 years	200	150	130
51 up to under 65 years	180	150	130
65 years and above	180	150	130
Pregnant women	230	200	130
Lactating women	260	200	160

* Estimated value

For adults WHO proposes an intake of 2 µg/kg body weight and day (FAO/WHO, 2001; WHO/UNICEF/ICCIDD, 1996). For countries that still have an iodine deficiency (Germany is one), higher iodine intake is recommended until the iodine level in the thyroid has normalised. The differences in the safety margin between the recommended intake for countries with sufficient iodine accumulation in the thyroid, for instance Switzerland and those countries which are still considered to be endemic iodine deficiency areas, for instance Germany, are between 30 and 50 µg iodine per day.

The recommendations are for healthy individuals. During pregnancy and lactation women have higher intake requirements in order to avoid subclinical hypothyrosis of the mother and the foetus or the neonate (Liesenkötter et al., 1996).

11.2.3 Exposure (dietary and other sources, nutritional status)

Sources:
Drinking water/beverages: Generally speaking only low amounts of iodine are taken up from these sources. The iodine content of beverages prepared in the home and commercially (tea, coffee, beer, lemonade) depends on the iodine content of the drinking water which falls from 10 to 1 µg/l as the distance to the coast grows (Bittermann and Großklaus, 1999). The iodine content of mineral waters also depends on its geological origins and is on average 6.0 µg/l. The maximum value is 153 µg/L (Kirchner et al., 1996).

Foods: The main source of iodine intake is food whereby the iodine content in foods and overall diet varies considerably. It is influenced by geochemical and cultural factors as well as by the use of iodised table salt. Although saltwater fish have the highest iodine level (8 to 1210 µg/100 g), because of their low level of consumption they contribute little (9%) to iodine supply (Jahreis et al., 2001; Höhler et al., 1990; Pfaff and Georg, 1995). Foods of plant origin contain little iodine (0.3 up to 5.0 µg/100 g) (Anke et al., 1994; Karl and Münkner, 1999). The iodine content in milk (82 up to 115 µg/l) and dairy products, eggs (64 µg/100 g) and meat (2.1 up to 7.8 µg/100 g) only make a relevant contribution when the animals are given sufficient iodine in their feed (Rambeck et al., 1997). As a consequence of iodine fortification of animal feed (10 mg/kg) the iodine "balance" in humans can be improved by around 60 µg/day by taking into account the consumption of foods of animal origin (Table 30).

This value also correlates with the current estimates of adults' basic iodine intake. With the consumption of saltwater fish and milk an adult's average iodine intake without iodised salt is approximately 60 µg/day (Großklaus, 1999; Manz et al., 1998).

Table 30: "Balance" of iodisation of feed (10 mg iodine/kg) (Großklaus, 1999)

Food	Human consumption* [g/day]	Iodine content** [µg/100 g]		Iodine intake [µg/day]	
		without	with iodine	without	with iodine
Beef and veal	28	1.5	3.4	0.4	~1.0
Pork	105	1.0	2.1	~1.0	~2.0
Poultry	24	3.9	7.8	~1.0	~2.0
Eggs	36	4.6	64	2.0	23
Milk	184	2.2	8.2	4.0	15
Cheese	56	4.5	52.2	2.5	29
Total				~11	~72

*) Information from the Central Market and Price Reporting Office (ZMP) on consumption of plants of animal origin, 1997
**) Data according to Anke et al., 1994

Milk and dairy products are the main source of iodine intake (37%), followed by meat and meat products (21%) and bread and cereal products (19%) whereas fruit and vegetables make the smallest contribution (3%). Overall the iodine content in foods has steadily increased in Germany over the last 10 years. Food producers' growing acceptance of iodised table salt as well as the increasing use of iodised mineral mixtures for dairy cows explain the increased iodine content of foods, particularly of milk and dairy products (Jahreis et al., 1999; 2001; Preiß et al., 1997).

Iodised table salt: Iodised salt contains 32 mg potassium iodate/kg. This corresponds to 20 mg iodine per kg salt. When used in the home, in the commercial and industrial production of food, particularly bread and meat products, these foods constitute a good source of iodine intake (cf. Table 31). Ideally, the use of 5 g iodine salt per day in the overall diet would lead

to the additional ingestion of 100 µg iodine. Whereas the use of iodised table salt in the home has reached a share of over 70%, iodised table salt is only used in around 35% of food production. Of this around 20 µg is accounted for by the use of iodised salt in the home through the addition of salt and only 40 µg/day are taken up in addition through the use of iodised salt in large packages, i.e. via industrially produced foods (Manz et al., 1998; Meng and Scriba, 2002).

Table 31: Estimated iodine content of foods produced with iodised salt

Food	Portion	NaCl content (mg/portion)	Iodine content (µg/portion)
Bread	Slice	600	12
Pretzels	Unit	1000	20
Rolls	Unit	600	12
Cake	Unit	250	5
Sausage	Per slice bread	600	12
Yoghurt	Small beaker	200	10
Milk	Cup	250	10
Saltwater fish	180 g		140

(according to Manz et al., 1998)

Food supplements: Iodine-containing food supplements are available with an upper level of 100 µg. Dietetic food supplements for pregnant and lactating women contain up to 200 µg iodine per recommended daily portion (BgVV, 1999). Mineral products are taken at least once a week by 8.8% of men and 12.5% of women (Mensink and Ströbel, 1999). In 5% of cases in which food supplements were administered, iodine-containing food supplements were also taken by children (Kersting and Alexy, 2000).

Medicinal products: Iodide tablets are available as pharmacy-only medicinal products. They contain doses of 100, 200 and 500 µg per day for the prophylaxis and treatment of endemic goitres (BGA, 1989; Fachinformation, 2002). Healing waters are also deemed to be medicinal products and may contain between 100 and 250 µg/l iodine (Zanger, 2003). In the case of iodine-containing medicinal products, cosmetics (e.g. iodopropynyl butylcarbamate (IPBC) used as preservatives) and disinfectants, it should be borne in mind that iodine can also be taken up percutaneously and from body cavities. This can lead to an unintended significant iodine intake. Large doses of iodine are administered in iodine-containing x-ray contrast media [~ 5000 mg/dose]. Most iodine is, however, organically bound and not freely available (Rendl and Saller, 2001).

Nutritional status:

Intake: According to the results of "Iodine Monitoring 1996" the average estimated iodine intake of the 2500 interviewed adolescents (>13 years old) and adults was 119 µg/day. Men were shown to have above average iodine intake (126 µg/day); women had below average iodine intake (111 µg/day) as did the over 70s (105 µg/day). The median (5-95 percentiles) of men and women was 116 (66.4-209.6) µg and 106 (59.8-185.8) µg /day. The maximum iodine intake, including iodine tablets, of men and women was 437.8 and 414.3 µg per day (Manz et al., 1998). In only 5-10% of the examined adolescents and adults was iodine intake found to be in line with the recommendations (180-200 µg/day) and in 1.2% it was higher (approximately 300 µg/day). Compared to the recommended intakes there is still overall an average supply deficit of around 60-80 µg iodine/day (reference intake value: 180-200 µg/day). This corresponds to one-third of the recommended intake (Gärtner et al., 2001; Manz et al., 1998; 2002). The intake of 150 µg/day recommended by WHO is not reached either. Germany is still seen as an iodine deficiency region even if iodine supply has improved markedly in recent years (D-A-CH, 2000).

One criticism is that the determination of iodine intake in comparison to other nutrients is less reliable for methodological reasons (large fluctuation range in iodine contents in foods, pre-

paration losses). That is why WHO recommends indirect methods with a suitable biomarker for the characterisation of iodine nutritional status (Manz et al., 1998).

Biomarkers: Iodine excretion in urine (ioduria) is considered to be a suitable biomarker for determining the iodine nutritional status of the population (Ovesen and Boeing, 2002). According to the new WHO criteria, the median of ioduria in school pupils and adults in the case of optimum iodine intake should be between 100-200 µg/l (Table 32). There is no endemic iodine deficiency when <50% of the population manifests ioduria under 100 µg/l and <20% of the population ioduria under 50 µg/l. A mild iodine deficiency (grade 1) exists when the median of ioduria is between 50-99 µg/l. Moderate iodine deficiency (grade II) is found in the range of 20-49 µg/l, whereas in the case of serious iodine deficiency (grade III) the median of ioduria is <20 µg/l.

Table 32: Criteria for adequate iodine supply and the incidence of iodine deficiency diseases

Iodine deficiency severity indicator	No deficiency	Grade I mild	Grade II moderate	Grade III severe
Median of ioduria in school pupils and adults [µg/l]	100-200 <50% of the population under 100 µg/l and <20% under 50 µg/l	50-99	20-49	<20
Median of ioduria in school pupils and adults [µg/g creatinine]	>100	50-100	25-50	<25
Iodine content in human milk [µg/dl]	>5	3.1-5.0	1.5-3.0	>1.5
Goitre prevalence in school pupils (%)	<5	5-19.9	20-29.9	>30
Thyroid volume in school pupils. Share of enlarged thyroid glands (>97 percentile) using ultrasound (%)	<5	5-19.9	20-29.9	>30
Neonate TSH screening Share of neonates with a level >5 mU/l blood (%)	<3	3-19.9	20-39.9	>40

(according to Delange and Bürgi, 1989; WHO/UNICEF/ICCIDD, 1994; 1996)

Table 32 also gives the criteria of WHO/UNICEF/ICCIDD for the classification of the severity of iodine deficiency after ioduria referred to g creatinine, the iodine content of human milk, the percentage incidence of enlarged thyroids (goitre) and the share of cut-off values (97 percentile) of normative thyroid volume using ultrasound in school pupils and the share of neonates with a TSH level >5 mU/l blood (%). In iodine deficiency regions there is an elevated incidence of neonates with transient hypothyrotic metabolism. A false positive elevated TSH test (>15 mU/l) can, therefore, be seen as an indicator for the scale of iodine deficiency in an iodine deficiency region (Manz et al., 1998).

The median ioduria values (iodine creatinine quotients) measured during the iodine monitoring of 83 µg/l (57 µg/g) and a number of spontaneous urine samples below 100 µg/l (only 62% instead of less than 50%) and below 50 µg/l (20.5% instead of less than 20%) of 772 conscripts (17.5-21 years) put this group, according to the WHO criteria, in the category "mild iodine deficiency". The 574 seniors (50-70 year olds) were also found to have median values of ioduria of 99/88 µg/l (73/95.6 µg/g). That put them in this category, too, whereby the proportion of spontaneous urine samples under 100 µg/l was 51/58% instead of less than 50% and the proportion under 50 µg/l was 19/21% instead of <20%.

The median ioduria values for lactating mothers not on iodine tablets were 71 µg/l (43 µg/g creatinine) and for those on iodine tablets it was 120 µg/l (78 µg/ g creatinine). In the case of breastfed neonates of mothers not on iodine tablets it was 51 µg/l (143 µg/ g creatinine) and for those on iodine tablets it was 86 µg/l (179 µg/g creatinine). The inadequate iodine supply of lactating mothers on and not on iodine tablets is also reflected in the proportion of mothers with an inadequate iodine content in breast milk (<5 µg/dl). 39% of lactating mothers not on

iodine tablets were found to have an iodine content in their milk <5 µg/dl. In the case of neonates of mothers on iodine tablets, the corresponding values were 8.6 µg/dl and 21%. Neonates of mothers who did not take iodine tablets were close to the threshold for iodine deficiency Grade II lactating mothers not on iodine tablets are, therefore, the group with the worst iodine supply (Gärtner et al., 2001; Manz et al., 1998; 2002).

More recent non-representative studies show a further improvement in iodine supply, particularly amongst pregnant women, lactating women, newborn babies and school children based on ioduria and measurement of thyroid volume. Endemic goitre and the frequently related transitory hypothyrosis have become very rare (<1%). Iodine deficiency related thyroid enlargements could be successfully combated, particularly in children, thanks to improved iodine intake. In some regions, they could even be completely eradicated. The optimum range (ioduria median 100-200 µg/l) has not, however, been achieved in all regions. Whereas 70% of the population has a sufficient supply, 30% still suffer from a mild to moderate iodine deficiency. The iodine deficiency currently amounts to 50-100 µg, measured against the DGE recommended intakes (Bühling et al., 2003; Hampel et al., 2000; Jahreis et al., 1999; Meng and Schindler, 1998; Meng and Scriba, 2002; Rendl et al., 2001; Roth et al., 2001; Wünschmann et al., 2002; Zöllner et al., 2001).

Hence iodine deficiency has not yet been completely eradicated in Germany or in some other regions in Europe (Manz et al., 2000; WHO, 2000). It is far more the case that more than half of the population in western and central Europe live in iodine deficiency countries (Table 33).

The differences can be explained by the fact that the legal preconditions for universal iodised salt prophylaxis vary considerably in Europe. On average only 27% of all households in Europe use iodised table salt (WHO target >90%). A WHO survey involving a total of 38 countries in Europe revealed that 28 countries currently have iodised salt prophylaxis, 12 countries have additional use of iodised salt in food processing and 13 countries have additional iodisation of animal feed. Whereas for instance in Germany the legal preconditions are in place for voluntary iodised salt prophylaxis with uniform maximum levels (15-25 mg iodine/kg salt) for use in the home, mass catering and for the production of bread, bakery and meat products as well as the iodisation of feed (10 mg/kg), there are for instance in the Netherlands different maximum levels for household salt (30-40 mg iodine/kg salt), bread (70-85 mg iodine/kg salt) and meat, minced meat and sausage with nitrite curing salt (20–30 mg iodine/kg salt). However, there are no legal provisions for the iodisation of feedstuffs (Delange et al., 2002a; Delange and Hetzel, 2003; WHO, 2000).

Table 33 : A comparison of iodine nutritional status in some European countries in Germany

Country	Ioduria median [µg/l]	Iodine intake	Iodine nutritional status
Belgium	80	Inadequate	Mild iodine deficiency
Denmark	38-110	Inadequate	Mild/moderate iodine deficiency
Germany	83-99	Inadequate	Mild iodine deficiency
France	83	Inadequate	Mild iodine deficiency
Greece	84-160	Partially inadequate	Mild iodine deficiency to optimum
Netherlands	155	Adequate	Optimum
Austria	98-120	Adequate	No iodine deficiency
Poland	>100	Possibly adequate	No sign of iodine deficiency apart from in pregnant women
Spain	50-100	Inadequate	Mild iodine deficiency
Sweden	>100	Possibly adequate	No sign of iodine deficiency, lack of monitoring
Switzerland	115	Adequate	Optimum
Hungary	<100	Inadequate	Mild iodine deficiency
United Kingdom	141	Adequate	Optimum

(according to ICCIDD, 2003)

11.3 Risk characterisation

11.3.1 Hazard characterisation (NOAEL, LOAEL)

A distinction must be made between:

1. Acute iodine intoxications after ingesting very large amounts of iodine;
2. Disruptions of thyroid function through low or high dietary iodine intake and
3. Rare oversensitivity reactions, normally after the administration of very high doses of iodine-containing x-ray contrast media, disinfectants, cosmetics or medicinal products (Pennington, 1990).

on 1: An acute iodine intoxication may occur when large amounts of, for instance, iodine tincture (up to 15000 mg iodine) are ingested intentionally or unintentionally. The individuals affected suffered from vomiting, abdominal cramp, anuria, high temperature, cyanosis and coma. In some cases there was a fatal outcome (Clark, 1981; Pennington, 1990; Saller et al., 1998).

on 2: Iodine has a complex effect on the thyroid gland. There is a u-shape association between iodine intake and the risk of thyroid disorders as both an overly low intake (<50 µg/day) as well as overly high intake (>500 µg/day) are linked with a growing risk. Iodine deficiency leads to the onset of a series of iodine deficiency diseases (see 11.3.2.1 Deficiency). A disrupted thyroid function as a consequence of excessive iodine intake can manifest itself either as a thyroid overfunction (hyperthyroidism) or as a thyroid underfunction (hypothyroidism) with or without goitre. Normally, healthy adults can tolerate iodine intakes of more than 1000 µg per day without any side effects. This tolerance limit corresponds to urinary iodine excretion of 600 µg/l. However, this upper level is far lower in groups who have been exposed to an iodine deficiency in the past (Delange and Hetzel, 2003; FAO/WHO, 2001; Stanbury and Dunn, 2001; WHO, 1994).

This also explains the different approaches adopted by the US-American Food and Nutrition Board (FNB, 2001) and the EU Scientific Committee on Food (SCF, 2002) when it comes to deriving the **LOAEL** (Lowest Observed Adverse Effect Level) and **NOAEL** (No Observed Adverse Effect Level). Based on the studies by Gardner (1988) or Paul et al. (1988) in healthy, euthyroid test persons with sufficient iodine supply, who were fed doses of 250 to 4500 µg/day in addition to their basic supply of 200-300 µg/day over a period of two weeks, both bodies derived a **LOAEL** between 1700 and 1800 µg/day, i.e. the lowest dose at which no or only marginal changes in the TSH level in the serum were observed without any clinically adverse effects. Based on a LOAEL of 1700 µg/day and an uncertainty factor (UF) of 1.5, FNB proposed a **NOAEL** of 1000 to 1200 µg/day for adults. This low UF is justified to the extent that there has been no endemic iodine deficiency in the USA since the 1920s which means that the prevalence of functional autonomies as a consequence of a chronic iodine deficiency is very low in the USA (Kimball and Marine, 1918; Lee et al., 1999; Mann, 1998).

In the opinion of SCF, one major reason for the choice of the higher UF of 3 is the uncertainty about whether relevant clinical sequelae can occur in individuals with normal thyroid function in conjunction with longer-term, chronic exposure to the above doses (SCF, 2002). By contrast the Expert Group on Vitamins and Minerals (EVM) in the United Kingdom considered the same available data to be inadequate for the laying down of a threshold dose (Food Standards Agency, 2003; 2002).

on 3: An iodine over-sensitivity or iodine allergy can occur after very high doses of iodine, for instance following the administration of iodine-containing x-ray contrast media, iodine-containing disinfectants, iodine-containing cosmetics or a few iodine-containing medicinal products (Chang et al., 1997; Curd et al., 1979; Rasmussen, 1955; Rendl and Sal-

ler, 2001; Vaillant et al., 1990). Here epicutaneous and intravenous administration play a decisive role in triggering these rare side effects which have not been observed in conjunction with the uptake of physiological iodine amounts from food (Gärtner, 2000; Scriba and Gärtner, 2000; Scriba and Pickardt, 1995) (see 11.3.4.1 Excessive intake).

11.3.2 Deficiency, possible risk groups

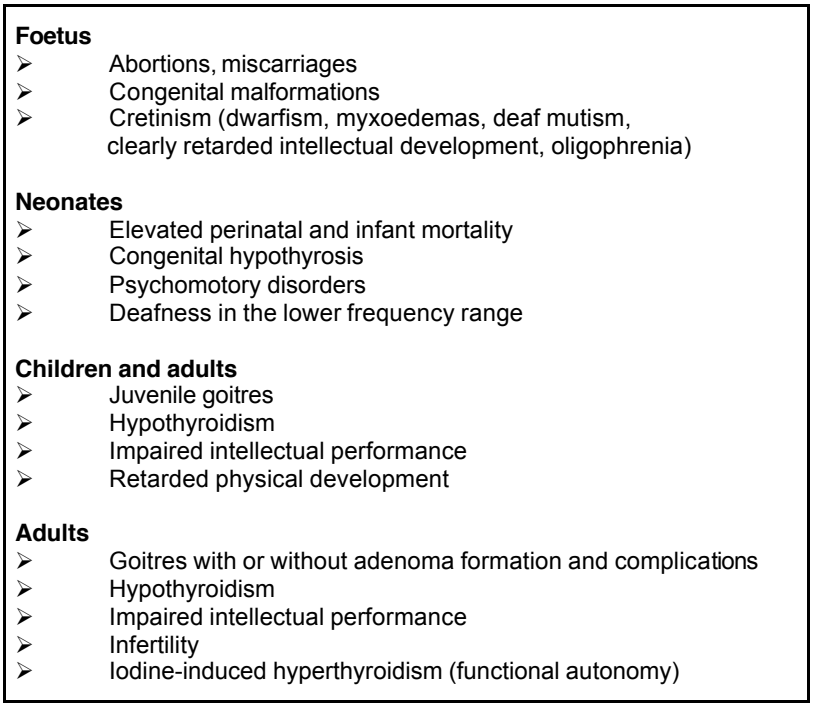
11.3.2.1 Deficiency

In the case of chronic iodine deficiency the thyroid endeavours to maintain hormone synthesis and, by extension, a euthyroid state by releasing more thyroid-stimulating hormone (TSH) (Delange, 1985). This leads to compensatory growth of the thyroid follicles (increase in thyroid tissue = goitre). This is followed by increased uptake of iodide from the plasma pool through an increase in the sodium-iodide symporter, increased production and secretion of T_3 as well as elevated thyroidal and peripheral conversion of T_4 to T_3 (Arthur et al., 1999). The hormone levels may still be in the normal range which means that most endemic goitre carriers do not suffer from any thyroid function disorders. More than 10% of the German population manifest a palpably enlarged thyroid (Meng and Scriba, 2002). According to a nationwide survey of more than 100,000 employed people, on average 33.2% of the (healthy) working population have an enlarged thyroid gland and/or nodules whereby men and women are affected to the same degree (Papillon, 2003). Since an enlarged thyroid can trigger a series of disorders, this is not merely a cosmetic problem. Besides causing purely mechanical constraints like respiratory disorders, difficulty swallowing and neck vein distentions, an enlarged thyroid can lead, if it persists, to structural anomalies (functional autonomy = hot nodules which produce too many hormones independent of requirements), hypothyroidism and thyroid carcinomas (develop from 5% of cold nodules). Iodine deficiency alone does not cause thyroid cancer but it does promote specific forms which have a poorer prognosis. Sufficient iodine supply reduces the risk of this type of cancer (Bacher-Stier et al., 1997; Franceschi, 1998). As a consequence of the functional autonomy of some thyroid tissue nodules, there is the risk of a manifestation of (latent) hyperthyroidism. The trigger is frequently acute exposure to high iodine doses (see 11.3.4.1 Excessive intake).

The general symptoms of iodine deficiency with thyroid underfunction include changes in general state of health like a drop in perfomance, tiredness, cold sensitivity, low blood pressure, weight increase, loss of appetite, constipation, cold and pale skin and mental imbalance (Großklaus, 2003).

Iodine deficiency disorders today are understood to include not only severe forms like endemic goitre and endemic cretinism but also all mild forms of dietary iodine deficiency that can have a detrimental effect on the physical and mental development of children and adults (Delange and Hetzel, 2003; FAO/WHO, 2001; Grossklaus, 2003; Hetzel and Dunn, 1989). Related to age group the range of iodine deficiency disorders includes the following: (Figure 3).

Figure 3: Range of iodine deficiency disorders



- Maternal iodine deficiency in particular can lead to a wide range of iodine deficiency disorders in the foetal and neonate stages. They include fertility disorders, an increase in the number of malformations, abortions and stillbirths as well as endemic cretinism as the complete clinical picture of a severe iodine deficiency (Dunn and Delange, 2001; Krassas et al., 1999; Krassas, 2000; Xue-Yi et al., 1994). The related intellectual disability and perceptive deafness are seen as an expression of prenatal damage. In Europe today neurological cretinism as an endemic problem (iodine intake <25 µg/day) has largely disappeared partly thanks to improvements in iodine supply (WHO, 2000). However, even in the case of minor iodine deficiency during the critical period of brain development, disruptions in brain maturation including hearing defects and psychomotor development can occur (Forrest, 1996; Hesse, 1994; Hetzel, 2000). In a retrospective study it could be shown that children of mothers who suffered from a minor thyroid underfunction (TSH increase) during pregnancy, had on average a slightly lower intelligence quotient than children of mothers with a normal thyroid function and, by extension, sufficient iodine supply of the child (Haddow et al., 1999). Furthermore, the syndrome of the hyaline membrane as an expression of disturbed maturation of the lung as well as growth retardation of the skeleton can be observed in conjunction with iodine deficiency in neonates. In order to avoid damage to the foetus, the iodine deficiency must already be overcome prior to conception (Delange and Hetzel, 2003; Großklaus, 1993; 2003; Hesse, 1994).

- During puberty the frequency of enlarged thyroids in Germany increases to around 50% in girls and around 30% in boys without taking into account regional differences. Recently, disruptions to neurointellectual development like learning and attention difficulties could be identified in "normal school pupils" with goitre (Azizi et al., 1993; 1995; Delange and Hetzel, 2003). The "big neck" of children and adolescents is, therefore, by no means a cosmetic problem which they "grow out of".

- In adults the health risks of iodine deficiency disorders are often only linked to the appearance of goitre particularly as many people see thyroid enlargement as a purely cosmetic problem. It is far more frequently the case that moderate iodine deficiency induces malfunction of the thyroid frequently linked to reduced hormone production. Ex-

perience shows that the full clinical picture of hypothyroidism with extensive goitre is only encountered rarely. Far more frequent are less developed stages of the disease unless efforts are specifically made to identify individual symptoms. Slow reflexes and a growing cold intolerance are almost obligatory as is dry skin. Obstipation and difficulty concentrating also occur more frequently than goitre (Großklaus, 2003).

- In Germany, as in other countries, it has been observed (Bürgi et al., 1982; Phillips et al., 1988) that many cases of undiagnosed functional autonomies of the thyroid are to be expected as a consequence of persistent iodine deficiency, particularly in older people. With increasing age the incidence of autonomous goitres in iodine deficiency regions rises to 50% whereas it is less than 1% in regions with sufficient iodine supply (e.g. USA). By overcoming iodine deficiency we can, in the long-term, reduce the onset of this iodine deficiency disorder to the scale found in USA and Switzerland (Baltisberger et al., 1995; Pickardt, 1994).

11.3.3 Possible risk groups for insufficient intake

Pregnant and lactating women are particularly at risk as are infants and then small children (BgVV/BZgA, 2001; Bohnet et al., 1995; Gärtner et al., 2001; Glinoer and Lemone, 1992; Liesenkötter et al., 1996; Manz et al., 1998). Female smokers and their newborn babies are a very high risk group (Chanoine et al., 1991). The incidence of endemic goitres also correlates with low socio-economic status in the population where the differences could be explained by smoking and iodine intake (Knudsen et al., 2003). Women are affected five times more frequently than men by acquired thyroid underfunction as a consequence of iodine deficiency. The prevalence based on diagnosed and medicinally treated hypothyroses is 8.1% and 1.6% in Germany (Melchert et al., 2002).

Individuals on a lacto-vegetarian (e.g. wholefood) or a strictly vegan diet are also more at risk particularly if they do not use any iodised salt, iodine tablets or iodine-rich products like seaweed (Davidsson, 1999; Lightowler and Davies, 1998; Rauma et al. 1994; Remer et al., 1999).

The data available for the Federal Republic of Germany on iodine nutritional status indicate that around 30% of the population runs the risk of a clinically manifest deficiency or store depletion. Women are affected five times more frequently than men. According to the WHO criteria there is a mild iodine deficiency. Heavy smokers, pregnant and lactating women as well as infants and small children are particularly at risk. A vegetarian diet also increases the risk – particularly when it does not contain any iodised salt or other iodine rich products (supply category 1).

11.3.4 Excessive intake, possible risk groups

11.3.4.1 Excessive intake

Excessive iodine intake (>1000 µg and more per day) (so-called iodine excess) can damage health. Depending on dose and sensitivity of the test persons, the following clinical pictures are possible:

1. Triggering of hyperthyroidism particularly in conjunction with a functional autonomy (overfunction through "nodular goitre");
2. Immunothyropathy (misdirection of the immune system: Basedow's disease);
3. Hashimoto's thyroiditis (immunological thyroid inflammation);
4. Acute blockade of iodine intake in the thyroid (Wolff-Chaikoff effect) with and without hypothyroidism and

5. Possible rare oversensitivity reactions for instance in patients with dermatitis herpetiformis, Duhring's disease, iodine allergy or intolerance reactions to iodine-containing x-ray contrast media, disinfectants, cosmetics or medicinal products.

High iodide amounts lead primarily to a failure of thyroidal self-regulation (Wolff-Chaikoff effect) in an abnormal thyroid gland. This, in turn, leads to the increased production and release of the thyroid hormones. The administration of higher amounts of iodine does not automatically trigger **hyperthyroidism** in a normal thyroid gland. Predisposing factors are the structural changes in thyroid tissue frequently found in older patients in conjunction with multinodular goitres (functional autonomy) and a latent or manifest Basedow type immunothyropathy.

on 1: Iodine amounts of 500-2000 µg/day do not automatically trigger hyperthyroidism in a normal thyroid gland. For this higher doses of 2000-10000 µg/day are clearly necessary (Savoie et al., 1975; Skare and Frey, 1980). Predisposing factors are the structural changes in thyroid tissue frequently found in older patients in conjunction with multinodular goitre (**functional autonomy**) and a latent or manifest Basedow type immunothyropathy. As a consequence of the functional autonomy of thyroid tissue nodules, there is the risk of the manifestation of a (latent) hyperthyroidism already in conjunction with excessive iodine intake of 500 µg/day and above (Bravermann and Roti, 1996; Ermans and Camus, 1972). Up to 90% of these patients are primarily euthyroid (Bauch, 1998). The trigger is frequently acute exposure to high iodine doses (e.g. iodine-containing x-ray contrast media [~5000 mg/dose] or iodine-containing medicinal products [0.250-0.375 mg/dose] or also the consumption of iodine rich seaweed (BgVV, 2001; De Smet et al., 1990; Eliason 1998; Heufelder and Wiersinga, 1999; Pennington, 1990; Salas Coronas et al., 2002; SKLM, 1988; Stanbury et al., 1998).

Iodine-induced hyperthyroidism can be triggered above all in older test persons (>40 years) when the mean iodine excretion in urine of 200 µg/l is rapidly exceeded in a relatively short period of 1-2 years following commencement of iodine prophylaxis. The frequency distribution of urinary iodine excretion was mostly asymmetrical with an oblique distribution towards the higher values (maximum values 1600 µg/l). This also points to unnecessarily high iodine intake. The risk of iodine-induced hyperthyroidism was particularly high in countries like Tanzania, Zimbabwe or the Democratic Republic of Congo in which there is no monitoring of the quality of iodised table salt (exceeding of the maximum levels) or of iodine intake in the population. In Zimbabwe the incidence rate of iodine-induced hyperthyroidism more than doubled following the sudden increase in iodine intake within 18 months from 2.8 per 100000 in 1991 to 7.4 per 100000 inhabitants in 1995 (Delange et al., 1999; Stanbury et al., 1998). Depending on the development stage of autonomy and the iodine dose, hyperthyroses are to be expected (Livadas et al., 1977).

An increase in the hyperthyroidism incidence rate was recorded in the former GDR between 1984 and 1989 following the introduction of iodised salt prophylaxis and the feeding of iodised mineral mixtures to cattle, pigs and sheep (Deckart et al., 1990; Klaua et al., 1991). As the use of iodised salt is slowly spreading in the Federal Republic of Germany and the related additional iodine intake has not led up to now to any exceeding of the normal upper limit of iodine excretion in urine (median: 200 µg/l), the manifestation peak observed in Zimbabwe will probably not occur in Germany. For instance the median of urinary iodine excretion was 99 µg/l for senior citizens (Manz et al., 1998). Therefore, no threat to older thyroid sufferers is to be expected. In any case the incidence of toxic nodular goitre will decrease considerably in conjunction with the steady improvement to the population’s iodine supply (Baltisberger et al., 1995; Pickardt, 1994).

on 2: Genetic predisposition, viral infections and environmental factors, including iodine and selenium supply, are discussed as causes of **Graves' disease**, an autoimmune disease of the thyroid gland. So far autoimmune processes, that have not yet been fully clarified, have led to the thyroid gland producing uncontrollably large amounts of thyroid hormones. Autoantibodies above all to the THS receptor (TRAK) but less to the sodium iodide symporter (NIS) could be detected which imitate the effect of the thyroid-stimulating hormone (TSH) (Ajjan et al., 1998; 2000; Seissler et al., 2000). Graves' disease occurs more frequently amongst women in the third and fourth decade of life.

The incidence of Graves' disease seems to be influenced by dietary iodine supply (Laurberg et al., 1991; 1998). A multicentric study by Reinwein et al. (1987) revealed for Basedow patients in regions with sufficient iodine supply a higher prevalence of thyroid antibodies than in iodine deficiency regions. This difference has also been confirmed in the healthy population. The underlying mechanism is not clear. It may be that higher doses of iodide promote antigen presentation of the immune system as well as the proliferation and functional activation of cells involved in the immune process. Based on these studies it is not, however possible to determine a range for optimum iodine supply in order to keep the incidence of autoimmune diseases as low as possible (Laurberg et al., 1998; 2000; Mann, 1994). According to the WHO/UNICEF/ ICCIDD (2001) criteria, the median of urinary iodine excretion should not exceed 300 µg/l in order to keep the risk of disease as a consequence of iodine excess for these patients as low as possible (Delange et al., 2002b). The use of physiological doses, like for instance in conjunction with iodised salt, is however completely safe (Gärtner, 2000).

The growing use of CT studies, angiographs and cardiac catherisations with iodine-containing contrast media, the use of iodine-containing disinfectants and the spread of the iodine-containing anti-arrhythmic agent, amiodarone, are by far the most frequent causes of iodine-induced hyperthyroidism (Fassbender et al., 2001; Harjai and Licata, 1997; Heufelder and Wiersinga, 1999; Hintze, 1987; Roti and Uberti, 2001; Usadel, 1985). Although the risk of iodine-induced hyperthyroidism after the application of iodine-containing x-ray contrast media is classified as low (incidence is 0.25-0.34%), hyperthyrosis or even thyrotoxic crisis in conjunction with iodine contamination do constitute a clinical picture which should be taken seriously and may even be life-threatening particularly in older patients. Hyperthyroid patients suffer, amongst other things, from unfounded nervosity, palpitations, sweating, a feeling of hunger coupled with weight loss, diarrhoea and sleep disorders (Fajfr et al., 2003). Thyroid function should, therefore, be examined prior to the administration of iodine-containing substances like medicinal products or x-ray contrast media and before operations (Fachinformation, 2002; Heufelder and Wiersinga, 1999; Pickardt, 1994; Rendl and Saller, 2001).
The prevalence of medicinally treated hyperthyroidism with/without goitre is 0.9% for women and 0.2% for men in Germany. Iodine-induced hyperthyroses account for roughly half of all overactive thyroid glands (Klaua et al., 1991; Melchert et al., 2002; Rendl and Saller, 2001).

on 3: The manifestation of a sub-clinical **auto-immune thyroiditis** (Hashimoto's thyroiditis) increases sensitivity to the inhibitory effects of excessive iodine exposure (Heufelder and Wiersinga, 1999; Saller et al., 1998). In these patients with and without a functional disorder, a manifest hypothyroidism can develop earlier when more than 200 µg iodide is administered in addition to normal daily iodide intake (Mann et al., 1997).

The mechanisms which lead to an abnormal immune reaction and which favour the onset of auto-immune thyroiditis as a consequence of excessive iodine intake have not yet been fully clarified. The decisive factor for the onset of auto-immune thyroiditis is, however, genetic predisposition whereby environmental factors also play a role. According to the previous studies it can be assumed that an elevated incidence of auto-

immune thyroiditis (AIT) does not occur following higher iodine substitution coupled with sufficient selenium supply. A selenium deficiency promotes the onset of AIT (Duntas et al., 2003; Gärtner et al., 2002; Hotz et al. 1997). Furthermore, a thyroid gland with inadequate iodine supply reacts more sensitively to an iodine excess (Foley, 1992; Mariotti et al., 1996; Schuppert et al., 2000). Iodide doses (100-200 µg/day), as used for the prophylaxis and treatment of endemic goitre, cannot provoke an immune thyroiditis (Braverman, 1998; Delange and Lecomte, 2000; Gärtner, 2000; Liesenkötter et al., 1996; Nohr et al., 2000).

Older studies from Japan show that around half of patients, who developed hypothyroidism in conjunction with high iodide intake (>1 mg iodide daily), suffered from lymphocytic thyroiditis (Mizukami et al., 1993). In a prospective, randomised German study patients with goitre and without any symptoms of auto-immune thyroiditis were given 200 µg iodide per day over 12 months. The enlarged thyroid shrunk, three patients developed lymphocytic thyroiditis whereby two patients had hypothyroidism and one patient hyperthyroidism. After discontinuation of iodide substitution thyroid function returned to normal and the antibody titres and lymphocytic infiltrates were also reduced (Kahaly et al., 1997).

In a placebo-controlled study in women with subclinical Hashimoto's thyroiditis and older women (60-75 years) who had previously been exposed to an iodine deficiency, there was a significant increase in average urinary iodine excretion (95% confidence interval) to 221 (141-344) and 402 (250-644) µg/l in comparison to the controls with 41 (16-108) and 82 (56-120) µg/l after 28-day supplementation of 500 µg iodine in addition to customary iodine intake (255 µg/day). All supplemented groups showed a similarly significant decrease in free thyroxine (fT_4) and a compensatory increase in the TSH level in serum as a sign of a negative effect on thyroid function. The authors concluded that intake of 750 µg and more per day cannot be accepted at all for sensitive individuals (Chow et al., 1991).

In a study in euthyroid patients (n=40) with Hashimoto's thyroiditis, 6 patients developed a subclinical hypothyrosis and 1 patient a clinically manifest hypothyroidism after 4-month supplementation of 250 µg potassium iodide. This means that even at this low dose in addition to customary dietary iodine intake, it cannot be ruled out that iodine administration can progressively edge the natural course of this auto-immune disease towards hypothyroidism (Braverman, 1998; Reinhardt et al., 1998).

There is a higher incidence rate of inflammatory auto-immune diseases of the thyroid gland in regions with a severe selenium deficiency as a consequence of the reduced enzyme activity of selenium-dependant glutathione peroxidase leading to elevated formation of radicals. Gärtner et al. therefore gave patients with auto-immune thyroditis of this kind (n=70) a 200 µg selenium supplement in a prospective, placebo-controlled clinical trial with follow-up. The supplemented patients may experience a drop in the average concentration of TPO-Ab (thyroid peroxidase antibodies) or even a normalisation of values. Clearly the inflammatory activity in patients with chronic auto-immune thyroiditis can be improved even in the case of a mild selenium deficiency through selenium substitution (Gärtner et al., 2002; Gärtner and Gasnier, 2003). Similar results were obtained in a comparable clinical trial in patients of this kind (n=65) in Greece (Duntas et al., 2003). The results of the SU.VI.MAX Study in France also indicate that selenium offers protection against this auto-immune disease (Derumeaux et al., 2003).

on 4: Pharmacological iodine doses (more than 1000 µg iodide/day) can trigger the following effects:

1. Acute blockade of iodine intake in the thyroid gland (**Wolff-Chaikoff effect**). High intrathyroidal iodide concentrations (normal 0.7 ± 0.3 mg/g) (Reiners et al., 1998) inhibit the organification of iodide itself as well as the secretion of the thyroid hormone.
2. In the case of a persistent iodine surplus, adaptation may also lead to a reduction in the sodium-iodide symporter (NIS) and thyroid peroxidase (TPO) mRNA. In the long-term this means that **hypothyroidism** and goitres can develop (Eng et al., 1999; Roti and Vagenakis, 1996).
3. The reduction of intrathyroidal iodine turnover and colloid proteolysis and, by extension, the reduction of hormone release is particularly evident in hyperthyroidism, an effect which was used in the past in conjunction with high-dose iodide treatment (Bürgi et al., 1982; Wolff, 1969).

It should also be borne in mind that substances with a high iodine content (sodium iopodate), other iodine-containing x-ray contrast media and iodine-containing medicinal products like amiodorane can also intervene in the thyroid hormone metabolism. The excessive amounts of iodide released during the metabolisation of these substances inhibits, by means of the above-mentioned mechanism, the formation and release of thyroid hormone. A 7 to 400 times higher serum concentration of inorganic iodide was measured in patients after the administration of amiodorane, a iodine-containing medicinal product (range 3.5-208.2 µg/dl, median 36.6 µg/dl) (Saller et al., 1998).

Iodine-induced hypothyroidism in neonates plays a clinical role after the administration of iodine-containing skin disinfectants to mother or infant. Neonates are particularly sensitive to the Wolff-Chaikoff effect as their immature thyroid gland is not yet able to reduce the iodide intake from the plasma in the event of overload (Sherwin, 1982; Smerdely et al., 1989).

Iodine-induced hypothyroidism as a consequence of the Wolff-Chaikoff effect can also be dietary, for instance after consumption of iodine rich seaweed (167-36700 µg/100 g) or drinking water with a high iodine content (>460 µg/l) (BgVV, 2001; Hou et al., 1997; Konno et al., 1994; Laurberg et al., 2001; Mu et al., 1987; Zhao et al., 2000). Fishermen on the island of Hokkaido in Japan developed the so-called coastal goitre (Suzuki et al., 1965) as a consequence of their traditionally high consumption of iodine rich marine algae and kelp. More than 50% of the Japanese patients examined became euthyroid again, i.e. their thyroid function returned to normal when the high dietary iodine intake from marine algae was reduced. The iodine concentration in serum was 122 µg/dl (normal 4-9 µg/dl) and the urinary iodine excretion of these patients was in some cases 13.05 mg/day (normal less than 2 mg/day) (Haraguchi et al., 1986; Matsubayashi et al., 1998; Tajiri et al., 1986).

on 5: A distinction must be made between rare oversensitivity reactions in patients with Duhring's disease, an iodine allergy or pseudoallergic reactions following the administration of iodine-containing contrast media, iodine-containing disinfectants, iodine-containing cosmetics or iodine-containing medicinal products or the iodine-containing food colour erythrosine.

Duhring's disease is an auto-immune disease which is frequently linked to a gluten-sensitive enteropathy (coeliac disease). The preferred treatment is a gluten-free diet which leads to an improvement in the typical symptoms of a highly itchy skin rash (Reunala, 1991). The characteristic feature of this disease is that it can be provoked by halogens which have been used in the past for the purposes of diagnosis. The amount used here is, however, far higher than recommended iodine intake (Merk, 1994; Plewig and Strzeminski, 1985).

In the case of a **iodine allergy** a distinction must be made between the extremely rare late type allergic reaction to iodine which manifests as contact eczema and the far more frequent intolerance reaction to iodine-containing x-ray contrast media or medicinal products (Baumgartner, 1976; Kincaid et al., 1981; Soria et al., 1990; Vaillant et al., 1990). This can lead to non-specific iodine attachment to amino acids of body proteins which then change their properties and act as haptens or antigens. People suffering from Duhring's disease or an iodine allergy must avoid exposure to larger amounts of iodine, for instance an x-ray with iodine-containing contrast media, treatment with iodine-containing solutions or tinctures and the uptake of *high* iodine amounts (1 mg/day). Following the consumption of kelp preparations (15 mg iodine per tablet) inflammatory skin changes (so-called kelp acne) were observed in the USA which quickly disappeared after discontinuation of the tablets. Iodine and iodine salts, as used in iodised table salt, are not able to act as allergens because of their low molecular size and cannot, therefore, trigger or exacerbate any allergic skin reactions (Gärtner, 2000; Großklaus, 1994; Merk, 1994; Scriba and Pickardt, 1995; Seif, 1991).

The iodine-containing food colour **erythrosine** (E 127) is wrongly accused of triggering an iodine allergy and disruptions of thyroid function. Erythrosine is a four-fold iodised disodium salt of fluorescein. 57.7% of its weight consists of iodine. It is a known trigger of pseudo-allergic reactions which are similar to allergies but which are not immunologically mediated. Erythrosine is only approved as a food colour in the EU for specific foods, e.g. bigarreaux cherries in syrup and fruit cocktails (150 mg/kg). Individuals, who cannot tolerate this colour, can easily avoid it by not eating these foods. No information on the incidence of intolerance to erythrosine is available. Erythrosine has been repeatedly evaluated by JECFA (IPS, 2000). Based on a human NOAEL of 60 mg/day for changes in thyroid hormone status, an ADI of 0 to 0.1 mg/kg/day was established. A person weighing 60 kg would exceed this ADI if he regularly consumed 30 g cocktail cherries daily. An exceeding of the NOAEL in order to bring about changes in the thyroid hormone level could be achieved by eating 300 g coloured cherries. Erythrosine is scarcely absorbed by human beings. The administration of 75 to 80 mg erythrosine, labelled with iodine^{131}, led to 100% excretion in faeces in four test persons. Two test persons excreted between 80 and 90% of the labelled iodine amount without iodine^{131} being detectible in the body, urine or serum (incomplete faeces collection?). Potential initial retention in the body of 1.2 ± 0.4% was calculated. The T_4 and T_3 levels did not change. It was not possible to identify the mechanism which influenced the thyroid hormone level (elevated TSH and T_4, lower T_3) following the administration of high doses of erythrosine, 200 mg/day. In animals erythrosine seems to inhibit type 1 deiodase (Poulsen, 1993). From the available studies it can be concluded that erythrosine is only absorbed to a minor degree (Katamine et al., 1987). Absorbed erythrosine is not reliably deiodinated in the body but bound intact to proteins. The influence of high doses on thyroid hormone secretion cannot be reliably attributed to a release of iodine from erythrosine.

11.3.5 Possible risk groups

Pregnant women, premature babies, neonates, infants and older people who have grown up with an iodine deficiency, with a functional autonomy or patients with a genetic predisposition for auto-immune thyroiditis are the risk groups sensitive to iodine excess (Bürgi et al., 1982; Gärtner, 2000; Food Standards Agency, 2002). In this context there is a degree of uncertainty when it comes to determining the "window of iodine intake" at which fewer thyroid diseases generally occur (Laurberg et al., 1998; 2001). According to WHO/UNICEF/ICCIDD (2001) there is no risk for sensitive groups with an undiagnosed functional autonomy in the range of optimum iodine supply, i.e. at an ioduria median of 100-199 µg/l. An increased health risk for sensitive individuals with functional autonomy or auto-immune disease of the

thyroid gland is only to be expected at excessive iodine intake where the ioduria median is >300 µg/l.

11.4 Tolerable upper intake level for iodine

FAO/WHO indicates doses of 50 and 30 µg iodine per kg body weight and day (FAO/WHO, 2001) as probable safe upper limits. This corresponds, for instance, to a daily amount of 1900 µg for a 12-year-old girl weighing 38 kg or 1800 µg for an adult weighing 60 kg. An uncertainty factor (UF) was not taken into account (FAO/WHO, 2001).

The Food and Nutrition Board (FNB) of the USA and Canada has established different tolerable upper intake levels (UL) of between 200 and 1100 µg/day for children, adolescents and adults (= 19 years) taking into account an uncertainty factor (UF) of 1.5 (FNB, 2001).

Based on a higher uncertainty factor (UF) of 3, the then Scientific Committee on Food of the European Commission (SCF) derived a UL of 600 µg per day for adults. ULs for children were calculated by adjusting the adult UL on the basis of the body surface area (body weight$^{0.75}$) (SCF, 2002).

An overview of the ULs for iodine of the various age groups of the three bodies is given in Table 34.

The various bodies (FAO/WHO, FNB, SCF) all focus in their risk assessment on the effects described here, in particular the impact of iodine surplus on thyroid function which depends on current iodine nutritional status. The differences in the derived tolerable upper intake levels (ULs) mainly result from the very different handling of the uncertainty factor. This testifies to a certain degree of uncertainty when it comes to assessing the same study results. However, in the final instance, it is due to the ongoing, in some cases, very different iodine nutritional supply situation in individual countries which determines the "window of iodine intake" at which fewer thyroid diseases generally occur (Laurberg et al., 2001). In this respect SCF is of the opinion that the ULs do not apply to populations with iodine deficiency disorders, as these are more sensitive to iodine exposure (SCF, 2002).

Table 34: Comparison of the ULs of the FAO/WHO Expert Consultation, FNB and SCF

Age group	UL (FAO/WHO, 2001) µg/kg bw/day	UL (FNB; 2001) µg/day	UL (SCF, 2002) µg/day
Premature babies	100	–	–
Infants, 0-6 months	150	–	–
Infants, 7-12 months	140	–	–
Children, 1-3/4-6 years	50	200/300	200/250
School pupils, 7-10/11-14 years	50	600	300/450
Adolescents, 14-18 years	30	900	500
Adults (= 19 years)	30	1100 (900)[1]	600
Pregnant and **lactating women**	40	1100 (900)[1]	600

[1] 14-18 years

By contrast, the Expert Group on Vitamins and Minerals of the United Kingdom (EVM) was unable to derive a safe upper level for a tolerable upper intake level for iodine. Instead, it laid down a guidance level of 0.5 mg/day (corresponding to 0.003 mg/kg body weight for an adult weighing 60 kg) for supplements. At this amount of iodine, which can be taken up additionally with dietary iodine (0.43 mg/day = 97.5 percentile), EVM does not expect any side effects of any kind for adults (corresponding to an intake of 0.94 mg and 0.015 mg/kg body weight and day in total). Unlike SCF, EVM is not of the opinion that a UF should be taken into account (Food Standards Agency, 2003).

At that time BgVV and DGE had recommended, on precautionary grounds to protect sensitive consumers as a consequence of the given chronic iodine deficiency, that dietary iodine intake in adults should not exceed 500 µg/day in general (BgVV, 2002; D-A-CH, 2000). The current iodine supply has continued to improve in Germany and in numerous other European countries; however the consequences of chronic iodine deficiency in the older generations have not been overcome. For that reason no UL can be accepted as the tolerable upper intake level for iodine which does not take this vulnerable group of people into account. BfR is, therefore, of the opinion that the ULs derived by SCF are not applicable either. Hence it is not possible to establish maximum levels in individual products using the formulae presented (see Chapter 3.3.2.1).

Hence, as in the past, a dietary intake amount of 500 µg/day should not generally be exceeded as the tolerable upper intake level for iodine in adults. This corresponds to urinary iodine excretion of 300 µg/l. As a rule no hyperthyroidism can be triggered even in the case of existing compensatory autonomy of the thyroid. Physiological iodine amounts of 150-200 µg per day, as are ingested in a disseminated manner from dietary iodised salt, neither have a negative impact on excess hormone production of the Basedow thyroid gland nor can they lead to a metabolic imbalance in conjunction with existing autonomy or trigger any other side effects. Furthermore, the setting of maximum levels (10 mg/kg) for the iodisation of feedstuffs ensures that only amounts of iodine in this physiological range can be ingested from food of animal origin, in particular milk and eggs (Großklaus, 1999).

Greater iodine supplementation of feedstuffs is under discussion as a supplementary measure to iodised salt prophylaxis in order to increase the basic iodine supply of people from food of animal origin (Rambeck et al., 1997). The counter-argument is that for instance cow milk would then contain four times more than the maximum levels of iodine indicated by the World Health Organisation (WHO) if iodine-containing feedstuffs or iodine-containing teat disinfectants were to be used. It is undoubtedly the case that outbreaks of iodine-induced hyperthyroidism have been registered in the past in Australia and in the United Kingdom which could be attributed to contamination of the milk following the use of iodine-containing udder disinfectants or overly high iodine content in feedstuffs (Nelson et al., 1988; Phillips et al., 1988; Wheeler et al., 1982). In the case of the iodine-containing teat disinfectants approved in the

Federal Republic of Germany with 3000 mg/kg in the application-ready preparation, the iodine contamination of milk is minimal and, following dripping losses, is between 0 and 40 µg/kg milk. This low amount results from the poor availability of organically bound iodine in the teat disinfectants, e.g. povidone iodine (BGA, 1991; Heeschen, 1997). The frequently used argument concerned the earlier use of teat disinfectants with iodine contents of 5000-10000 mg/kg, whereby iodine contents in the milk of 200-500 µg/kg were possible. Teat disinfectants of this kind are no longer on the market in the Federal Republic of Germany.

Excessive intake of iodine through uncontrolled iodisation of mineral mixtures or feedstuffs is also ruled out in Germany as a consequence of the setting of maximum levels in accordance with the Feedstuffs Act. The iodine feed concentrations have been established at 4 mg/kg for equids and 10 mg/kg for other species of animals in order to guarantee an optimum supply of animals taking into account performance and to rule out any damage to the health of animals and human beings (Großklaus, 1999). The Committee "Residue problems through medicinal products" of DVG e.V., recommends that the total iodine content of milk should not exceed 500 µg/kg and the iodine increase in bulk milk caused by teat disinfection processes should not be more than 150 µg/kg (Hamann and Heeschen, 1982; Preiß et al., 1997). The above-mentioned maximum level in accordance with feedstuff legislation (10 mg/kg) does, however, correspond to four times the requirement recommendations for dairy cows and breeding sows (0.5 and 0.6 mg iodine/kg dry feed substance). Studies with growing pigs confirm that the T_3 serum concentrations could be reduced through supplementation of 10 mg/kg feed (Schöne, 1999). Where appropriate, the iodine feedstuff concentration should be further reduced for livestock in order to avoid an iodine excess and possible health damage to animals. This would also reduce the exposure of human beings to iodine from foods of animal origin. But there is definitely no "multiple iodisation" via iodised salt and animal feed (Braunschweig-Pauli, 2000).

Control measures should, however, ensure that the median of urinary iodine excretion of school pupils and adults is, if possible, in the optimum range of 100-199 µg/l. More particularly, there should be no sudden increase in iodine intake in order to avoid any rapid exceeding of the median of urinary iodine excretion of 200 µg/l. According to WHO/UNICEF/ICCIDD (2001), the risk of an iodine-induced hyperthyroidism in sensitive individuals increases with iodine excretion of 200-299 µg/l. In the case of an ioduria >300 µg/l, there is also a higher risk of the development of immunological thyroid disorders (Delange et al., 2002b; Stanbury and Dunn, 2001).

In countries with sufficient iodine supply of the population over several generations, for instance the USA or Asian countries in which no iodised salt prophylaxis is necessary because of the habitual consumption of iodine rich seaweed and kelp, the probability of the occurrence of health damage is very low or only appears at larger iodine levels (1000 µg and more) through algae products of this kind. In one epidemiological survey in China involving 16287 inhabitants from three regions with differing degrees of iodine supply, it was shown that the prevalence of sub-clinical hyperthyroidism in regions with iodine deficiency was 3.9%. It was, therefore, higher than in regions with an iodine surplus (1.9%). The median of urinary iodine excretion was 103 and 615 µg/l in these regions (Yang et al., 2002). The onset of an iodine-induced hyperthyroidism following iodine exposure is, therefore, dependent on the iodine dose and the geographical region or goitre prevalence. In endemic iodine deficiency regions, which include Germany, a ten-fold higher incidence of iodine-induced hyperthyroidism is to be expected than in regions or countries which have not seen an iodine deficiency for several generations, like for instance the Netherlands and the USA (Henzen et al., 1999).

11.4.1 Derivation of a maximum level for iodine in food supplements

11.4.1.1 Possible management options

a) Continuation of existing practice

At present, iodine additions of **100 µg** are accepted in food supplements per recommended daily dose (BgVV, 1999). This upper level does not apply to dietetic food supplements which take into account the specific nutritional needs for instance of pregnant and lactating women. In purely arithmetic terms, based on the 95 percentile (209.6 µg/day) and the additional intake of 100 µg per daily portion of a food supplement, there is still enough scope to avoid exceeding the tolerable upper intake level of 500 µg.

Advantages: This offers the individual option of food supplementation, particularly for people on a vegetarian diet and/or who eat an insufficient amount of iodine-containing products (milk and dairy products, saltwater fish) and foods prepared with iodised salt.

Disadvantages: None

b) Setting of a recommended maximum level of **500 µg** for adults based on the proposal of the Expert Group of the United Kingdom (Food Standards Agency, 2003)

Advantages: Food supplements from the UK could also be placed on the market in Germany.

Disadvantages: The upper intake level considered to be safe in Germany of 500 µg would be considerably exceeded. This would mean that there would be an acute health threat for sensitive consumers, in particular older people with undiagnosed autonomy of the thyroid gland. Preparations of this kind with such high levels of iodine have been given marketing authorisation in Germany as medicinal products for the treatment of iodine deficiency conditions. They would have to carry a warning (Fachinformation, 2002).

11.4.2 Derivation of a maximum level for iodine in fortified foods

The preferred method for improving the iodine nutritional status of the population is the use of iodised table salt (Clar et al., 2002; WHO/UNICEF/ICCIDD, 1996; Wu et al., 2002). By means of the statutory set maximum level of 15-25 mg per kg salt, around 100 µg iodine are additionally ingested given a daily consumption of 5 g salt. The share of iodine in salt is calculated in such a way that there is no overdose even if all foods were to be manufactured with iodised table salt. The nutritional-physiologically desirable goal of increasing the iodine content of food makes technological sense. The target addition can only be achieved with any degree of reliability by means of standard use of table salt. This facilitates on the one hand controlled intake of iodine and prevents on the other excess supply which could not be ruled out if foods were directly fortified.

For that reason BfR recommends that pressure be exerted on the European Commission that in the “Whereases” of the Regulation of the European Parliament and the Council of 10 November 2003 (COM (2003) 671 final) about the addition of vitamins and minerals and of certain other substances to foods – currently under discussion - the use of iodine, similar to what is recommended for fluoride, be restricted to salt. On the international level WHO, UNICEF and ICCIDD support the iodisation of table salt but not the addition of iodine to other foods. The excessive use of iodine can be harmful for consumers. An extension of iodine fortification to other foods, with the exception of food supplements, should be rejected because of the risk of triggering a life-threatening thyrotoxic crisis in older people with undi-

agnosed thyroid autonomy. In the same way, Europe-wide uniform maximum levels (20-40 mg/kg salt) should be established for the iodisation of table salt and iodine content in food supplements. In order to dismantle trade obstacles, the iodine compounds mentioned in Annex 2 to this Regulation should also be approved for use in salt. This would mean that the current trade obstacles for products manufactured with iodised salt would be removed.

In order to optimise iodine supply, efforts should be made to increase urinary iodine excretion to 100-199 µg/l. In order to achieve this goal one decisive step would be to counter iodine deficiency by increasing the turnover of iodine sack salt in the food trade and food industry. If the share of iodised salt in the total sales volume of large package salt were to be increased from currently 35 to 70%, this would correspond to an additional intake of on average 80 micrograms per day. In terms of iodine supply this would place the population of Germany on a par with the populations of Switzerland and Austria. It would mean that an iodine supply level would be reached which meets the recommendations of the German Nutrition Society (adults 180-200 µg/day) as well as the WHO criteria (adults >150 µg/day) (D-A-CH, 2000; Manz et al., 1998; WHO, 1996).

Exemptions granted up to now for the direct iodine fortification of butter and eggs should remain the exception for foods. Further exemptions should not be issued. In the long-term, additional iodine supply should only be undertaken by means of iodised salt.

Special attention must be given to the iodine supply of non-breastfed babies and infants who have a relatively low salt consumption (Clar et al., 2002). For that reason a minimum amount of 5 µg iodine per 100 kcal is prescribed under EU legislation in infant formula and follow-on formula as well as in industrially manufactured processed cereal-based foods and other complementary food where a maximum level of 35 µg iodine per 100 kcal should not be exceeded. Manufacturers are called on to use the statutory options for iodine fortification of pure wholegrain products as well. When it comes to the self-preparation of baby foods, iodine supply of the infant is always a problem (Kersting et al., 1999).

11.4.2.1 Possible management options

a) Continuation of existing practice

Advantages: The use of iodised salt is the preferred method for improving the iodine supply of the population since everyone uses salt daily and salt iodisation is the only way of controlling iodisation.

Disadvantages: As a consequence of added salt, the average consumption of adults of iodised salt is around 1 g/day. Iodine intake from this is correspondingly low (20 µg/day). Increasing table salt consumption in the home is not desirable amongst other things for reasons of hypertonia prophylaxis. On the other hand the share of iodine sack salt turnover including curing salt turnover in total edible sack salt turnover is currently only 35%. This means that the desired improvement of iodine supply of 150-200 µg/day has not yet been achieved at all through the sole use of iodised salt in overall diet (Manz et al., 1998).

b) Extension of fortification to specific groups of foods combined with the setting of maximum levels

The revised Proposal for a Regulation of the European Parliament and Council on the addition of vitamins and minerals and of certain other substances to foods of 10 November 2003 (COM (2003) 671 final) permits voluntary iodine fortification of foods. Iodine must then be present at least in a significant amount as defined in the Annex to Directive 90/496/EEC. Consequently, a minimum amount of 22.5 µg/ 100 g product

would be necessary (e.g. around 225 µg/kg body weight could be added to breakfast cereals, sweets, bread, beverages etc.).

Advantages: It is possible to further raise iodine intake, particularly as the current iodine supply in Germany is not optimal.

Disadvantages: A threat to health from uncontrolled iodine intake cannot be ruled out as, in the case of conventional foods, the amount of these foods consumed is not dictated by the levels of nutrients contained therein but by factors like hunger, thirst, appetite and availability. The addition of the above-mentioned minimum amount would for instance already lead to an additional intake of 243 µg iodine from 60 g breakfast cereals, 20 g sweets or 1 litre of a refreshment beverage. In purely arithmetic terms, taking into account the 95 percentile (209.6 µg) (Manz et al., 1998) and a daily portion of 100 µg from food supplements (BgVV, 1999) the tolerable upper intake level of 500 µg would already be exceeded.

Bearing in mind the most sensitive consumers with undiagnosed functional autonomy of the thyroid gland, BfR is of the opinion that iodine carries, by way of definition, a high risk of adverse effects linked to its use in food supplements or for the purposes of food fortification. BfR, therefore, recommends that the current maximum level for food supplements (100 µg/day) be maintained (Option a) and that only iodised salt be used as a suitable carrier food as this can certainly guarantee that foreseeable amounts of iodine can be ingested by the general population and the tolerable upper intake level of 500 µg iodine is not exceeded. The iodisation of feedstuffs makes an indirect but significant contribution to iodine supply. Control measures are necessary in order to reach and maintain optimum iodine supply.

11.5 Gaps in knowledge

- Regular iodine monitoring every 5 years to record iodine supply and the iodine nutritional status of the German or European population is urgently needed as the planned sweeping statutory provisions on the EU level are expected to lead to changes in the proportions of various iodine sources in total iodine supply.
- No up-to-date data are available on current trends of thyroid disease prevalence in Germany and Europe.
- No up-to-date data are available on the iodine content of iodine rich foods or foods fortified with iodised salt or on total diet in order to rule out a possible overdose of iodine from foods.

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12 Risk Assessment of Fluoride

12.1 Summary

Data on the fluoride intake of the German population are very sparse (supply category 2). With special eating habits (consumption of black tea and fluoride-containing (mineral) water (>1 mg/l) and inappropriate use of fluoride-containing dental care products, the normally low dietary intake of fluoride (<1.5 mg/day) can be increased to ranges which lead to adverse effects: dental fluorosis in children up to age 8, skeletal fluorosis or an increased risk of bone fracture in all other individuals.

The guidance values for the caries preventive effect of fluoride are only three times lower than the UL derived in the USA (risk category "high" and "moderate") if we take basic intake without fortification or supplements.

Besides the intake of fluoride from natural foods and water, only one form of systemic fluoridation should be selected, either fluoridised table salt or fluoride supplements as medicinal products. In addition, fluoride should be administered locally by using fluoride-containing dental care products. Fluoride uptake from other additional sources like food supplements as well as the addition of fluoride to other foods aside from table salt would lead to uncontrollable intake. Adverse effects could not be ruled out. BfR recommends that fluoride should not be used in food supplements and that the addition of fluoride to conventional foods be restricted to table salt.

Guidance value for total fluoride intake for caries prevention	2.9-3.8 mg/day
Intake [mg/day]	**Only estimates**
Median	? * ? *
P 2.5	? * ? *
P 97.5	? * ? *
	* No representative intake data for the Federal Republic of Germany
Tolerable Upper Intake Level (FNB)	Adults and children from 9 years 10 mg/day Children up to 8 years depending on age 0.7-2.2 mg/day
Proposal for **maximum levels** in:	
Food supplements	Zero
Fortified foods	Only table salt

12.2 Nutrient description

12.2.1 Characterisation and identification

Fluorine is the most electronegative electron element in the periodic system. Because of its high reactivity it occurs in nature mostly in chemically bound form. Fluorides are the neutral salts of hydrofluoric acid (Einwag et al., 2000). Traces of fluorides are ubiquitous. Fluorides are to be found in all tissues in the human organism. According to Directive 2002/46/EC of the European Parliament and the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, the following fluoride compounds are approved for the manufacture of food supplements: potassium fluoride (CAS No. 7789-23-3) and sodium fluoride (CAS No. 7681-49-4). These compounds are also listed in Directive 2001/15/EC of 15 February 2001 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses. In the case of foods for special medical purposes the fluoride content is limited to a maximum of 0.2 mg/100 kcal (Ordinance on Foods

for Special Dietary Purposes – DiätVO, Annex 6). The Drinking Water Ordinance permits a maximum fluoride content of 1.5 mg/l. According to the Mineral and Table Water Ordinance water containing more than 1 mg fluoride/l may claim "to contain fluoride" whereas only water containing less than 0.7 mg fluoride/l may be labelled as "suitable for the preparation of infant formula". Pursuant to Council Directive 2003/40/EC, from 1 January 2004 onwards mineral water containing more than 1.5 mg fluoride/l must carry wording that it is not suitable for regular consumption by infants and children under the age of seven and from 1 January 2008 onwards the distribution of water containing more than 5 mg fluoride/l will be banned.

Annex III Part 1 of the updated Council Directive 76/768/EEC on cosmetic products contains a list of 20 fluoride compounds which may be used in dental care products up to a concentration of 1500 mg/kg.

12.2.2 Metabolism, functions, requirements

Metabolism: Dietary fluoride is absorbed in the gastro-intestinal tract. Absorption is dependent on the solubility of the fluoride, the pH value in the stomach and the valence of the cations (Hellwig, 1996). Absorption is by means of passive diffusion as undissociated hydrogen fluoride. In plasma fluoride is mostly available in ionised form and from there it diffuses into the tissue. The plasma fluoride concentration is not controlled homoeostatically and increases or falls depending on fluoride intake and kidney function (Hellwig, 1996). The maximum fluoride concentration in the plasma is measured approximately 30-60 minutes after the intake of soluble fluorides (Einwag et al., 2000; Heseker, 1999). After this the concentrations gradually decrease. The fluoride contents in plasma and saliva fluctuate over the day depending on the amounts and types of food ingested between 0.01-0.08 µg/ml in plasma and between 0.01-0.03 µg/ml in saliva (Einwag et al., 2000).

Absorbed fluoride is either bound by calcified hard tissue like bones and teeth or excreted in urine. Elimination is almost completely via the kidneys and, to a lower degree, via sweat (Einwag et al., 2000). Fluorides are filtered glomerularly and reabsorbed tubularly. Adults excrete around 50% of the absorbed fluoride daily (Heseker, 1999). In the case of infants with a higher bone uptake capacity for fluoride, renal excretion may only amount to 10% of the amount ingested (Bergmann, 1994). Numerous bioavailability studies in animals and human beings have shown that 75-90% of dietary fluoride is rapidly absorbed in the upper gastro-intestinal tract and only a small proportion (10-25%) is excreted in faeces. Fluorides dissolved in drinking water and sodium fluoride and monofluorophosphate (MFP) swallowed with toothpaste are fully absorbed. In the presence of calcium, magnesium, aluminium, iron or other cations, the bioavailability of fluoride can be considerably reduced. The absorption rate from milk, infant formula and other calcium-containing foods can fall to 25% (Heseker, 1999).

The body fluoride store in adults is 2-6 g. More than 99% of fluoride is to be found in bones and teeth. The skeleton of a neonate contains, by contrast, only 5 to 50 mg fluoride (Heseker, 1999).

Function: Fluoride is probably not essential for human beings although the scientific debate is still ongoing. It is being discussed whether sufficient supply in infancy is decisive for normal growth and eruption of teeth (Bergmann and Bergmann, 1987; Bergmann, 1994). Fluoride is, however, attributed a favourable effect on dental health and the mineralisation of bones and teeth (Bowman and Russell, 2001; Heseker, 1999; IOM, 1997).

Prior to teeth eruption fluoride reaches the dental germs via blood and is deposited in the enamel crystals of the immature dental enamel by forming fluorohydroxyapatite. Fluorohydroxyapatite is less sensitive to organic acids than hydroxyapatite. This means that the

chemical resistance of the dental enamel is higher (Bergmann, 1994). The fluoride content of dental enamel is largely dependent on fluoride supply during teeth formation (NRC, 1993). After teething local fluoride is taken up lifelong in the outermost layer of enamel and helps to prevent the formation of caries. Fluoride contained in saliva and dental plaque also contributes to a cariostatic effect by inhibiting bacterial enzymes and, by extension, acid production from carbohydrates. In this way it reduces the bacterial colonisation of the surface of the teeth (Heseker, 1999). Above all, fluoride promotes the remineralisation of the dental enamel through demineralising acids (Bowman and Russell, 2001).

Around 99% of fluoride in the human body is to be found in bones and teeth where it is mainly present in the form of hydroxyapatite. Fluoride has a special affinity to mineralised tissue which means that circulating fluoride can be more quickly removed from the plasma via this route than via the kidneys. Fluoride uptake from the interstitial fluid by the bones is done in three phases:

- by ion exchange in the hydration sheath of the crystallites
- by an exchange reaction with an ion or an ion group on the crystal surface
- through migration of these surface fluoride ions to free spaces in the crystal structure (Hellwig, 1996).

The amount of fluoride incorporated depends on the age and stage of bone growth. During the growth and development period a great deal of fluoride is incorporated. The crystallites of the bone are smaller at this time, available in a larger number and hardly arranged. They are surrounded by a substantial hydration sheath. Therefore they offer a far greater surface for fluoride uptake than fully developed bones. In older people fluoride can be released through bone resorption (Hellwig, 1996). The incorporation of fluoride into the bone matrix goes hand in hand with increased bone density. This effect is more extensive in the spinal column than in the extremities.

The fluoride content of bones and dentin is normally between 600 and 1500 ppm. It depends on intake and age (Stipanuk, 2000).

Requirements: Since fluoride is not essential to man, requirements cannot be defined. A recommended intake can only be indicated with a view to its favourable impact on dental health. WHO notes that there are no proven clinical symptoms of fluoride deficiency in man and there are no diagnostic parameters which correlate with a fluoride deficiency (WHO, 1994).

The Scientific Committee on Food of the EU (SCF) has not issued any recommendation for fluoride intake (SCF, 1993). The German Nutrition Society, like the Institute of Medicine (IOM, 1997) has formulated "guidance values for total fluoride intake (from food, drinking water and supplements) as well as for fluoride supplements for the purpose of caries prevention (DGE/ÖGE/SGE/SVE, 2000).

Table 35: Recommended fluoride intake

Age	Adequate total fluoride intake mg/day	
	m	f
Infants		
0 up to under 4 months		0.25
4 up to under 12 months		0.5
Children		
1 up to under 4 years		0.7
4 up to under 7 years		1.1
7 up to under 10 years		1.1
10 up to under 13 years		2.0
13 up to under 15 years	3.2	2.9
Adolescents and **adults**		
15 up to under 19 years	3.2	2.9
19 up to under 25 years	3.8	3.1
25 up to under 51 years	3.8	3.1
51 up to under 65 years	3.8	3.1
65 years and older	3.8	3.1
Pregnant women		3.1
Lactating women		3.1

These recommendations are based on the current level of scientific knowledge and practical experience with the prophylactic caries preventive action of fluoride doses of around 0.05 mg/kg body weight and day. They aim firstly to guarantee optimum caries prevention and, secondly, to rule out excessive intake (DGE/ÖGE/SGE/SVE, 2000).

12.2.3 Exposure (dietary and other sources, nutritional status)

Sources:

Fluoride is taken up from solid foods, drinking water, mineral water, black tea, fluoride-containing toothpaste, dental care products, fluoridised table salt and, eventually, from fluoride-containing medicinal products. As a rule the fluoride content of solid foods is under 1 mg/kg fresh weight (Heseker, 1999). One exception is fish, particularly where the bones, with a particularly high fluoride content, are eaten as well (e.g. sprats and anchovies). Aside from a few exceptions drinking water has a low level of fluoride in Germany. In 1040 West German groundwater samples examined, the mean fluoride concentration was 0.1 mg/l, the 90 percentile was 0.26, the 97.7 percentile 0.49 and the maximum level 1.1 mg/l (Schleyer and Kerndorf, 1992). Drinking water has been fluoridated above all in the USA for many years (fluoride content depending on the climate between 0.7 and 1.0 mg/l). In older studies a 50 to 60% reduction in the incidence of caries in the population could be shown (WHO, 1994). In Germany drinking water is not fluoridated.

Some mineral waters have fluoride concentrations of more than 0.3 mg/l. Eight out of 150 waters examined were found to have fluoride contents of more than 1.5 mg/l and the highest level was 4.5 mg/l (Schulte et al., 1996). Depending on the water used, beer and fruit juices may also contain higher fluoride concentrations (Hellwig, 1996). Unlike other plants, tea has a very high fluoride content which can amount to a few 100 mg/kg. In infused tea the fluoride content varies between 0.6 and 3.7 mg/l, depending on the time and type of water used (Chan and Koh, 1996; Heseker, 1999). Fluoridised table salt has been on sale in Germany since 1991. It contains 250 mg fluoride/kg salt and must be correspondingly labelled (Schulte, 2003). Table salt has an easily predictable consumption level which is self-restricting for reasons of taste (Hetzer, 1997). Fluoridised table salt has only been approved up to now for 500 g packs, i.e. for use in the home. Each gram of ingested fluoridised table salt increases dietary fluoride intake by 0.25 mg. In Germany daily salt consumption is in the 90 percentile for men around 12 g and for women around 10 g. The home consumption of fluoridised table salt for the preparation of food was determined as being on a scale of 2

g/day corresponding to a fluoride intake of 0.5 mg/day. Fluoridised table salt is recommended instead of taking fluoride tablets and when drinking water contains less than 0.7 mg fluoride/l. Only children below the age of 2 years, to whose food salt should not be added, should take 0.25 mg fluoride daily as tablets when drinking water contains less than 0.3 mg fluoride/l. This is the case for more than 90% of drinking water supplies from central water utilities (Bergmann and Manz, 1994).

Bergmann (1994) has put together an overview of fluoride contents [mg/kg] in foods on the Federal German market between 1981 and 1989:

Table 36: Fluoride contents in foods on the Federal German market

Food	Number	Mean	SD	Minimum	Maximum
Milk and dairy products	170	0.049	0.061	0.019	0.16
Minced meat and chicken, cooked	3	0.060	0.030		
Meat products (tins, sausage)	6	0.29	0.13	0.47	0.47
Pig and chicken bones	3	717	205	394	848
Fish fingers	2	0.48	0.15		
Bread	24	0.29	0.08	0.18	0.39
Cereal/flour	4	0.13	0.05	0.07	0.19
Vegetables	19	0.023	0.039	-	0.16
Potatoes	2	0.02	0.003		
Fruit	14	0.03	0.03	-	0.09
Dry herbs/spices	41	2.02	2.5	0.08	9.51
Black tea 1% with distilled water	3	0.76	0.34	0.37	1.01

Fluoride is also taken up from fluoride-containing toothpaste and dental care products which act locally in the oral cavity. Infants sometimes swallow toothpaste (between 10 and 100%) which increases total fluoride intake by up to 0.3 mg every time the teeth are brushed (Ekstrand et al., 1983). Other authors established that for a 4-year-old child fluoride-containing toothpaste accounted for between 30 and 50% of total daily intake of 3.6 and 2.3 mg fluoride (Richards and Banting, 1996). In its model calculations for children under the age of 6 the Scientific Committee on Cosmetic Products assumes fluoride intake from swallowed toothpaste of 0.016 up to 0.15 mg every time teeth are brushed (SSCNFP, 2003).

Another possible source of fluoride intake are fluoride-containing medicinal products which are given in particular to infants usually together with vitamin D for the purpose of caries prophylaxis. Fluoride-containing medicinal products are also used to treat osteoporosis.

Nutritional status: There are no studies on the fluoride intake of the German population. The fluoride nutritional status of the German population was neither recorded in the National Food Consumption Survey nor in the Nutrition Survey from 1998. Total intake varies individually depending on eating habits and, more particularly, the fluoride content of water used for cooking and drinking (Hunt and Stoecker, 1996). The following daily fluoride intake of adolescents and adults in German was estimated (Bergmann, 1994):

Table 37: Estimated daily fluoride intake of adolescents and adults in Germany

Food	15-18 years		Adults	
	Male	Female	Male	Female
Solid food and milk	0.119	0.097	0.129	0.112
Beverages (juices, lemonade, beer, other alcoholic beverages, table and mineral waters, tea)	0.339	0.308	0.366	0.265
Sub total	0.458	0.405	0.495	0.377
+ 500 ml drinking water with 0.13 mg F^-/l	0.065	0.065	0.065	0.065
Total	0.523	0.470	0.560	0.442

Generally speaking, the estimated daily intake of fluoride in adults in Germany is between 0.4 and 1.5 mg and in children between 0.1 and 0.2 mg/day (Bergmann, 1994; DGE/ÖGE/SGE/SVE, 2000; Heseker, 1999; WHO, 1996). Compared to the intake recommended by the German Nutrition Societ, this means that the recommended intake is not normally achieved, not even through the use of fluoridised table salt. Some mass catering kitchens were given permission to use fluoridised (and iodised) table salt for the preparation of food so that people who eat away from home can also have access to improved fluoride intake (Schulte, 2003).

It cannot, however, be ruled out that some individuals in Germany reach or even exceed the recommended fluoride intake, for instance tea drinkers, people who drink mineral water with a high level of fluoride instead of tap water with a low level of fluoride, when larger amounts of fluoride-containing dental care products are swallowed or when fluoride-containing supplements are taken. Fluoride-containing supplements are currently only authorised as medicinal products.

12.3 Risk characterisation

12.3.1 Hazard characterisation (NOAEL, LOAEL)

The toxicity of fluorine or fluorides has recently been evaluated by several bodies. In studies in male rats fluoride was linked to a possible carcinogenic effect but this observation was not made for female rats or other animal species. Fluoride is not mutagenic in prokaryotic cells. The effects which occurred at high concentrations are attributed to chromosomal damage. In animal tests fluoride did not lead to impaired reproduction or malformations. Epidemiological studies in human beings did not find an elevated rate of disease or mortality as a consequence of isolated fluoride exposure nor of elevated miscarriage or malformation rates. The adverse effects of fluoride impact the skeleton (fluorosis and/or elevated susceptibility to bone fractures) and teeth (dental fluorosis) (ATSDR, 2002; IPCS, 2002).

The Scientific Committee on Food and the European Food Safety Authority have not yet completed their assessment of fluoride. An Expert Group from the United Kingdom has compiled and published a report on the health effects of fluoride (EVM, 2001). However in January 2002 it explicitly stated that it was not appropriate to comment on the level of addition of fluoride to foods as this was a public health measure.

The American Food and Nutrition Board has defined a Lowest Observed Adverse Effect Level (LOAEL) for children under the age of eight on the basis of increased incidence and severity of dental fluorosis at fluoride intakes of 0.1 mg/kg body weight/day. A No Observed Adverse Effect Level (NOAEL) of 10 mg fluoride/day for adults was derived from the fact that individuals who had consumed drinking water with a fluoride content below 4 mg/l for several years did not present any radiological signs of osteosclerosis. In individuals who had consumed drinking water with a fluoride content of 8 mg/l for an average of 37 years, signs of symptom-free osteosclerosis were only found in 10-15%. In both cases it was not deemed necessary to establish an uncertainty factor given the broad database. Hence, the UL corresponds to the LOAEL or NOAEL as shown in Table 38 below (IOM, 1997):

Table 38: No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) of fluoride

Age	NOAEL [mg/day]	LOAEL [mg/kg/day]	Negative impact
Infants 0 up to 6 months	–	0.1	Moderate dental fluorosis
Infants 7 up to 12 months	–	0.1	Moderate dental fluorosis
Children 1 to 3 years	–	0.1	Moderate dental fluorosis
Children 4 to 8 years	–	0.1	Moderate dental fluorosis
Children 9 to 13 years	10	–	Skeletal fluorosis
Adolescents 14 to 18 years	10	–	Skeletal fluorosis
Adults over 19 years	10	–	Skeletal fluorosis
Pregnant women	10	–	Skeletal fluorosis
Lactating women	10	–	Skeletal fluorosis
Older people over the age of 70	10	–	Skeletal fluorosis

12.3.2 Deficiency, possible risk groups

There are no known cases of fluorine deficiency symptoms in man. A completely fluoride-free diet is not possible. It has not yet been fully clarified whether fluoride is one of the essential nutrients for man (Bergmann, 1994; Bergmann and Bergmann, 1987). In Germany there is a major discrepancy between estimated dietary fluoride intake including drinking water and fluoride intake recommended for caries prophylaxis in each age group. If one takes the D-A-CH reference values as the basis for adequate fluoride intake, then adults normally achieve around 10-30% of the recommendations, infants on average around 30%. Breastfed infants receive less than 0.01 mg fluoride per day, around 5-7% of the recommended intake because of the low fluoride content of breast milk. In the case of non-breastfed children fluoride intake mainly depends on the fluoride content of the water used to prepare the formula as most products have a low fluoride level and, when prepared with demineralised water, are shown to have a fluoride content below 0.05 mg/l. If these products were to be prepared with water containing 0.3 mg fluoride/l, a child weighing 5 kg would take in 70 µg fluoride/kg body weight/day or less (Kramb et al., 2001).

Dental caries, however, is not a fluoride deficiency disease. Fluoride is one of the pillars of caries prevention; the two others are a healthy diet and proper dental hygiene (Einwag et al., 2000).

12.3.3 Excessive intake, possible risk groups

Fluoride intake of more than 100 µg/kg/day during teeth development, i.e. up to around age eight, leads to dental fluorosis of the permanent teeth, too (Einwag et al., 2000). Dental fluorosis, in its mild form, is first and foremost an aesthetic problem. It reduces susceptibility to caries and often disappears as a consequence of natural wear and tear of the outer dental layers (Hetzer, 1999; Mascarenhas, 2000; NRC, 1993). Dental fluorosis occurs around the world particularly in regions with a high fluoride content (>1.00 ppm) in drinking water (NRC, 1993). In young children fluorosis can also be triggered by swallowing fluoride-containing toothpaste which is why only toothpaste containing no or only a low level of fluoride (up to 500 ppm fluoride) should be given to small children (DAKJ, 2000). Considerably higher fluoride intake at this age may lead to brown discolouration of teeth with dental enamel defects and increased brittleness (NRC, 1993). In the case of longer-term (10 to 20 years) high fluoride intake (10-25 mg/day) skeletal fluorosis may occur. Initially it may only manifest itself as an increase in radiological bone density followed by bone pain, stiff joints, osteosclerosis and calcification of ligaments, in the worst case with bone deformities, muscular atrophy and neurological symptoms. The symptoms develop in parallel to the fluoride content of the bones. In all cases disruptions of bone mineralisation are observed and occasionally osteomalacia, particularly when dietary calcium intake is low. Crippling bone fluorosis is mainly observed in

tropical areas with a high natural content of fluoride in drinking water or high fluoride exposure from industrial plants (Heseker, 1999; IOM, 1997; NRC, 1993). Following extremely high fluoride intakes (300-600 mg/day) over several months, kidney damage was observed in animals (Einwag et al., 2000).

Whereas in some studies the bone density increased in regions with fluoridised drinking water (0.7-1.0 mg/l) and the fracture rate seemed to fall (Phipps et al., 1994), studies in China for instance seem to indicate that a naturally high fluoride content in water (more than 4 mg/l) with an estimated daily intake of 14 mg fluoride leads to an increase in bone fracture rate. A trend towards an increased occurrence of fractures outside the spinal column was already observed from an uptake of more than 6 mg fluoride/day (Li et al., 2001). Intervention studies with high doses of fluoride to prevent and treat post-menopausal osteoporosis over periods of two to six years show that bone density does increase with the exception of the radius but that the risk for non-spinal fractures in treated women is three times higher than in women who were given the placebo (Riggs et al., 1990; 1994). On average the treated women were given 0.57 mg fluoride/kg body weight/day. This dosis can be seen as the LOAEL for a special population group (ATSDR, 2002).

There are reports of acute fluoride intoxications in people caused by accidents, attempted suicide or erroneous fluoridation of drinking water. The symptoms are nausea, vomiting, abdominal pain, diarrhoea, heavy salivation, cardiac arrest, cramp and coma. Severe hypocalcaemias were observed (Augenstein et al., 1991; Boink et al., 1994; Infante, 1974; Spak et al., 1999; Whitford, 1996). An amount of 5-10 g fluoride has been calculated as the "certainly lethal dose" = CLD for adults (Hellwig, 1996).

12.4 Tolerable upper intake level for fluoride

The following Tolerable Upper Intake Levels were defined in the USA (IOM, 1997):

Age	UL [mg/day]
Infants 0 up to 6 months	0.7
Infants 7 up to 12 months	0.9
Children 1 up to 3 years	1.3
Children 4 up to 8 years	2.2
Children 9 up to 13 years	10
Adolescents 14 up to 18 years	10
Adults over 19 years	10
Pregnant women	10
Lactating women	10
People over the age of 70	10

The German-speaking nutrition societies have taken over these values for children up to the age of eight (DGE/ÖGE/SGE/SVE, 2000). ULs for older children and adults have not yet been defined in EU Member States.

If one accepts a fluoride intake of 14 mg/day, which was associated in China with an increased incidence of bone fractures, particularly of the hip (Li et al., 2001) as the LOAEL and if one applies an uncertainty factor of 2 because of the demonstrated increase in the risk of fractures from a daily intake of 6 mg fluoride, this would result in a UL of 7 mg fluoride.

If, by contrast, one uses the fluoride dose of (rounded up) 0.6 mg/kg/day, which can be derived from the therapeutic intervention studies in women with osteoporosis (Riggs et al., 1990; 1994), a LOAEL of 7.5 mg fluoride/day can be defined after adding the daily fluoride intake from other sources. Using a proposed (ATSDR, 2002) an uncertainty factor of 10, a UL of 0.07 mg/kg/day results.

A fluoride intake of 5-7 mg/day is indeed possible in individuals who drink a lot of tea, who drink water with fluoride contents of more than 1 mg/l and use it for cooking, who do not correctly use fluoride-containing dental care products, who take fluoride-containing medicinal products and who eat a lot of fish. However, no figures are available on how many people are affected. If all the above-mentioned sources for fluoride are used, an intake of 10 mg fluoride/day cannot be ruled out.

Based on these considerations it seems appropriate to limit the number of possible sources of fluoride to those currently available in order to guarantee control of intake.

12.4.1 Derivation of a maximum level for fluoride in food supplements

Fluoride-containing supplements are currently only available as registered medicinal products. Around 80% of infants are regularly given fluoride tablets usually combined with vitamin D. Prior to prescribing of fluoride tablets the doctor should record medical history and ask about other fluoride sources (DAKJ, 2000). Freely available fluoride-containing food supplements, which are taken in an uncontrolled manner, carry a risk of overly high total fluoride intake including other possible sources without achieving the same caries preventive effect afforded by fluoride-containing dental care products and the use of fluoridised table salt. From foods, particularly from fluoride-containing water and fluoride-containing dental products a fluoride amount, that is on the level of the upper tolerable intake can result. This leaves no scope for a safe maximum dose of fluoride in food supplements.

BfR believes that a maximum dose for fluoride of zero in food supplements is the only safe management option.

12.4.2 Derivation of a maximum level for fluoride in fortified foods

Fluoridised table salt has been available for use in the home in Germany since 1991. It accounts for 75% of household salt sold. It contains 0.25 mg fluoride per gram salt. This means that average consumption of 2 g of this salt leads to an additional fluoride intake of around 0.5 mg/day. Salt consumption is self-restricted by taste itself. Hence salt is a good carrier food for micronutrients which can be added in transparent amounts. No other food offers this advantage as their consumption is dictated by appetite or thirst. Given the theoretically possible total fluoride intake from various sources on a level of fluoride which goes hand in hand with adverse health reactions – without relatively accurate figures being available about the fluoride intake of the population in Germany – there is no room for additional fluoride supplementation of food. Therefore, fluoridised table salt should be the only available food fortified with fluoride. If, in future, data on the fluoride supply of the German population become available which confirm the suspicion that the majority of the population has a lower fluoride intake than recommended, then adjustment of the fluoride amount in table salt should be given priority over fortification of other foods.

Besides fluoride uptake from natural food and water, only one form of systemic fluoridation should be selected, either fluoridised table salt or fluoride supplements as medicinal products. In addition, fluoride should be locally applied through the use of fluoride-containing dental care products. Fluoride intake from other additional sources like food supplements as well as the addition of fluoride to other foods apart from table salt would lead to uncontrolled intake. Adverse reactions could not be excluded. BfR recommends that fluoride should not be used in food supplements and that the addition of fluoride to conventional foods should be restricted to table salt.

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13 Risk Assessment of Zinc

13.1 Summary

The data available for the Federal Republic of Germany indicate that in healthy individuals inadequate zinc intake is not to be expected. However, valid and sufficiently evaluated biomarkers to record the zinc status have not been available up to now (supply category 2).

Deviating tolerable upper intake levels derived by several scientific bodies (SCF, FNB, EVM, WHO/FAO) highlight uncertainty concerning the risk assessment of nutrients. BfR upholds the precautionary principle and the lowest UL for adults derived by the above-mentioned bodies is taken as basis for the setting of maximum levels for zinc in food supplements and fortified foods, i.e. the SCF value of 25 mg/day (same procedure for children and adolescents). In accordance with the risk classification of nutrients taken over by BfR zinc is, therefore, to be assigned to the risk class "high risk".

In adults the 97.5 percentile of intake (NFCS/VERA Study: 20.5 mg) comes very close to the UL (25 mg/day). In children and adolescents the 97.5 percentile for zinc intake in some male age groups is already above the derived ULs (4-6 years, 7-9 years, 13-14 years). Hence, in respect of children or adolescents there is no margin for additional zinc intake from food supplements or fortified foods.

In the case of food supplements it is recommended that no zinc supplementation be undertaken for children and adolescents and that for adults the addition be reduced to a daily maximum level of 2.25 mg zinc. An extension of the current practice of zinc addition to conventional foods cannot be supported.

Recommended intake	10 mg/day (m)	7 mg/day (f)
Intake [mg/day] (NFCS, 1994)	**m**	**f**
Median	12.1	9.7
P 2.5	6.4	5.1
P 97.5	20.5	16.0
Tolerable Upper Intake Level	25 mg/day	
Proposal for **maximum levels** in:		
Food supplements	2.25 mg/daily dose (no zinc-containing food supplements for children or adolescents up to completed age of 17)	
Fortified foods	No fortification	

13.2 Nutrient description

13.2.1 Characterisation and identification

Zinc (CAS No. 7440-66-6) is a group IIB post-transition metallic element and has an atomic mass of 65.38. Zinc compounds which may be added to foods for special dietary purposes and food supplements include: zinc acetate (CAS No. 557-34-6), zinc chloride (CAS No. 7646-85-7), zinc citrate (CAS No. 546-46-3), zinc gluconate (CAS No. 4468-02-4), zinc lactate (dihydrate; CAS No. 16039-53-5), zinc oxide (CAS No. 1314-13-2), zinc carbonate (CAS No. 5970-47-8) and zinc sulphate (anhydrate: CAS No. 7733-02; heptahydrate: CAS No. 7446-20-0) (Ordinance on Foods for Special Dietary Uses; Ordinance on Food Supplements and Amendment to the Ordinance on Vitamised Foods).

13.2.2 Metabolism, functions, requirements

Zinc is necessary for growth and development, testicular maturation, neurological functions, wound healing and immunocompetence. On the molecular level zinc has structural, regulatory and catalytic rolls in a number of enzymes and is of importance for the configuration of non-enzymatic proteins (SCF, 2003).

Zinc is absorbed in the small intestine. Besides carrier-mediated absorption, uptake particularly at high intakes is also by means of passive diffusion (SCF, 2003). Zinc is mainly excreted via the intestinal tract, a smaller amount (<10%) is excreted by the kidneys. There are further losses via the skin, sweat, sperm, hair and menstruation cycle (FAO/WHO, 2002; IOM, 2002).

The bioavailability of zinc from food is negatively influenced by high phytate contents. Negative interactions with copper, iron and calcium have been reported as well. Depending on their digestibility proteins also have a promoting or inhibiting impact on zinc absorption.

The D-A-CH recommended intakes are 7 mg/day for female adolescents and adult women, 10 mg/day for male adolescents and adults, 10 mg/day for pregnant women and 11 mg/day for lactating women. For children up to age 15, age and gender-dependent intakes of 3-9.5 mg/day are given (D-A-CH, 2000). SCF published recommended intakes (Population Reference Intake) of 7 mg for women and 9.5 mg for men (SCF, 1992).

In the case of vegetarians, particularly strict vegetarians, whose main food sources are cereals and pulses and whose diet has a high phytate-zinc ratio (>15:1), the zinc requirements may be increased by up to 50% (IOM, 2002). However, up to now no special intake recommendations have been derived for this group of individuals because of inadequate data.

13.2.3 Exposure (dietary and other sources, nutritional status)

Sources:
Zinc is to be found in a number of foods. Lean red meat, wholemeal products and pulses have high zinc levels but different bioavailability (25-50 mg/kg gross weight) whereas only low levels (<10 mg/kg gross weight) are reported for fish, root vegetables, tuberous fruits, green leafy vegetables and fruits (FAO/WHO, 2002).

Medicinal products: In the medicinal monograph on zinc daily doses of 10-50 mg (in the case of acrodermatitis up to 100 mg/day) are indicated for the treatment of proven zinc deficiency (e.g. acrodermatitis enteropathica), Wilson's disease and penicillamine therapy (BGA, 1994). As medicinal products zinc salts and zinc oxide are governed by the prescription-only provision when they exceed a dose of 25 mg/day (BMG, 1991; BMJFFG, 1990).

Nutritional status: According to the results of the VERA Study the median intake in women was 9.7 mg/day and in men 12.1 mg/day. The 97.5 percentile was 16.0 mg/day in women and 20.5 mg/day in men (Heseker et al., 1994). More recent studies of the German National Health Interview and Examination Survey identified mean intakes of 10.9 mg/day in women and 14.5 mg/day in men who did not take any food supplements. No information on the 95 or 97.5 percentile of zinc intake is available from that study (Mensing and Ströbel, 1999).

Regarding children and adolescents the 97.5 percentiles of intake of female subjects in all age groups determined in the VERA Study were lower than for male subjects. For the latter they were 12.6 mg/day in age group 4-6 years, 14.6 mg/day in the age group 7-9 years, 17.8 mg/day in the age group 10-12 years, 20.2 mg/day in the age group 13-14 years and 21.9 mg/day in the age group 15-18 years (Adolf et al., 1995).

Up to now valid and sufficiently evaluated biomarkers to record zinc status are not available. It is indeed the case that some parameters (zinc plasma level, zinc content of erythrocytes and hair, urinary zinc excretion) are decreased in severe zinc deficiency. However, they are influenced by other parameters independent of zinc status as well (FAO/WHO, 2002)

The data available for the Federal Republic of Germany on zinc intake indicate that inadequate zinc intake is not to be expected in healthy individuals. Up to now no valid or sufficiently evaluated biomarkers have been available to record the zinc status (supply category 2).

13.3 Risk characterisation

13.3.1 Hazard characterisation (NOAEL, LOAEL)

With regard to the chronic and subchronic toxicity of zinc, the EU Scientific Committee on Food (SCF) noted that various changes were observed in individuals following prolonged consumption of zinc supplements in the ranges of 50-300 mg/day. These include hypocupraemia, leucopaenia, neutropaenia, anaemia, impaired immune function, lower activity of superoxide dismutase and ceruloplasmin and altered lipoprotein-cholesterol metabolism. Many of the changes were observed in a similar way in conjunction with copper deficiency. However, the changes are not specific for a deficiency of this kind and the clinical relevance of some changes is unclear (SCF, 2003).

Regarding the influence of zinc on copper balance the available study results indicate that zinc intakes which are roughly 9 mg/day or more above the intakes recommended by SCF (men 9.5 mg/day) (SCF, 1992), can influence copper balance at least in the short-term. However, the significance of these study results is questionable when it comes to long-term effects on copper homoeostasis (SCF, 2003). Furthermore, it is pointed out that lower activity of erythrocytic superoxide dismutase, one of the most frequently observed effects of elevated zinc intakes (Fischer et al., 1984; Milne et al., 2001; Samman and Roberts, 1988; Yadrick et al., 1989), is not linked to any adverse effects and cannot be used as an indicator of lower copper status. Hence, the physiological relevance of this observation remains unclear (SCF, 2003).

Concerning negative effects of elevated zinc intakes (50-160 mg supplemental zinc/day) on lipoprotein and cholesterol metabolism observed in studies (Black et al., 1988; Hooper et al., 1980) and by taking into account other investigations it should be pointed out that there are no consistant results concerning such adverse effects in conjunction with zinc intakes in the range of 40-160 mg/day (SCF, 2003).

Prolonged elevated zinc intakes caused anaemia and changes in red and white blood cells (whereby the symptoms pointed to induced copper deficiency). Individual case reports are available concerning the onset of hypocrupaemia, anaemia, leucopaenia and neutropaenia at intakes of 150-300 mg/day (Hoffmann et al., 1988; Porter et al., 1977; Prasad et al., 1978; Salzmann et al., 2002; SCF, 2003). In addition lower haematocrit values were observed in conjunction with zinc administration of 50 mg/day (Yadrick et al., 1989). Taking into account other studies which did not observe adverse effects, SCF, however, comes to the conclusion that at intakes below 60 mg/day there are no consistent results concerning adverse effects on blood profiles (SCF, 2003).

Impaired immune response was another adverse effect observed with elevated zinc intakes (300 mg over 6 weeks); at an intake of 53 mg over 90 days increased activity of bone specific alkaline phosphatase was reported (Chandra, 1984; Davis et al., 2000). With a supplemental intake of 50 mg zinc/day (28 days) diabetics showed elevated haemoglobin A_{1c} va-

lues whereby the clinical relevance of this increase remains unclear (Cunningham et al., 1994; SCF, 2003).

Furthermore, in an epidemiological study on the association between additional zinc intakes via supplements and the occurrence of advanced prostate carcinomas no elevated relative risk compared with the control group (non-users) was observed with intakes up to 100 mg/day. However, supplemental zinc intake of more than 100 mg/day was associated with an elevated relative risk (relative risk = 2.29; 95% confidence interval = 1.06-4.95). Regarding duration of zinc supplementation (with no differentiation concerning level of zinc supplementation) an elevated risk was observed after more than 10 years' supplementation (relative risk = 2.37; 95% confidence interval = 1.42-3.95). As the authors were not able to rule out residual confounding factors, the relevance of this more recent epidemiological study remains unclear (Leitzmann et al., 2003).

In summary, SCF derives a NOAEL of 50 mg/day based on the fact that in the study published by Davis et al. and Milne et al. and the study published by Bonham et al. no adverse effects on a series of relevant parameters of copper metabolism, the critical endpoint, were observed (Bonham et al., 2003a; b; Davis et al., 2000; Milne et al., 2001). In the case of Davis et al. and Milne et al. the intake was 53 mg zinc per day (Davis et al., 2000; Milne et al., 2001). In the case of Bonham et al. it was 30 mg from supplements plus the (calculated) intake of 10 mg from normal diet (Bonham et al., 2003a; b).

13.3.2 Deficiency, possible risk groups

Clinically relevant zinc deficiency rarely occurs in western countries. In sick individuals zinc deficiency was observed in conjunction with malabsorption syndrome, parenteral nutrition, treatment with chelating agents (e.g. penicillamine) and acrodermatitis enteropathica (D-A-CH, 2000; SCF, 2003).

13.3.3 Excessive intake, possible risk groups

Up to now there have been no reports on adverse effects caused by high zinc intakes from conventional foods. However, there have been such reports in conjunction with additional intake from supplements and medicinal products. Please refer to Chapter 13.3.1 "Hazard characterisation (NOAEL, LOAEL)" for more information on the observed adverse effects of prolonged elevated intakes.

13.4 Tolerable upper intake level for zinc

Based on a NOAEL of 50 mg/day and the application of an uncertainty factor of 2, SCF derived for adults a tolerable upper intake level (UL) of 25 mg/day. The size of the uncertainty factor took into account the small number of subjects included in above mentioned studies and short study durations (SCF, 2003). The American Food and Nutrition Board (FNB) derived a UL of 40 mg/day for adults. This UL was based on a LOAEL (Lowest Observed Adverse Effect Level) of 60 mg/day and an uncertainty factor of 1.5 (IOM, 2002). The British Expert Group on Vitamins and Minerals (EVM) derived a safe upper level for supplemental zinc intake of 25 mg/day based on a LOAEL of 50 mg for supplemental zinc and an uncertainty factor of 2. Assuming an intake of 17 mg from a normal diet (= 97.5 percentile) a total intake of 42 mg/day is considered to be tolerable (Food Standards Agency, 2003). WHO gives a value of 45 mg as the upper level for adults (FAO/WHO, 2002).

Based on the tolerable upper intake level for adults, SCF extrapolated ULs for children and adolescents. In age group 1-3 years the UL is 7 mg/day, 4-6 years 10 mg/day, 7-10 years 13 mg/day, 11-14 years 18 mg/day and 15-17 years 22 mg/day, respectively.

People suffering from haemochromatosis and diabetes are classified as a possible risk groups. However, at the present time not enough data are available in order to derive tolerable upper intake levels for these groups (Food Standards Agency, 2003; SCF, 2003).

For the derivation of the tolerable upper intake level SCF, FNB and EVM focus on interaction between zinc and copper metabolism. Even if in detail there are different assessments of study results and, in some cases, different endpoints and studies have been used to derive the ULs, the NOAEL or LOAEL used for this purpose are in narrow ranges (50-60 mg/day). The differences in the derived ULs mainly result from the application of differing uncertainty factors (factor 1.5 versus 2) or the use of different departure parameters (UL for total daily intake versus UL for supplemental intake). This highlights a certain degree of uncertainty concerning the derivation of upper levels for nutrients which extends beyond the mere evaluation of study results. BfR upholds the precautionary principle and takes the lowest UL which has been derived by the above-mentioned bodies for adults, i.e. the SCF value of 25 mg/day, as the basis for the derivation of maximum levels for zinc in food supplements and fortified foods.

13.4.1 Derivation of a maximum level for zinc in food supplements and fortified foods

In its opinion on zinc, SCF notes that the 97.5 percentile of zinc intake in EU Member States is close to the ULs in all age groups. It does not, therefore, see any reason for concern.

Given that the 97.5 percentile of intake (VERA Study: 20.5 mg) is already very close to the UL (25 mg/day) and the fact that zinc is to be assigned to the highest risk group based on the risk classification of nutrients taken over by BfR, the Institute cannot advocate for adults maximum levels in food supplements and modes of food fortification leading to higher daily intakes of zinc. There is, therefore, no justification for extending the current practice of zinc addition to food supplements and conventional foods.

In some age groups of male children and adolescents the 97.5 percentile of zinc intake is already above the derived ULs (4-6 years, 7-9 years, 13-14 years). Hence with children and adolescences there is no margin for additional zinc intake from food supplements of fortified foods.

13.4.1.1 Possible management options

13.4.1.1.1 Food supplements

a) Adherence to current practice for adults and a change for children and adolescents
At present, 5 mg of zinc per recommended daily dose are accepted for food supplements (BgVV, 2001). With regard to adults, because of the reasons outlined above, there is no justification for extending the addition of zinc to food supplements beyond the currently tolerated level. Furthermore, the margin between the UL and 97.5 percentile of zinc intake (from normal daily diet) is so low (= 4.5 mg/day) that it would already be used-up or even slightly exceeded by taking one food supplement per day.

   Children and adolescents (up to completed age of 17) should abstain from taking food supplements with added zinc for the above-mentioned reasons.

b) Change in current practice for adults, children and adolescents
When deriving maximum levels for food supplements, multiple consumption of these products cannot ruled out and must be taken into account. The proposed procedure for the derivation of maximum levels is presented in Chapter 3.3.2.

The residual amount (R)[2] available for additional zinc intake from food supplements and fortified foods of 4.5 mg is fully allocated to the category of food supplements because of the low level (45% of the D-A-CH recommended intake) and the low zinc quantum that would result from a split between food supplements and fortified foods. Factor 2 is taken in order to take into account possible multiple consumption of food supplements and because there is no fortification of conventional foods. This leads to the calculation of a maximum level of **2.25 mg**.

The same applies to children and adolescents as outlined in Option a).

13.4.1.1.2 Fortified foods

Because of the high risk category of zinc and the low margin between the UL and the 97.5 percentile of intake, an extension of the current practice of zinc addition to conventional foods cannot be supported.

In line with the risk classification of nutrients taken over by BfR, zinc is to be assigned to the highest risk class. There is no justification for an extension of the current practice of zinc addition to food supplements and fortified foods. For food supplements BfR recommends reducing the current maximum level to 2.25 mg. Children and adolescents should be excluded form zinc supplementation (Option b). As in the past, it should be abstained from zinc addition to conventional foods.

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[2] R = UL - DINF
4,5 mg (R) = 25 mg (UL) - 20,5 mg (DINF)
DINF =97,5. percentile of dietary intake by normal food

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14 Risk Assessment of Selenium

14.1 Summary

In Germany there are no representative food consumption surveys with data on selenium intake, and there are only estimated values for the adequate intake of this nutrient. Hence it is difficult to assess the selenium status of the German population. The available data from regional food consumption surveys indicate that average selenium intake is in the lower range of the estimated values for adequate intake. The selenium plasma levels measured in the population are, however, higher than expected when compared with dietary intake. There are no reports of clinical symptoms which could be clearly attributed to inadequate selenium intake in Germany (supply category 2).

Selenium cannot be clearly classified in any of the risk categories for nutrients defined by BfR [margin between RDA (or the estimated value) and the UL would be <5 (high risk) with respect to the higher estimated value of 70 µg and 10 (moderate risk) with respect to the lower estimated value of 30 µg].

According to BfR, the maximum level for food supplements should be oriented towards estimated requirements, while conventional foods should not be fortified with selenium in the future.

Estimated values for adequate intake	30-70 µg/day	
Intake [µg/day]	**m**	**F**
Median	? *	? *
P 2.5	? *	? *
P 97.5	? *	? *
	* No representative intake data for the Federal Republic of Germany	
Tolerable Upper Intake Level	300 µg/day	
Proposal for **maximum levels** in:		
Food supplements	25-30 µg/daily dose	
Fortified foods	No fortification	

14.2 Nutrient description

14.2.1 Characterisation and identification

Selenium (CAS No. 7782-49-2) is one of the essential trace elements. It is present in food mainly as selenium-containing amino acids – in foods of plant origin mainly as selenomethionine and in foods of animal origin as selenocysteine. Inorganic selenium compounds like sodium selenite (Na_2SeO_3) and sodium selenate (Na_2SeO_4) are used as food supplements or as medicinal products for supplementation and treatment (Ekmekcioglu, 2000).

In Germany up to now the addition of selenium to conventional foods was only possible in conjunction with exemptions pursuant to § 37 and general dispositions pursuant to § 47a.

Annex 2 to European Directive 2002/46/EG (of 10 June 2002) states that the compounds sodium selenate (CAS No. 13410-01-0), sodium hydrogen selenite (CAS No. 7782-82-3) and sodium selenite (CAS No. 10102-18-8) may be added to food supplements. The above three selenium compounds may also "be added for specific nutritional purposes in foods for particular nutritional uses" (Directive 2001/15/EC, 2001). They are listed in the Annex to the Pro-

posal for a "Regulation on the addition of vitamins and minerals and certain other substances to foods" (COM(2003)671 final of 27 August 2003).

According to the above-mentioned Directives and Regulations the use of organic selenium compounds and selenium yeasts is not permitted in food supplements or for food fortification. Therefore, they are not taken into account when deriving maximum levels for individual products.

14.2.2 Metabolism, functions, requirements

Metabolism: Dietary selenomethionine follows the metabolism of the amino acid methionine. It is absorbed in the small intestine by means of a sodium-dependant neutral amino acid transport system and can be incorporated non-specifically instead of the sulphur-containing amino acid methionine into proteins (e.g. albumin, haemoglobin), particularly in skeletal muscles but also in erythrocytes, liver, pancreas, kidneys and stomach. The replacement of methionine with selenomethionine is dependent on the selenomethionine-methionine ratio in the diet and does not seem to be homoeostatically controlled (Behne and Kyriakopoulus, 2001; Daniels, 1996). Selenomethionine is converted to selenocysteine in the course of protein and amino acid breakdown whereas selenomethionine, which is not incorporated into proteins, can be directly converted through transsulphuration to selenocysteine (Brigelius-Flohé et al., 2001).

In contrast to selenomethionine, selenocysteine – be it the natural food-derived form of selenium, or the conversion product of selenomethionine – does not follow the metabolic path of the amino acid cysteine. Instead it is degraded in the liver erythrocytes through selenium lyase by formation of elemental selenium to serine and selenide. The latter is either used for selenoprotein synthesis or is exhaled after methylation as methlyselenol, dimethyl selenide or trimethyl selenium ions or it is excreted in urine (Schrauzer, 2000a).

Selenite is taken up through passive diffusion and selenate through a sodium-dependent transport system (Brigelius-Flohé et al., 2001). Without intermediate storage both forms are converted in the liver to selenide whereby selenite is directly reduced in a NADPH dependent manner to selenide by glutathione reductase (Ganther, 1999) whereas selenate is first converted to selenite and then to selenide (Brigelius-Flohé et al., 2001).

Selenoprotein synthesis: For selenoprotein synthesis selenophosphate is formed from selenide which reacts with serine, that is bound to a specific tRNA(ser)sec, to form selenocysteine. The tRNA(ser)sec loaded with selenocysteine makes selenocysteine available for incorporation into the peptide chain. One condition for the smooth course of protein synthesis in the eukaryotes is the presence of a selenocysteine-inserting sequence (SECIS) on the mRNA (Brigelius-Flohé et al., 2001).

During selenoprotein synthesis there is a series of regulatory options which in their totality are described as the "hierarchy of selenium proteins" (Allan et al., 1999; Brigelius-Flohé et al., 2001; Hesketh and Villette, 2002): In the case of marginal selenium supply selenium is only incorporated into a few preferred selenium proteins which means that some proteins quickly lose activity whereas others only become inactive in conjunction with a severe chronic deficiency. On the other hand, proteins which react more slowly to deficiency are more quickly reactivated through selenium supplementation than others. This means that proteins which react to a selenium deficiency at a late stage with activity loss are higher up in the hierarchy and seem to be of greater importance than the other selenium proteins in the organisms. Furthermore, it was observed that selenium proteins in the case of deficiency are less susceptible to loss of activity in some tissues than in others. This seems to indicate that some organs are less sensitive to a selenium deficiency than others (Hesketh and Villette, 2002): For instance, the activity of phospholipid hydroperoxide-GPx is preferentially maintai-

ned in the brain, in the reproductive organs and in endocrinological tissue. Therefore it can be assumed that glutathione peroxidase plays a particularly important role there (Arthur, 2000).

The total body store of selenium in adults is 5-15 mg (0.12-0.9 mmol). Selenium is to be found in differing concentrations in all organs. 40-50% of the total store is to be found in skeletal muscles (Gaßmann, 1996). The kidneys and liver are also rich in selenium. The half-life of selenium in the form of selenomethionine in the human body is 252 days: for selenite it is only 102 days (Schrauzer, 2000a). Furthermore, selenomethionine leads to higher selenium plasma levels than the intake of the same amounts of inorganic selenium compounds (Barcelouox, 1999).

Unlike other trace elements selenium homoeostasis is not regulated by intake but by urine excretion (Sunde, 2001; Wolfram, 2000 in: Fischer, 2002) and at very high selenium levels via respiration (e.g. as dimethyl selenide) (Henning and Zidek, 1998). Renal excretion in selenium-low regions in Europe is 10-30 µg/l, in selenium-rich regions like the USA it is 40-80 µg/l (Daniels, 1996). Selenium passes from the maternal organism to breast milk and through the placenta to the foetus.

Bioavailability: Selenomethionine has a bioavailability of more than 90%. The bioavailability of selenocysteine is very good, too, whereas the inorganic selenium forms - selenite and selenate - only are bioavailable to 50-60% (IOM, 2000).

Selenium is more readily available from foods of plant (85-100%) than from foods of animal origin (~15%). Fish contains relatively high amounts of selenium; however the bioavailability of selenium from fish is relatively low (20-50%; normally <25%) (Combs Jr., 2001; Heseker et al., 1992; Navarro-Alarcón and López-Martínez, 2000). Overall, the bioavailability of selenium from a mixed diet is between 60 and 80% (Daniels, 1996). The bioavailability of selenium from water is lower than from food (Valentine, 1997 in: Barceloux, 1999).

The bioavailability of selenium in food supplements is dependent on various factors: Aside from the daily dose, the form in which selenium is added, interactions with other nutrients, possible parallel intake of medicinal products or the time of administration (on an empty stomach or during meals) influence bioavailability. In principle, the bioavailability of inorganic selenium compounds from food supplements is lower than that of organic ones (Navarro-Alarcón and López-Martínez, 2000).

Function: As an integral part of proteins, selenium plays various roles in the organism. The number of selenium proteins in mammals is estimated to be between 30-50. The ones which have been characterised and identified up to now include selenium-containing glutathione peroxidases (GPxs), like for instance the cytosolic GPx, gastro-intestinal GPx, plasma GPx and phospholipid hydroperoxide GPx as well as three thioredoxin reductases (TrxR), three deiodases, selenophosphate synthetase and the selenoproteins P and W (Allan et al., 1999; Arthur, 2000; Behne and Kyriakopoulus, 2001; Brigelius-Flohé et al., 2001; Holben and Smith, 1999).

Although each of the **glutathione peroxidases** (GPx) has its specific functions, it can generally be said that GPxs catalyse the reduction of organic peroxides like hydrogen peroxide and lipid hydroperoxides. In this way they protect cells against oxidative damage. There are high concentrations of selenium in the thyroid. As a component of glutathione peroxidase, it helps protect this organ from hydrogen peroxide exposure during thyroid hormone synthesis. Adequate selenium intake is, therefore, the precondition for normal thyroid function.

As a component of **deiodases** selenocysteine catalyses the deiodation of the prohormone thyroxine (T4) to active thyroid hormone 3,3'5-triiodothyronine (T3) and the deiodination of T3

and reverse T3 (rT3) to inactive 3,3'diiodothyronine (T2) (type 1 deiodase). In the case of inadequate selenium supply the ratio of T4 to T3 increases in the serum which leads to disruptions of thyroid function and can be used as a functional marker of selenium status (Brown and Arthur, 2001). By means of type 2 diodase T4 from the plasma is converted intracellularly to T3 and rT3 in T2 (tissue-specific regulation). The inactivation of thyroid hormone by means of deiodation of T4 to rT3 and from T3 to T2 is catalysed by type 3 deiodase. During pregnancy the latter regulates the supply of the foetus with T4 and T3 from the mother and protects the foetus from excessive amounts of T3 (Anke et al., 2000). In other organs, too, but particularly in the brain, T3 concentration is regulated through type 3 deiodase.

The various forms of **thioredoxin reductases** catalyse the reduction of oxidised thioredoxin and other substances like dehydroascorbic acid and lipid hydroperoxides. Furthermore, thioredoxin reductases are essential for DNA synthesis, redox regulation of transcription factors and for the regulation of cell growth and apoptosis (Behne and Kyriakopoulos, 2001).

Selenoprotein P accounts for the largest share (65%) of selenium in plasma. It is thought that the selenoprotein P is of importance as an extracellular antioxidant (Burk et al., 2003). Furthermore, the protein could also be responsible for the distribution of selenium from the liver to other organs like the brain and kidneys (Schomburg et al., 2003).

Selenoprotein W is of importance for muscular metabolism in animals. Its role in human muscular metabolism has still to be clarified. Muscular dystrophy could, however, also be influenced in a positive manner in human beings through selenium supplementation (Brown and Arthur, 2001).

Nutrient interaction: Selenium and vitamin E play a synergistic role in offering protection from lipid oxidation (Henning and Zidek, 1998; DGE/ÖGE/SGE/SVE, 2000). This can be attributed to the function of phospholipid hydroperoxide-GPx which reduces peroxides in the same way as vitamin E. It interrupts the chain reaction in conjunction with autoxidation of unsaturated membrane lipids (Fischer, 2002). Furthermore, thioredoxin reductase is also of importance for the renewal of vitamin E (Sunde, 2001).

Selenium and vitamin B_6: Vitamin B_6 is involved in the conversion of selenomethionine to selenocysteine. A deficiency of this vitamin impairs selenocysteine formation and, consequently, the formation of serine and selenide as the starting materials for selenoprotein synthesis (Biesalski et al., 1997).

Selenium and vitamin B_{12}: In rats with vitamin B_{12} deficiency the methylation and excretion of selenium was impeded (Chen et al., 1993). As vitamin B_{12} is a co-factor of methionine synthesis, not enough methione is available for the formation of S-adenosylmethione in the case of a deficiency of this vitamin. Methionine is needed for selenium methylation and therefore for its excretion. Hence, high selenium intake coupled with a vitamin B_{12} deficiency could lead to an unwanted increase in the selenium concentration in the organism.

Selenium and iodine: Since selenium, as selenocysteine, is a component of deiodasis, sufficient selenium intake during the entire phase from intrauteral development up to adulthood is of extreme importance for iodine status. Both inadequate selenium intake as well as intake beyond the requirements leads to changes in the metabolism of the thyroid hormones (Anke et al., 2000; Eder et al., 1995). The selenium concentration in the thyroid gland is very high which means that deiodase activity can also be maintained in conjunction with moderate selenium deficiency (cf. Chapter 11.2.2).

Selenium and zinc: Zinc and selenium seem to inhibit one another during absorption (Schrauzer, 2000a). Furthermore, it has been shown in selenium-rich regions of Venezuela,

where selenium intake is between 250 and 980 µg/day (mean: 552 µg/day), that a growing selenium concentration clearly reduces the content of zinc-binding proteins in breast milk. Therefore, only small amounts of zinc are found in breast milk, even where there is adequate zinc supply of the mother. In these regions a reduced zinc concentration in breast milk led to stunted growth in children (Brätter et al., 1997). This phenomenon could also be of relevance in conjunction with high selenium intake in other regions, e.g. from supplements.

Selenium and metals: A number of metals which occur in foods, the environment or in drinking water, compete with selenium intake. They form non-reacting selenides or protein complexes and/or inhibit selenium-dependent enzymes. In this way selenium can weaken the toxic effect of metals like As, Ba, Pb, Cd, Hg, Ag, Tl, Sn, (Goyer, 1997; Henning and Zidek, 1998; UBA, 2002). On the other hand, the need for selenium is raised by exposure to these metals (Schrauzer, 2000a).

Requirements: Definitive selenium requirements have still to be determined; intake of 1 µg/kg body weight seems to be sufficient to meet requirements (Biesalski et al., 1997). Studies conducted in Chinese men show that selenium intake of 40 µg/day is sufficient to saturate the activity of plasma GPx (Yang et al., 1989 in: Erdinger and Stelte, 1992). On the other hand, it was observed in studies in New Zealand that the GPx reaches its activity maximum at a selenium intake of 60-80 µg/day (Thomson et al., 1993). Taking into account more recent findings on selenium, in 2000 FNB evaluated the studies from China and New Zealand again and defined a EAR of 45 µg/day for all North American women and men above the age of 14. Based on a variation co-efficient of 10%, a RDA of 55 µg/day was calculated. For pregnant women additional intake of 5 µg/day is recommended, for lactating women additional intake of 15 µg/day (Gaßmann, 2000; IOM, 2000; Monsen, 2000).

Although in many other countries in the world the American RDAs are not reached, no apparent health impairment has been observed. The American recommendations may, therefore, be too high (Sunde, 2001).

SCF believes an intake of 40 µg/day for adult men and 30 µg/day for women to be adequate (SCF, 2000). WHO recommends, as an individual basic requirement, daily selenium intake of 0.2 µg/kg body weight (women) and 0.22 µg/kg body weight (men). The normative storage requirement is given as 0.39 µg/kg body weight for women and 0.42 µg/kg body weight for men (WHO, 1996).

DGE, ÖGE, SGE and SVE define estimated values for adequate selenium intake which are given in the following table for the various age groups (DGE/ÖGE/SGE/SVE, 2000):

Table 39: Estimated values for adequate selenium intake

Age (years)	Estimated values for adequate intake (µg)
Children	
1-3	10 - 40
4-6	15 - 45
7-9	20 - 50
10-12	25 - 60
13-14	25 - 60
Adolescents and adults	
15-18	30 - 70
>19	30 - 70
Pregnant women	30 - 70
Lactating women	30 - 70

14.2.3 Exposure (dietary and other sources, nutritional status)

Sources:
Foods: The selenium content in foods depends on selenium uptake by plants and animals. It can, therefore, vary considerably depending on the region of origin. In Germany selenium contents of between 13 and 24 µg/kg dry substance were measured in cereals and of 1-2 µg/100 g in bread (Canadian types of bread contained up to 60 µg/100 g). The selenium amounts in wheat flour, semolina, barley, podded peas and rice were 25-49 µg/kg dry substance. In egg pasta and leguminous plants they were 100 up to >500 µg/kg dry substance (Anke et al., 2002; Biesalski et al., 1997).

Extremely high selenium contents were measured in Brazil nuts. According to the Food Database of the US Department of Agriculture (USDA) 100 g Brazil nuts contain 1917 µg selenium. Consumption of one nut would, therefore, lead to selenium intake of approximately 70-90 µg. Hence, adults could easily achieve the estimated value for adequate intake. Children up to the age of 6 would even reach the UL defined for this age group by eating one Brazil nut (cf. also Chapter 14.4: Tolerable upper intake level for selenium). Brazil nuts grow in the Amazon, primarily in Brazil and Peru. They are scarcely cultivated which means that the ones sold in Germany very likely come from South America. It can, therefore, be assumed that the selenium contents indicated in the USDA database also apply to nuts consumed here. In Germany Brazil nuts are part of nut mixtures (like trail mix). Aside from this, they only play a minor role in the diet of the German population.

Foods of animal origin which are a particularly good source of selenium are kidneys, poultry and liver/sausage with contents of between 300 and 9000 µg/kg TS. Mutton, beef and pork contain 200 up to 300 µg/kg dry substance. Because of the selenium fortification of animal feed undertaken in Germany, particularly for pigs and poultry, the selenium content of meat intended for human consumption is also higher. In fish the selenium content depends on the concentration of selenium in water; it is between 500 and 2000 µg/kg dry substance. In milk, cheese and quark selenium levels of between 100 and 200 µg/kg dry substance were measured (Anke et al., 2002).

In drinking water the selenium content is mostly less than 1 µg selenium per litre. Natural mineral waters may contain selenium up to a limit value of 0.01 mg/l (Mineral- and TrinkwasserVO, Anlage 1 zu § 2, as per: 03.03.2003).

In Germany fish, meat, sausage and eggs are the best sources of selenium (Biesalski et al., 1997). In a study on the contribution of various foods to selenium supply Anke et al. (2002) found that between 2/3 and 3/4 of daily selenium intake comes from foods of animal origin. According to the study 44% of the selenium taken up by men comes from meat and sausage, 16% from fish, 8% from dairy products and 7% from eggs. In the case of women the share from meat, sausage and eggs is lower than for men. Bakery goods provide 14% (women) and 9% (men) of daily selenium intake (Anke et al., 2002).

It should not be forgotten that the bioavailability of selenium from foods of plant origin is far better than from foods of animal origin (cf. also Chapter 14.2.2: bioavailability). Although the bioavailability of selenium from fish is relatively low, the consumption of fish can contribute to covering selenium and iodine requirements. This is of importance in the context of the close association between the metabolism of selenium and iodine.

Food supplements: There is no overview of the food supplements containing selenium which are on the market and their doses. Moreover, we do not know whether and, if so, what amounts of selenium-containing food supplements are ingested by the population.

For reasons of preventive health protection BgVV had proposed a maximum level for selenium of 30 µg per daily portion of a food supplement (BgVV, 1998). This maximum level was derived on the basis of the estimated values given by DGE (1991). For precautionary reasons it was recommended that half of the mean estimated value not be exceeded as a daily dose for additional intake from food supplements. As a precautionary measure BgVV/BfR had also recommended a **warning** to be included in the label of the supplement that selenium-containing food supplements are not suitable **for children under 7**. The maximum level was calculated using the following formula:

$$\left[\frac{\text{lower estimated value} + \text{estimated upper value}}{2}\right] * 0.5 = \left[\frac{20\ \mu g + 100\ \mu g}{2}\right] * 0.5 = \mathbf{30\ \mu g}$$

* DGE, 1991

Although according to Annex 2 of the Food Supplements Directive 2000/46/EC only sodium selenate, sodium hydrogen selenite and sodium selenite may be used as sources of selenium, selenium yeast products are sold in Germany in pharmacies, health food stores, supermarkets and on the Internet. The manufacturers distributing their products on the Internet rarely indicate the amounts of selenium (or other nutrients or ingredients) which have been added. Hence, neither consumers nor risk assessors/monitoring authorities can estimate the additional selenium intake from these sources. There are indications that the selenium contents of many of these products exceed the maximum level of 30 µg per daily dose considered to be safe by BgVV/BfR.

Medicinal products: In order to correct a proven selenium deficiency, which cannot be remedied through diet, pharmacy-only and prescription-only (from 100 µg selenium) medicinal products are available with 50 to maximum 300 µg selenium per daily dose (Fachinformation, 2003/1).

Nutritional status:
Intake: In representative food consumption surveys like the National Food Consumption Study (NFCS), the EPIC Study or the German Nutrition Survey conducted in conjunction with the Federal Health Survey, no selenium intakes were identified for the German population.

In the 1980s a daily gross selenium intake was calculated on the basis of the foods eaten in West Germany of 73.8 (men) and 61.3 (women) µg per day. Taking into account possible losses during preparation of food an actual intake was estimated of 47 (men) and 38 (women) µg/day (Oster and Prellwitz, 1989).

In 1995 selenium intake of East German women and men who had a mixed diet was calculated using duplicate studies. The mean intake was 30 and 42 µg/day for women and men, respectively. Although intake had increased by 60% compared with 1988, overall 20% of men and women took less than 25 and 20 µg selenium per day. A comparative study involving vegetarians showed that these men had on average a non-significantly lower selenium intake (34 µg/day) than the people on a mixed diet. Female vegetarians did not have a lower selenium intake than the comparative group (Anke et al., 2000; Drobner et al., 1996).

There are indications that individuals on the basis of gene polymorphisms are able to adapt to very different selenium intake situations without developing deficiency symptoms (Hesketh and Villette, 2002). Corresponding studies have been conducted in the United Kingdom where average intake is 0.5 µg/kg body weight (i.e. approximately 30 µg/day for a person weighing 60 kg) (Jackson et al., 2003). However, no diseases were registered which were clearly attributable to selenium deficiency.

Since foods are available today in Germany from all over the world, the low natural selenium occurrence in foods of plant origin produced here is possibly compensated in some groups of the population. Furthermore, it should be borne in mind that a non-quantifiable proportion of the population probably regularly takes high amounts of selenium from food supplements which do not correspond to the maximum level provisions agreed up to now in Germany (cf. also Chapter 14.2.3: Exposure, dietary and other sources, nutritional status). Hence, given the available data no reliable statements can be made about the selenium intake of the population.

The average selenium intakes in other European countries are between 30 and 90 µg/day with the exception of Finland (100-110 µg/day) as selenium-containing fertilisers are used there (SCF, 2000).

Selenium status in plasma: The plasma selenium concentrations and the concentration in erythrocytes (referred to Hb) seem to be reliable indicators for medium-term and long-term selenium status. However, there is a problem when it comes to setting normal and reference ranges which are only based on estimates from studies (Bähr et al., 1999).

Biesalski et al. (1997) indicate that an impairment of enzyme activity of GPxs does not occur until serum levels are below 50 µg/l (0.6 µmol/l). Values below this must be considered as suboptimal. Other authors consider concentrations below 40 µg/l (0.5 µmol/l) (Thomson et al., 1993), below 70 µg/l (0.9 µmol/l) (Nève, 1995) or below 80 µg/l (1 µmol/l) (Hambidge, 2003) to be an indicator for marginal selenium status. In a current review a selenium concentration in blood of 80-95 µg/l (1.0-1.2 µmol/l) is considered to be necessary for maximum GPx and selenoprotein-P-activity (Thomson, 2004).

In conjunction with the National Food Consumption Study the following selenium concentrations in the serum were measured in a sub-group of 652 men and 832 women:
The mean values for both genders were approximately 80 µg/l (1 µmol/l). In men the serum values were between 54 µg/l (0.7 µmol/l) (P 2.5) and 111 µg/l (1.4 µmol/l) (P 97.5) and for women between 57 µg/l (0.7 µmol/l) (P 2.5) and 115 µg/l (1.4 µmol/l) (P 97.5). In the case of men the lowest values were measured in the group of = 65-year-olds whereas in the case of women 18-24-year-olds had the lowest concentrations (Erdinger and Stelte, 1992; Heseker et al., 1992).

In 15 studies conducted in Germany which examined the selenium status of adults, the mean plasma values were between 63 µg/l (0.8 µmol/l) and 94 ± 27 µg/l (1.2 ± 0.3 µmol/l) (Behne and Wolters, 1979; Bergmann et al., 1998; Bononmini et al. 1995; Kasparek et al., 1982; Koehler et al., 1988; Meissner, 1997; Oster et al., 1983; 1986; 1988a; Oster and Prellwitz, 1982; 1990b; Reinhold et al., 1989; Rukgauer et al., 1997; Theile et al., 1995; Thorling et al., 1986 (all quoted in: Combs Jr., 2001)). In four study groups the mean value was below 70 µg/l (0.9 µmol/l) and only in one group was it below 50 µg/l, i.e. 48 µg/l (0.6 µmol/l). According to the GISELA Study the senior citizens examined showed a selenium status which indicated adequate supply (Gritscheneder et al., 1998).

In 1918 school pupils from Baden-Württemberg (mean age: 10.3 years) average selenium concentrations were identified between 54.5 ± 10.5 µg/l (0.7 ± 0.1 µmol/l) and 71.9 ± 15.1 µg/l (0.9 ± 0.2 µmol/l). The minimum was 14 µg/l (0.2 µmol/l), the maximum 216 µg/l (2.7 µmol/l). The 5 percentile in almost all sub-groups was below 45 µg/l (0.6 µmol/l) (Piechotowski et al., 2002). It should be borne in mind that selenium levels during childhood are generally far lower than during adulthood; only when children reach school age do their selenium levels reach approximately 90% of the normal levels for adults (Robberecht and Deelstra, 1994).

Selenium status in breast milk: In central Europe the selenium content of breast milk, depending on dietary intake of mothers, is between 5 µg/l (0.06 µmol/l) and 20 µg/l (0.25 µmol/l) (Anke et al., 2002; Gaßmann, 1996). In Germany mean values were measured between 9.9 µg/l (0.1 µmol/l) (Jochum et al., 1995) and 59 µg/l (0.7 µmol/l) (Brätter, 1996 in: Dorea, 2002).

In Germany there are no representative food consumption studies with data on selenium intake. There are only estimated values for the adequate intake of this nutrient. Hence it is difficult to assess the supply of the German population with selenium. The available data from regional food consumption studies indicate that average selenium intake is in the lower range of estimated values for adequate intake. The selenium plasma levels measured in the population are, however, higher than dietary intake would lead us to expect. There are no reports of clinical symptoms which could be clearly attributed to inadequate selenium intake in Germany (supply category 2).

14.3 Risk assessment

14.3.1 Hazard assessment (NOAEL, LOAEL)

The toxicity of selenium depends on the compound in which it is available, but it is generally low. Particularly toxic reactions to selenium exposures from the environment are extremely rare in man (Barceloux, 1999). There are no reports of carcinogenicity for relevant dietary selenium compounds. However, no data from human studies are available on this. Nor was any genotoxicity observed in humans in conjunction with the intake of normal amounts of selenium. There is no indication of teratogenicity of selenium (SCF, 2000). No data on the mutagenicity of selenium are available.

Soluble selenium salts (from supplements or drinking water) seem to have a higher acute toxicity than organic selenium from food. On the other hand, organic compounds taken in chronically probably have a higher toxicity. Animal studies indicate that selenite is slightly more toxic than selenate and selenocysteine has a similar toxicity to selenite whereas selenomethionine is less toxic than selenite.

Knowledge about intoxications in man caused by selenium are mostly based on studies conducted in areas with selenium-rich soil and acute or chronic intoxications. Retrospective assessments of studies from West China showed that it was only selenium intakes above 800 µg/day (819 ± 126 µg/day) that led to toxic effects in man. An intake of 600 µg was defined as the NOAEL and 400 µg/day as maximum safe intake (Yang and Zhou, 1994). Individual case studies indicate that the intake of 5-22 mg sodium selenate per kg body weight led to adverse health effects (e.g. frequently soft faeces, elevated liver enzyme values, nausea and vomiting) which were, however, reversible (Barceloux, 1999).

The longest targeted study up to now involved the administration of 200 µg selenium (as selenium yeast) per day over 4.5 years which were tolerated without any symptoms of excessive supply. This was an intervention study in which the influence of selenium on the onset of cancer was investigated (Clark et al., 1996).

To describe a dose-response relationship SCF, EVM and FNB drew on the studies of Yang et al. which were conducted in selenium-rich regions with endemic selenium toxicity (Yang et al., 1983; 1989a; b; Yang et al., 1994 in: SCF, 2000). In the population group examined selenosis symptoms were described from a selenium intake of 1200 µg/day. Below 850 µg/day the symptoms did not occur. From these results SCF derived a LOAEL of 1200 µg/day and a NOAEL of 850 µg/day (SCF, 2000). The British Expert Group derived a LOAEL of 910 µg/day (EVM, 2003), and FNB set the NOAEL at 800 µg/day (IOM, 2000).

14.3.2 Deficiency, possible risk groups

The clinical symptoms of selenium deficiency are macrocytosis, pseudoalbinism, streaked finger nails and myopathies which can be so severe that they impede walking (Biesalski et al., 1997). Symptoms of this kind have occurred in individuals with a selenium intake of less than 20 µg per day.

One disease associated with a selenium deficiency is Keshan's disease (endemic cardiomyopathy) which was diagnosed particularly amongst children and young women in selenium-deficient areas in China. A preventive intake of selenium supplements did have a positive effect on the incidence and course of the disease but was not able to completely eradicate it. It was observed in epidemiological studies that not all individuals with a selenium deficiency developed this disease and that there were seasonal differences in the frequency of the d-sease. Hence it was concluded that this condition in not a clear selenium deficiency disease either but that there are confounders like viruses and other factors (Brigelius-Flohé et al., 2001; Burke and Opeskin, 2002; Henning and Zidek, 1998; SCF, 2000). It has since been proven that, besides a selenium deficiency, infection with the coxsacki virus also plays a role in the onset of the disease (Beck et al., 2003).

Another disease associated with a selenium deficiency is Kashin-Beck's disease, a osteoarthropathy whose aetiology has not yet been clarified. Besides selenium deficiency, iodine deficiency, the consumption of cereals contaminated with mycotoxin-producing fungi, and drinking water contaminated with organic substances and fulvic acid are under discussion as causes of this disease. A current study involving Kashin-Beck sufferers in Tibet shows that selenium supplementation did not have any impact on this disease whereas the administration of iodine led to a clear improvement in their condition (Moreno-Reyes et al., 2003).

In industrial countries there have been no observations up to now of a clear selenium deficiency in healthy individuals. It is, however, being discussed whether supply with this trace element is sufficient and what consequences sub-optimal supply could have. Given the many antioxidative mechanisms in which it is involved as part of the active centre of the GPxs and other selenium proteins, selenium has been under discussion for years in conjunction with a possible anti-carcinogenic potential. In a series of case control studies low selenium status was associated with a higher risk of cancer. However, prospective studies provided contradictory results and up to now no cause-effect relationship could be established (Brigelius-Flohé et al., 2001; Clark et al., 1996; Navarro-Alarcón and López-Martínez, 2000; Rayman, 2002; Sanz Alaejos et al., 2000; Schrauzer, 2000b). So far a positive effect of selenium on the risk of coronary heart disease, diabetes or liver disease could not be proven (Brigelius-Flohé et al., 2001; Navarro-Alarcón and López-Martínez, 2000).

Because of the close association between selenium and iodine metabolism, sole supplementation with selenium without prior eradication of iodine deficiency in regions with a severe iodine and selenium deficiency led to a worsening of thyroid hormone status down to myxoedematous cretinism (Vanderpas et al., 1993). In the case of a moderate iodine deficiency, which is widespread in Germany (cf. also Chapter 11.3.2.1 in this report) additional selenium intake does not seem to have a negative effect on thyroid hormone status.

Risk groups for dietary selenium deficiency include vegans (Larsson and Johansson, 2002) and people who have a one-sided diet. Furthermore, insufficient selenium intake may also be found in people with eating disorders (anorexia nervosa, bulimia) and patients who must keep to a special diet (e.g. PKU), are on a low selenium formula diet or parenteral nutrition. Insufficient selenium intake may also be observed amongst dialysis patients and in conjunction with diseases like acute myocardial infarction, coronary heart diseases, cirrhosis of the liver and absorption disorders (mucoviscidosis, short bowel syndrome etc.)

High selenium losses, a risk for selenium deficiency, may occur for instance in conjunction with severe and persistent diarrhoea, maldigestion, malabsorption, kidney diseases, heavy bleeding or very lengthy breastfeeding.

14.3.3 Excessive intake, possible risk groups

Selenium intoxications as a consequence of vapours have been repeatedly reported from industry where selenium is used in varnishes and electrical items. In certain regions in the world (e.g. Hubel Province in China) where concentrations of selenium in the earth are high, chronic selenium overload can occur as a consequence of its migration to food (Henning and Zidek, 1998).

The typical signs of selenium intoxication are nausea, retching, changes in nails, dry hair, loss of hair, selenium and garlicky breath (dimethyl selenide) or underarm perspiration. Other intoxication symptoms which have been described are (Sunde, 2001):

- gastro-intestinal disorders
- tiredness, exhaustion, headache, hoarseness
- selenium rhinitis
- skin eczema, hair loss, soft nails
- weight loss.

The administration of a very selenium-rich diet (~300 µg/day) was observed to lead to weight increase in healthy men which was obviously due to a change in energy metabolism (increase in TSH in serum, decrease in T3) (Hawkes et al., 2003; Hawkes and Keim, 2003). This observation requires further studies in order to estimate the risk for the overall population. A drop in T3 formation in conjunction with high selenium intake is attributed to the fact that from 350-450 µg selenium/day the activity of type 1 deiodase is reduced (Brätter and Negretti de Brätter, 1996).

Given the normal diet in Germany, excessive selenium intake is not to be expected as long as there is no uncontrolled taking of food supplements with high selenium contents available for instance on the Internet or of medicinal products.

14.4 Tolerable upper intake level for selenium

Based on a NOAEL of 850 µg/day and an uncertainty factor of 3, SCF derived a UL for adults of 300 µg from all sources. The UL also applies to pregnant and lactating women. As there are no data indicating that children and adolescents would be more sensitive to the harmful effects of selenium, the UL set for adults was adjusted to the respective body weight of children. It is stressed that the UL applies to dietary selenium and moreover only to sodium selenate, sodium selenite and sodium hydrogen selenite. The following table gives an overview of the ULs for the various age groups (SCF, 2000):

Age group (years)	UL [µg/day]
1-3	60
4-6	90
7-10	130
11-14	200
15-17	250
Adults	300

EVM gives a "Safe Upper Level" (SUL) of 450 µg/day for selenium from all sources (EVM, 2003). Because of a slightly lower uncertainty factor (UF=2) this is 1.5 times higher than the UL of SCF, although the LOAEL defined by EVM is lower (910 µg/day),than that of SCF.

To protect sensitive individuals FNB believes an uncertainty factor of 2 to be appropriate and establishes, based on a slightly lower NOAEL of 800 µg/day, a UL of 400 µg/day for adolescents (14-18 years) and adults >19 years of age. This UL also applies to pregnant and lactating women (IOM, 2000).

14.4.1 Derivation of a maximum level for selenium in food supplements

As there are no percentile data on selenium intake, it is not possible to use the formula proposed by BfR for the derivation of a maximum level for selenium in individual products. Instead, it is based on the following considerations:

We do not exactly know the selenium requirements of human beings. Hence the D-A-CH societies (DGE/ÖGE/SGE/SVE, 2000) only give estimated values for adequate intake. Furthermore, there are no representative food consumption studies in Germany which have identified the selenium intake for the various percentiles. The plasma levels measured in representative studies indicate that most of the population has an adequate selenium status. Up to now no endemic symptoms have been observed in Germany which could be clearly attributed to a selenium deficiency.

No long-term experience is available concerning the intake of inorganic selenium supplements at doses above the estimated values for adequate selenium intake in healthy individuals. In the Clark Study an additional intake of 200 µg selenium per day was tolerated over several years without any adverse effects. In this study, however, a selenium-enriched yeast was used for supplementation and the study group consisted of patients who had been diagnosed with skin cancer in the past. As the various selenium compounds are metabolised in different ways in the organism, no statements can be made on the basis of this study about the tolerance of similarly highly dosed inorganic selenium supplements for the normal healthy population.

Selenium interacts with a series of other nutrients. Its metabolisation is dependent on the sufficient presence of other nutrients. An increase in selenium intake only would shift the balance vis a vis nutrients which interact with selenium and could lead to adverse effects.

Because of the gaps in knowledge about selenium intake in Germany and the lack of long-term experience in the taking of inorganic selenium supplements, BfR is of the opinion that maximum levels for selenium should be oriented towards (estimated) requirements or average intake amounts particularly given the fact that a positive effect of higher selenium intake on the onset of cancer and other chronic diseases could not be proven up to now.

14.4.1.1 Possible management options

a) Adherence to the previous maximum level of 30 µg selenium in food supplements per daily dose

   Advantages: There are no known reports of side effects in conjunction with the maximum level used up to now. The value is oriented towards estimated nutritional-physiological requirements. Even if we assume that two selenium-containing food supplements are taken every day, additional intake remains in a range at which no adverse effects are to be expected.

   Disadvantages: None

b) Orientation towards estimated requirements and the prior derivation procedure (as described in Chapter 14.2.3) but taking into account the D-A-CH estimated values from 2000, which results in a maximum level of 25 µg selenium per daily dose in supplements

Advantages: Even in the case of minor selenium intake from normal diet, supplementation of 25 µg per daily dose would suffice in the normal healthy population in order to prevent deficiency symptoms. The additional intake of 25 µg selenium per day is not expected to lead to an exceeding of the UL

Disadvantages: None

14.4.1.2 Derivation of a maximum level for selenium in fortified foods

It cannot be ruled out that uncontrolled fortification of foods with selenium could lead to nutrient imbalances and an exceeding of the UL in groups in the population with a good supply. Furthermore, there are uncertainties about actual requirements and selenium intake from conventional food. As adequate selenium supply is possible from a rich diet, natural dietary sources should be given preference when it comes to ensuring optimum selenium status. For reasons of preventive health protection, BfR recommends that conventional foods should not be fortified with selenium. If endemic symptoms of a selenium deficiency were to become apparent in the future, general (health) policy measures would be needed, similar to those undertaken for iodine.

Selenium cannot be clearly classified in one of the risk categories for nutrients defined by BfR [margin between the RDA (or the estimated value) and the UL would be <5 (high risk) with respect to the higher estimated value of 70 µg and would be 10 (moderate risk), with respect to the lower estimated value of 30 µg].

According to BfR the maximum level for food supplements should be oriented towards estimated requirements (Option a or b), while conventional foods should not be fortified with selenium.

14.5 Gaps in knowledge

- There are no representative data on selenium intake in Germany, including intake from supplements.
- Selenium requirements are not exactly known.
- The reference values for the assessment of the plasma levels are only based on estimates which means that no reliable statements on the selenium status can be made using the biomarkers.

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15 Risk Assessment of Copper

15.1 Summary

The data available for the Federal Republic of Germany on copper intake indicate that no inadequate intake of the trace element copper is to be expected in otherwise healthy people (supply category 3).

In line with the risk classification of nutrients taken over by BfR, copper is to be classified in the highest risk category because of the relatively small "margin" between the UL and the 97.5 percentile of copper intake.

Because of the good supply situation of the German population with copper and the fact that the 97.5 percentile of total copper intake for all age groups is close to the ULs indicated by SCF, the addition of copper to food supplements cannot be recommended for reasons of preventive health protection.

As in the past no copper should be used to fortify conventional foods either.

Estimated values for adequate intake	1.0-1.5 mg/day (from 15 years)	
Intake [mg/day] (NFCS, 1994)	**m**	**f**
Median	2.25	1.84
P 2.5	1.27	0.91
P 97.5	4.0	3.3
Tolerable Upper Intake Level	Adults 5 mg/day Children/adolescents depending on age 1-4 mg/day Not specifiable for pregnant and lactating women	
Proposal for **maximum levels** in:		
Food supplements	No addition	
Fortified foods	No fortification	

15.2 Nutrient description

15.2.1 Characterisation and identification

Copper is an essential trace element. It is a bivalent or trivalent transition metal (heavy metal/semi-precious metal). It has the atomic number 29 and an atomic mass of 63.546. Copper (powder) has the CAS No. 7440-50-8. Copper mainly occurs as Cu1+ or Cu2+ whereby Cu2+ is predominant in biological systems. As copper tends towards the formation of complexes, it is not available as a free ion either in food or in the organism.

According to EU Directives only the correspondingly listed copper compounds may be used for nutritional purposes: copper carbonate, copper citrate, copper gluconate, copper sulphate, copper lysine complex (Directive 2001/15/EC of 15 February 2001; Directive 2002/46/EC of 10 June 2002). In addition some copper compounds are approved as additives, e.g. in accordance with the Food Colours Directive as food colour E 141 copper-containing complexes of chlorophylls and chlorophyllins (quantum satis).

15.2.2 Metabolism, functions, requirements

Metabolism: Copper is mainly absorbed from the stomach and upper small intestine (duodenum) (Löffler and Petrides, 2003). The absorption rate is homoeostatically regulated and amounts to 35-70% (Heseker, 1998). Other authors indicate this as being from 20% up to more than 50% depending on copper supply (Turnlund, 1998). In the case of a normal diet the average absorption rate is in the range of 30-40% (SCF, 2003; Wapnir, 1998). Proteins, amino acids, citrates or oxalates increase absorption; fibres, high calcium or phosphate levels as well as phytates reduce them (Marquardt and Schäfer, 1994). Absorbed copper is initially bound to albumins, transcuprein and low molecular ligands (e.g. amino acids). It is then transported via the portal vein to the liver (BGA, 1994). In the liver, the central copper metabolism organ, copper is partially stored, incorporated into the copper-containing liver enzymes and then bound to coeruloplasmin and secreted into the plasma. This means that 65% of copper in the plasma is bound to coeruloplasmin (Heseker, 1998; Löffler and Petrides, 2003). 95% of the serum Cu is bound to coeruloplasmin (Turnlund, 1999), 60% of the erythrocytes to erythrocuprein.

The regulation of the copper store in the body is done by adjusting biliary excretion and intestinal absorption. In the case of a deficiency the absorption rate is higher whereas in the case of elevated copper intake, further uptake and release into the bloodstream is reduced or blocked (SCF, 2003). Around 80% of copper is excreted with bile; 15% is excreted from the intestinal wall into the lumen and only 2-4% is excreted in urine (BGA, 1994). Via liver and gallbladder 0.5-2.5 mg/day are excreted in the intestine; the enterohepatic cycle is deemed to be less important (Heseker, 1998; SCF, 2003). Urinary losses are given as 0.1-0.3 mg/day or less (Heseker, 1998; Turnlund, 1999). Copper losses through the skin are variable and are estimated to be on average 0.34 mg/day. In adults around 1.25 mg copper per day can replace losses through faeces and urine (Klevay et al., 1980). The biological half-life of copper in the body is around 20 days in healthy adults; in the case of marginal supply (0.6 mg/2500 kcal) this increases to 35 days.

High concentrations of copper are mainly to be found in the liver and brain. The total copper body store of adults is on average 80-100 mg (D-A-CH, 2000). In this context values of 40-80 mg (Löffler and Petrides, 2003) and 50-150 mg (SCF, 2003) are given. Of this 40% is attributed to muscles, 20% to the skeleton, 15% to the liver, 10% to the brain and 6% to whole blood. The distribution of copper in the body of foetuses and infants deviates from that of adults; at birth half of the body store is to be found in the liver and spleen. A relatively high copper content in the foetal and neonatal liver is physiologically normal.

The normal copper concentration in the plasma is 0.8-1.2 µg/ml. On average 10% higher copper concentrations are measured in women than in men (Heseker, 1998). The plasma level is elevated during pregnancy and when taking oral contraceptives (Löffler and Petrides, 2003). The copper level in the serum is elevated in the case of infections, glomerulonephritis, myocardial infarction, thyreotoxicosis, lupus erythematosus, biliary cirrhosis, acute leucaemia, aplastic anaemia and when taking oestrogens. It is lower, for instance, in conjunction with conditions like kwashiorkor (Buddecke, 1980; Failla et al., 2001).

Interactions: The copper metabolism can be influenced by interaction with other elements, particularly by high uptakes of zinc, cadmium, molybdenum or iron. This can lead to changes in the absorption and excretion rate and copper distribution in the body. Highly dosed antacid medicines or penicillamine administration can have a negative effect on copper supply (Heseker, 1998).

Functions: Copper is a component in many metalloproteins or is necessary for their enzyme function (Table 40). Furthermore, copper is also partially bound to organ-specific proteins. Its two oxidation levels enable the trace element to participate in electron-transferring enzyme

reactions whereby the copper protein enzymes mostly belong to the class of oxidases or hydroxylases (Buddecke, 1980; Löffler and Petrides, 2003). Copper-containing enzymes are of essential importance for cellular energy metabolism (respiratory chain), for the synthesis of connective tissue and neuroactive peptide hormones (catecholamines, encephalines). The copper-containing enzymes coeruloplasmin and ferroxidase are directly involved in iron metabolism because of their ability to oxidise iron. In the nervous system copper is of relevance for the formation of myelin. Melanin synthesis is also dependent on copper (Heseker, 1998).

Table 40: Copper as a cofactor of metalloenzymes

Cuproenzyme	Function
Coeruloplasmin	Multiple oxidase activity, copper, iron, manganese transport
Cytochrome C oxidase	Electron transport, oxidative phosphorylation
Cu/Zn-superoxide dismutase	Antioxidant, detoxification of peroxide radicals
Dopamine ß hydroxylase	Synthesis of catecholamines
Tyrosinase	Melanin biosynthesis
Lysyloxidase	Deamination of lysine and hydrolysine, cross-linking of elastin and collagen microfibrils
Thioloxidase	Formation of disulphide bridges, e.g. in keratin
Uratoxidase	Degradation of uric acid

according to: Failla et al., 2001; Löffler and Petrides, 2003

Requirements: The estimated requirements of the German Nutrition Society from 1991 amounting to 1.5-3.0 mg/day were reduced to 1.0-1.5 mg following the new D-A-CH values in 2000 as an estimate for adequate intake for children from age 7, adolescents and adults (Table 41, according to D-A-CH, 2000).

Table 41: Estimated values for adequate copper intake (according to D-A-CH, 2000)

Age	Copper (mg/day)
Infants	
0 up to under 4 months	0.2 - 0.6
4 up to under 12 months	0.6 - 0.7
Children	
1 up to under 7 years	0.5 - 1.0
7 up to under 15 years	1.0 - 1.5
Adolescents and **adults,** as well as **pregnant** and **lactating women.**	1.0 - 1.5

Other bodies give requirements below 1 mg/day (WHO, 1998) or indicate the average requirements of adults as being 11 µg/kg body weight (WHO, 1996). In Europe a Population Reference Intake (PRI) was set in 1992 for adults of 1.1 mg/day (SCF, 1993). In the USA Recommended Dietary Allowances (RDA) or Adequate Intakes (AI) were fixed for daily copper intake depending on age as follows (FNB, 2001):

0-6 months:	200	µg (AI)	7-12 months:	220	µg (AI)
1-3 years:	340	µg (RDA)	4-8 years:	440	µg (RDA)
9-13 years:	700	µg (RDA)	14-18 years:	890	µg (RDA)
Adults:	900	µg (RDA)	Pregnant women:	1000	µg (RDA)
Lactating women:	1300	µg (RDA).			

15.2.3 Exposure (dietary and other sources, nutritional status)

Sources:

Food: Cereal products, innards (liver and kidneys from ruminants have particularly high copper levels), fish, shell fish, leguminoses, nuts, cocoa, chocolate, coffee, tea and some green vegetables are good sources of copper. The bioavailability of copper in these foods varies

between 35 and 70% (D-A-CH, 2000; Fairweather-Tait, 1997; SCF, 1993). Ground flour, refined sugar, milk and dairy products, potatoes and chicken are, by contrast, low in copper (FNB, 2001; Heseker, 1998).

Food supplements: An alimentary copper deficiency should be remedied by means of diet (BGA, 1994). There is no evidence that copper supplementation would be necessary in conjunction with a normal diet or that it would have favourable effects on athletes either (Jellin et al., 2002). In Germany a maximum level of 1 mg referred to daily portion was proposed for copper in food supplements on the grounds of preventive health protection (BgVV, 2001).

Drinking water: There are no reliable data on the incidence of copper in untreated water or in treated water released by water works. Given the geological situation in Germany, it is only to be expected in isolated cases that copper concentrations of more than 0.1 mg/l will occur at the outlet of waterworks (Dieter et al., 1991). However, depending on factors like pH, calcium carbonate saturation, channelling of water through copper installations, consumption of stagnant water, the copper content in drinking water can rise considerably. With a low pH (under 7.3) copper can increasingly migrate from copper pipes to drinking water. At a level of more than 2 mg copper per litre water, the safety margin to potentially harmful concentrations is not sufficient (D-A-CH, 2000). In the Drinking Water Ordinance (TrinkwV 2001) and the related EU standards (EU Directive 98/83), a maximum concentration of 2 mg per litre is given for the copper content in drinking water. WHO also recommends a guidance value of 2 mg per litre. In the USA a recommended maximum level of 1 mg/l applies (www.ifau.org/infos/smetallwinfo.htm). WHO considers a provisional drinking water guide value of 2 mg/l to be safe.

Medicinal products: Copper salts are used topically as disinfectants (in eye washes and gargling products, for compresses) and external caustics. Radiocopper (= 64 Cu; ß-, ß+, ?; HWZ 12.8 h) is used in diagnostic agents. Furthermore, some intrauterine devices contain copper. Insufficient evidence of efficacy was provided (not referred to parenteral diet) for the applications applied for in conjunction with the copper monograph (BGA, 1994).

Nutritional status:
Intake: In Germany dietary copper intake has increased over the last 10 years and in 1996 it was on average 1.1 mg for women and 1.2 mg for men per day (Anke et al., 1998; D-A-CH, 2000). Other authors indicate median values of daily dietary copper intake in Germany for adults of 1.8 mg/day for women and 2.2 mg/day for men whereby the 97.5 percentiles are 3.3 mg/day and 4.0 mg/day (Heseker et al., 1994; SCF, 2003).

For children aged four upwards and adolescents in Germany, based on surveys from 1985-1988, there are median values for daily copper intake in females of 1.4 mg/day up to 1.9 mg/day, for males 1.6 mg/day up to 2.3 mg/day whereby the 97.5 percentiles are 3.0 mg/day up to 3.7 mg/day and 3.2 mg/day up to 4.3 mg/day (Adolf et al., 1995).

The mean intake of dietary copper in adults in various European countries is estimated to be in the ranges of 1.0-2.3 mg/day for men and 0.9-1.8 mg/day for women (SCF, 2003; Van Dokkum, 1995).

Vegetarians, with a copper intake of approximately 2.1-3.9 mg/day, were shown to have a higher intake than individuals who were not on a purely vegetarian diet (1-1.5 mg/day) (Gibson, 1994; SCF, 2003).

According to the 1992 Nutrition Report the share of food groups in copper supply was 23.1% for bread and bakery goods, 19.2% for potatoes, vegetables and fruit, 18.3% for meat and sausage goods, 15.3% for beverages, 8.3% for milk, dairy products, cheese and curd cheese and 15.8% for all other foods.

The copper content in breast milk is not steady but falls during the first six months of lactation from 0.6 to 0.2 mg per litre. The exclusively breastfed baby receives on average around 60 µg copper per kg body weight. Because of the copper store in the liver available at birth (Widdowson, 1974) and the high absorption rate, it is assumed that copper requirements in the first months of life can be met exclusively by breast milk (D-A-CH, 2000; Dörner et al., 1989). Assuming a secreted milk amount of 750 ml/day and a bioavailability of 50% for breast feeding women, other authors describe an additional requirement of 0.3 mg copper/day (Heseker, 1998).

WHO indicates normal dietary copper intake as 0.94-2.2 mg/day; for children it is frequently below 1 mg/day (WHO, 1998).

In the USA median values are given for dietary copper intake which are in the range of 1.2 to 1.6 mg/day for men and 1.0 to 1.1 mg/day for women. Individuals who take copper supplements (in 1986 15% of US adults) ingest on average an additional 0.3-0.5 mg/day (FNB, 2001).

Biomarkers: Copper supply cannot be reliably assessed using one sole parameter. Several parameters have to be measured (Failla et al., 2001). Besides the analysis of the copper concentrations in the serum, urine and hair, determination of coeruloplasmin concentration and the activity of the erythrocytic superoxide dismutase can be used to assess copper supply. Copper transport disorder can be identified by measuring coeruloplasmin concentrations. A marginal copper deficiency cannot be reliably detected through hair analysis or by determining the copper concentration in the serum and urine (Heseker, 1998).

15.3 Risk characterisation

15.3.1 Hazard characterisation (NOAEL, LOAEL)

In 2001 FNB set a NOAEL (No observed adverse effect level) for human beings of 10 mg copper per day, referred to the endpoints liver effects, gastro-intestinal effects and various other laboratory parameters (FNB, 2001). In a clinical trial 7 participants were given 10 mg copper daily as copper gluconate for a duration of 12 weeks; the placebo was used as a control (Pratt et al., 1985).

15.3.2 Deficiency, possible risk groups

A copper deficiency first manifests itself through a reduction in the activity of the cuproenzymes, in particular coeruloplasmin because of the short half life of 5 days and erythrocytic superoxide dismutase. In the case of marginal copper deficiencies the serum values are not a reliable indicator. The typical copper deficiciency syndrome was first observed in premature babies as a consequence of inadequate foetal store and in full-term babies who were given non-modified cow's milk ("cow milk anaemia"). Furthermore, it was also observed in children recovering from a severe protein energy deficient diet and in patients with long-term parenteral nutrition. Microcytic, hypochromic, iron-unresponsive anaemia is observed in the case of acquired copper deficiency. What is also notable is the increased sensitivity for respiratory diseases. Furthermore there are bone abnormalities with osteoporosis and spontaneous fractures as well as vascular anomalies with spontaneous vascular ruptures as a consequence of disorders of elastin and collagen metabolism. There is also reduced pigmentation of hair and skin and, in the advanced stage, neurological disorders (Heseker, 1998).

Menkes Syndrome (kinky hair syndrome) is a rare congenital disorder with an X-linked recessive inheritance which leads to copper deficiency and severe development disorders. The symptoms include steel-like discolouration of the hair, impaired growth, severe neurological changes down to degeneration of the central nervous system, including tortuosity of the œ-

rebral arteries, vascular aneurysms as a consequence of intracellular copper distribution disorder (Löffler and Petrides, 2003).

The occurrence and symptoms of copper deficiency are less well documented in adults and generally speaking they are rare, e.g. in patients on longer-term parenteral nutrition (SCF, 2003). There are signs from experiments that a copper deficiency in adults can lead to disorders of the cardiovascular system and immune system (FNB, 2001). The postulated association between chronic sub-optimum copper supply and elevated atherogenic risk has not been sufficiently proven which means that further studies are needed (Heseker, 1998). There could also be impairment of cardiac function with dysrhythmia possibly in conjunction with changes in the catecholamine metabolism (FNB, 2001).

The data available to the Federal Republic of Germany on copper intake indicate that inadequate intake of the trace element copper is not to be expected in otherwise healthy individuals (supply category 3).

15.3.3 Excessive intake, possible risk groups

15.3.3.1 Excessive intake

There are differing descriptions of the toxicity of copper following oral intake. The accidental taking of 15-75 mg copper is said to cause gastro-intestinal disorders (Aaseth and Norseth, 1986). The emetic dose is said to be 25-75 mg (Bergquist and Sundbom, 1980). Other authors report that vomiting and heartburn are already observed as reversible effects at oral doses of 10-15 mg. Copper taken up from drinking water already led to toxic effects at far lower doses. Two studies identified the thresholds for acute gastro-intestinal effects of copper in water at around 4.8 mg/day, based on a concentration of 3 mg copper per litre water and a mean water intake of 1.6 litres per day (Donohue, 1997; Pizarro et al., 1999; SCF, 2003). According to another study the threshold for acute toxicity of copper in drinking water is approximately 6 mg per litre (Araya et al., 2001; SCF, 2003).

In human beings acute intoxication symptoms (copper poisoning) are only rarely observed, e.g. after consumption of contaminated foods or beverages from copper-containing containers or through other intake of copper salts (primarily copper sulphate, alkaline copper acetate = verdigris). The symptoms include greater salivation, abdominal pains, nausea, vomiting and bloody-watery diarrhoea (Heseker, 1998). At higher doses severe to very severe forms occur which can lead to ulceration, haemorrhagias in the gastro-intestinal tract, intravasal haemolysis, haemoglobinuria, hypotonia, liver necrosis and liver failure as well as to kidney and circulatory failure, collapse, coma and finally to death. The lethal dose of copper salts (normally copper sulphate) is said to be approximately 200 mg/kg body weight (WHO, 1993). The inhalation of metallic copper can lead to metal fume fever ("foundryman's fever"). Longer exposure to copper dust leads to the green discolouration of skin, hair, teeth and gums ("copper line") and to conjunctivitis.

In the case of chronically elevated exposure, copper accumulates in the liver which seems to be initially protected over a longer period by complexation of metallothionein or mitochondrocuprein. Chronic intoxication symptoms are far less striking and only occur once the elimination capacity of the liver for copper has been exceeded. Where there is a copper excess, biliary excretion is markedly increased. As this excretion mechanism only fully develops its ability in the course of the first years of life, infants are more at risk from excess copper than adults despite their higher copper requirements. This can lead to damage of the liver parenchyma, hepatitis, cirrhosis of the liver and to a haemolytic crisis (Heseker, 1998). Infants and small children are particularly sensitive; they can develop infant cirrhosis of the liver when their food has been prepared with acid water that has been standing for longer periods in copper installations (pipes, boilers, fittings) ("stagnant water") from private wells. Other fac-

tors like viral infections, deficiency of other trace elements, genetic predisposition or congenital biliary tract and metabolism anomalies are also of importance (Dassel de Vergara et al., 2000; Müller et al., 1999; Schimmelpfennig and Dieter, 1995). Besides other possible factors, high copper intake can lead to a disease which has become known as "Indian Childhood Cirrhosis" (ICC). It is considered to be the main trigger for the onset of "Idiopathic Copper Toxicosis" (ICT) (Dassel de Vergara et al., 2000; FNB, 2001; SCF, 2003).

In patients suffering from Wilson's disease, a rare hereditary autosomal gene defect, copper homoeostasis, is disordered. The incidence around the world is 1:30,000 (SCF, 2003). This is a defect paraproteinaemia with disorder of coeruloplasmin synthesis ("coeruloplasmosis") linked with a reduction in biliary copper excretion (Löffler and Petrides, 2003). When combined with lower plasma concentrations of copper and coeruloplasmin and increased copper excretion in the urine, this disorder leads (despite normal copper intake) to toxic copper accumulation (SCF, 2003). If untreated, the clinical consequences of this copper overload effect in particular the liver (cirrhosis), the central nervous system (degeneration of the basal ganglions "lenticular nucleus degeneration") as well as eyes (cornea), blood and kidneys (Buddecke, 1980; Heseker, 1998; Schmidt, 2003).

High serum copper levels have been discussed as a risk factor for coronary heart disease (Ferns et al., 1997; SCF, 2003). However, more research is necessary in order to determine the role of elevated serum levels of copper and coeruloplasmin ("acute phase protein") in conjunction with inflammatory processes and any associations between elevated copper levels and oxidative damage as a mechanism in arterial sclerosis.

15.3.4 Possible risk groups for excessive intake

The occurrence of acute or chronic copper intoxications in human beings tends to be rare. The population groups most affected are those which are exposed to elevated copper concentrations in drinking water, people who use copper containers for instance for cooking and storing milk and individuals with a hereditary predisposition (SCF, 2003). One particular risk group are infants whose formula is prepared using "soft" and "acid" (pH <6.0) tap water which has passed through copper installations (e.g. private wells) (Dieter, 1995; Schimmelpfennig et al., 1997; Schimmelpfennig and Dieter, 1995).

15.4 Tolerable upper intake level for copper

FNB set the tolerable upper intake level (UL) for adults at 10000 µg copper per day (10 mg/day) (FNB, 2001). FNB was not able to derive a UL for infants (0-12 months). For children (1-3 years of age) a UL of 1000 µg/day was derived, for children (4-8 years of age) 3000 µg/day, for children (9-13 years of age) 5000 µg/day. For adolescents (14-18 years of age) a UL of 8000 µg/day was fixed. For pregnant women a UL of 8000 µg/day was set and for lactating women a UL of 8000-10000 µg/day (FNB, 2001).

The United Kingdom also presented considerations on the derivation of a UL for copper (EVM, 2003). Based on data from animal experiments (toxicity study in rodents) a NOAEL was determined of 16 mg/kg body weight/day (Hebert et al., 1993). Based on this EVM derived a UL of 0.16 mg/kg body weight/day, corresponding to approximately 10 mg copper per day for an adult weighing 60 kg. It used an uncertainty factor of 100 and took into account data from human studies (Pratt et al., 1985; Turnlund et al., 1989) referred to adults. This value, therefore, correlates with that of FNB. EVM assumes for copper a worst case maximum estimated daily exposure for copper from foods and drinking water of 9 mg. This means that only approximately 1 mg per day is left for supplementation or other additional copper intake (EVM, 2003).

The tolerable upper intake level (UL) for copper was recently derived and published by the EU Scientific Committee on Food (SCF, 2003). The critical endpoint for the derivation of a UL in human beings are gastro-intestinal disorders for acute effects whereas when examining long-term toxic effects attention should focus more on liver disorders (SCF, 2003).

Taking into account the above value of 10 mg copper/day (FNB, 2001), the other related scientific data and the inclusion of a "uncertainty factor UF" of 2, SCF derived a UL of 5 mg copper per day for adults; for children and adolescents extrapolations were undertaken in conjunction with age (SCF, 2003).

Tolerable upper intake level (UL) for copper in mg per day (according to SCF, 2003):

01-03 years of age	1 mg per day	04-06 years of age	2 mg per day
07-10 years of age	3 mg per day	11-14 years of age	4 mg per day
15-17 years of age	4 mg per day	Adults	5 mg per day

Pregnant/lactating women: UL cannot be determined because of inadequate data situation.

The available studies show that mean copper intake of adults and children in the EU is below these above-mentioned ULs. The 97.5 percentile of total copper intake for all age groups is very close to the above ULs whereby there are no grounds for concern according to SCF. In this context it is stressed that additional copper intake from drinking water may be considerable and must be taken into account (SCF, 2003).

15.4.1 Derivation of a maximum level for copper in food supplements

BfR upholds the precautionary principle and for the derivation of maximum levels for copper in food supplements it takes as the basis the lower UL derived by the above-mentioned bodies for adults, i.e. the SCF value of 5 mg per day (SCF, 2003).

The available studies show that mean copper intake is below the UL of 5 mg per day whereby the 97.5 percentile of total copper intake for all age groups is very close to the above-mentioned ULs. They also highlight the fact that additional copper intake from drinking water may be considerable and must be taken into account (SCF, 2003). For Germany the values for the 97.5 percentile of copper intake of women and men are 3.3 mg/day and 4.0 mg/day respectively (Heseker et al., 1994; SCF, 2003). Hence in conjunction with the risk classification of nutrients taken over by BfR, copper is to be assigned to the highest risk group (risk category "high risk").

As the 97.5 percentile of copper intake for women of 3.3 mg/day and of 4.0 mg/day for men comes very close in Germany to the UL of 5 mg per day, arithmetically speaking there is very little scope left for the additional intake of copper from food supplements.

Based on surveys from 1985-1988, for children from age four and adolescents in Germany, there are median values of daily copper intake in female persons of 1.4 mg/day up to 1.9 mg/day, for male persons 1.6 mg/day up to 2.3 mg/day, whereby the 97.5 percentiles are 3.0 mg/day up to 3.7 mg/day and 3.2 mg/day up to 4.3 mg/day (Adolf et al., 1995). As the values for the UL for children from age four upwards and adolescents are between 2 and 4 mg depending on age as outlined above, arithmetically speaking there is no scope for any additional intake by these groups of individuals of copper from food supplements.

15.4.1.1 Possible management options

a) Continuation of current practice for adults and a change for children and adolescents

   At present, there is an upper level of 1 mg copper (BgVV, 2001) in Germany in connection with co-ordinated administrative practice for copper additions to food supple-

ments per daily portion. There have been no reports of adverse effects in conjunction with this practice. For the reasons outlined above there are no grounds for extending the addition of copper to food supplements beyond the level tolerated at present. The "margin" between the UL and 97.5 percentile of copper intake from diet is arithmetically speaking so low (approximately 1 mg per day) that it is already exhausted with the consumption of one food supplement. The consumption of several copper supplements would rapidly lead to the UL being exceeded. Arithmetically speaking for children and adolescents there is no scope for supplementation with copper from food supplements.

b) Change to existing practice with a reduction in previous maximum level

When deriving upper levels for food supplements, multiple consumption of these products must be taken into account. The "margin" between the UL and the 97.5 percentile of copper intake from a conventional diet is, arithmetically speaking, relatively low, approximately 1 mg per day. If a factor 2 is assumed in conjunction with assumed multiple consumption, this could lead – arithmetically speaking - to a tolerable upper intake level for adults of maximum 0.5 mg copper for the individual supplement. In the case of higher multiple consumption this would be correspondingly lower. For children and adolescents there is, arithmetically speaking, no scope for supplementation of food supplements with copper.

c) Change to the existing practice in that copper is not added to food supplements

Given the good cooper intake situation of the population in Germany and the fact that the 97.5 percentile of total copper intake for all age groups is close to the ULs indicated by SCF, the addition of copper to supplements cannot be recommended for reasons of preventive health protection.

15.4.2 Derivation of a maximum level for copper in fortified foods

Because of the high risk category of copper, the relatively low "margin" between the UL and the 97.5 percentile of copper intake and because the remaining scope for the addition of copper to food supplements has already been completely exhausted in arithmetic terms (see above), the addition of copper to conventional foods cannot be recommended.

In line with the risk classification of nutrients taken over by BfR, copper is to be assigned to the highest risk category because of the low "margin" between the UL and the 97.5 percentile of copper intake.

BfR cannot recommend the addition of copper to food supplements along the lines of Option c) outlined above for reasons of preventive health protection.

In the case of conventional foods, there should be no copper fortification as hitherto.

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16 Risk Assessment of Manganese

16.1 Summary

There are no indications of inadequate manganese intake for the Federal Republic of Germany. However, no representative consumption data (supply category 2) are available. Because of the small margin between estimated intake and the levels at which adverse effects have already been observed, manganese is assigned to the highest risk category. On the grounds of preventive health protection BfR recommends that manganese should not be added to food supplements or fortified foods.

Estimated values for adequate intake	2.0-5.0 mg/day	
Intake [mg/day]	**m**	**f**
Median	? *	? *
P 2.5	? *	? *
P 97.5	? *	? *
	* No representative intake data for the Federal Republic of Germany	
Tolerable Upper Intake Level	Not defined Inadequate database Very low safety margin	
Proposals for **maximum levels** in:		
Food supplements	No addition	
Fortified foods	No fortification	

16.2 Nutrient description

16.2.1 Characterisation and identification

Elemental manganese (Mn) is a white to silvery grey brittle metal. It is the twelfth most frequent element. After iron and titanium it is the most frequent transition metal. Some transition metals play an important role in biological systems. With the exception of manganese phosphate and manganese carbonate, manganese(II) salts are mostly water soluble. Manganese is a component in more than 100 minerals including sulphides, oxides, carbonates, silicates, phosphates and borates. Manganese is encountered in the oxidation levels from Mn^{-3} to Mn^{+7} whereby Mn^{2+}, Mn^{4+} and Mn^{7+} are the most important. In biological systems Mn^{2+} (manganese(II)) in addition to Mn^{3+}, which is a component of superoxide dismutase, is the prevailing form.

16.2.2 Metabolism, functions, requirements

Manganese is an essential trace element. In the organism it is a component of various ferments (arginase, pyruvate carboxylase and superoxide dismutase). Furthermore, it is a cofactor in certain enzyme systems. Orally ingested manganese is absorbed through the gastro-intestinal tract. The absorption rate is 3-8%; it may however be higher in infants and small children. As intake increases, bioavailability decreases. Dietary calcium and phosphates impair intestinal absorption. Iron and manganese impede each other during absorption (Heseker, 2000). Absorbed manganese is transported in free form or bound to a_2-macroglobulins via the portal vein to the liver. In the liver most of the manganese is withheld from portal circulation. A small amount reaches extrahepatic tissue after binding to transferrin. The total body store is indicated as 10-40 mg (180-720 mmol). 25% of the total retained manganese amount is to be found in bones. The highest tissue concentrations are in the liver, kidneys, pancreas and adrenals. In children and juvenile animals manganese tends to be deposited in specific regions in the brain. No specific store proteins are known for manga-

nese. It is excreted in faeces and in human beings it follows a two-phase rhythm with half lives of 13 to 34 days (Heseker, 2000; WHO, 1996).

A recommended daily allowance (RDA) has not been established either in the USA or in Europe up to now. There are however a number of estimated values. The US National Research Council indicated an estimated safe and adequate dietary intake, ESADDI, of 2 to 5 mg per day (Freeland-Graves, 1994). For children in the age groups 1-3, 4-6 and 7-10, 1.0-1.5 mg, 1.5-2.0 mg and 2.0-3.0 mg/day were still given in 1989 (US-NRC, 1989). In 2001 the US-Food and Nutrition Board (US-FNB) made more recent recommendations for adequate manganese intakes which differed considerably depending on gender and age group. They extend from 0.003 mg/day for infants up to 6 months over 1.9 mg/day for 9 to 13-year-old boys up to 2.6 mg/day for lactating women (US-FNB, 2001).

For Germany, Austria and Switzerland the different estimated values for adequate intake are given for various age groups as well. They are 0.6-1.0 mg/day for infants from 4 to 12 months, 1.0-1.5 mg/day for children aged between 1 and 4, 1.5-2.0 mg/day for children aged between 4 and 7 and 2.0-5 mg/day for age 13 upwards (D-A-CH, 2000).

16.2.3 Exposure (dietary and other sources, nutritional status)

The main sources of manganese for normal consumers not exposed to manganese at work are foods. The manganese concentrations in foods vary considerably. Most foods contain less than 5 mg/kg. Cereals, rice and nuts may, however, contain manganese amounts of more than 10 mg/kg and in some cases even more than 30 mg/kg. A particularly high level of manganese can frequently be determined in tea leaves (up to more than 900 mg/kg). In the infused tea 1.4 to 3.6 mg/l could be measured (WHO, 1981; 1996).

In drinking water the average manganese levels are normally between 0.004 mg/l and 0.032 mg/l (US-ATSDR, 1992). In the tap water of 100 towns in the USA manganese contents were measured ranging from "not detectable" up to 1.1 mg/l with a mean of 0.005 mg/l (WHO-ICPS, 1981). In Germany surveys in conjunction with the Environment Survey revealed that 98% of all German homes have tap water with less than 23 µg manganese per litre and 50% with less than 3 µg per litre (Krause et al., 1991).

Mineral waters may contain considerably more manganese. 98.1% of European mineral water contain less than 2 mg manganese per litre, 2.3% of total production between 1 mg/l and 2 mg/l and 6.6% between 0.5 mg/l and 1 mg/l (Chambre Syndicale des eaux minerales, 1994).

The air in non-contaminated regions contained manganese levels of 0.01 µg/m^3 up to 0.07 µg/m^3 as an annual average. In the vicinity of foundries the values can increase up to 0.3 µg/m^3 on average over the year and in the environs of large-scale industrial plants up to 0.5 µg/m^3 and sometimes even up to 8 µg/m^3 (WHO-ICPS, 1981).

Older information indicates slightly lower daily manganese intake than more recent information. In 1981 WHO indicated 2-9 mg (WHO, 1981) for adults. There are no representative data available from Germany about dietary manganese intake. For Germany 0.9 up to 7 mg were indicated for adults (Schlettwein-Gsell and Mommsen-Straub, 1973) and in Holland 1.2 up to 9.4 mg manganese per day (Ellen et al., 1990). Manganese intake from regular consumption of certain mineral waters may already be considerable and amount to several milligram per day in adults (Dieter, 1992). When analysing overall diet an average daily manganese intake of 2.7 and 2.4 mg for men and women respectively was determined in Germany (Anke et al., 1998).

The Scientific Committee on Food of the European Commission (SCF) and the US Food and Nutrition Board (FNB) today assume that an adult consumer normally ingests up to 10 or 11 mg manganese per day from a typically western diet. In the case of a special vegetarian diet this may be as much as 13 to 20 mg manganese per day (SCF, 2000; US-FNB, 2001).

16.3 Risk characterisation

16.3.1 Hazard characterisation (NOAEL, LOAEL)

Higher manganese doses or intake levels can have adverse effects down to intoxications. The typical symptoms of manganese intoxication, as observed for instance after occupationally-related chronic intake through the inhalation of manganese-containing dust, are muscle pain, weakness, slow clumsy movement of the limbs, mask-like facial expression, loss of appetite and speech impediment as a consequence of degenerative processes in the central nervous system. Generally speaking, they are irreversible. Up to now a threshold dose for neurological effects could not be reliably determined; it is, however, assumed that it must be in the range of 0.1 mg/m^3 and 1 mg/m^3 (WHO, 1996). Similar or weaker neurological effects were described after oral intake. The elevated intake of manganese was normally from contaminated drinking water (He et al., 1994; Kawamura et al., 1941; Kondakis et al., 1989; Vieregge et al., 1995). There are also signs of an association between elevated manganese contents in hair and learning difficulties in children (Barlow and Kapel, 1979; Collipp et al., 1983; Pihl and Parkes, 1977). There is also an indication of classical symptoms of manganese intoxication attributable to the four or five year consumption of large doses of food supplements with vitamins and minerals (Banta and Markesburg, 1977). On closer examination of all these studies it must, however, be noted that the authors do not provide clear evidence of a causal link with manganese in the cases described. The studies by Hejtmancik et al. (1987a; b) as well, on the basis of which a genotoxic potential was determined for manganese, are still the subject of controversial discussion and do not permit any clear statements.

The available data on dose-dependent changes in the central nervous system and in the reproduction system have not made it possible up to now to derive a no observed adverseeffect level (NOAEL) for manganese. There are, however, various proposals on deriving "acceptable" or "tolerable" intake levels from the results of existing studies. Nor was it possible up to now to derive any clear dose-response relationship for adverse effects from the results available from animal experimental studies. Although the animal experimental data are more comprehensive than experience in human beings, no NOAEL could be derived so far.

16.3.1.1 Deficiency

In animal experiments adverse effects were observed in conjunction with manganese deficiency like impaired growth, skeletal abnormalities, reproductive deficits, ataxia in neonates and defects in lipid and carbohydrate metabolism.

Up to now no deficiency symptoms have been observed in human beings which could be clearly attributed to inadequate manganese intake. There are vague, not sufficiently secured indications from a few experimental studies that a clear reduction in manganese intake could lead to detrimental effects. These studies are described in more detail in the report of the National Expert Group of the United Kingdom (Food Standards Agency, 2003)

16.3.2 Deficiency, possible risk groups

There are no reports of manganese deficiency conditions in the Federal German population.

There are no signs of inadequate manganese intake for the Federal Republic of Germany. However, no representative consumption data are available (supply category 2).

16.4 Tolerable upper intake level for manganese

The rapidly developing market for freely available food supplements and the growing tendency to also fortify conventional foods with vitamins and minerals and the related danger of an unwanted overdose by consumers were the reasons why several bodies recently turned their attention to deriving tolerable upper intake levels for vitamins and minerals.

In this context reassessments of manganese were undertaken amongst others by the Scientific Committee on Food (SCF, 2000), the US-Food and Nutrition Board (FNB, 2001), the Expert Group on Vitamins and Minerals, a national expert group of the United Kingdom (Food Standards Agency, 2003).

The EU Scientific Committee on Food (SCF) gives an acceptable range of intake of 1 up to 10 mg per person and day for manganese (SCF, 1993).

According to SCF the available data clearly show that overly high manganese intakes can have detrimental effects in both humans and animals. Because, however, **no oral NOAEL** could be determined from the available animal experiments, SCF did not think it was in a position in its more recent assessment to indicate a tolerable upper intake level for manganese. It is now of the opinion that, from the toxicological angle, manganese intake which goes beyond what is normally ingested from beverages and solid foods (up to 10 mg/day) should not be undertaken (SCF, 2000).

The US Food and Nutrition Board (US-FNB) assumes the same dietary manganese intake in terms of scale as SCF in its assessment of manganese published in 2001. It notes that consumers with a diet typical in western countries ingest up to 10.9 mg manganese per day. A special vegetarian diet may even lead to intakes of 13 to 20 mg manganese per day. As no detrimental effects have been observed in consumers with a typically western diet which could be attributed to manganese, FNB considers a daily manganese intake from food of 11 mg to be a reasonable NOAEL. It derives from this a tolerable upper intake level (UL) of 11 mg/day **using an uncertainty factor of 1**.

BfR shares the opinion of SCF that given the inadequate data for human beings and because of the lack of NOAELs from animal experiments for critical endpoints, there is so much uncertainty that the derivation of a numerical UL cannot be justified. Aside from this, it is also clear in the assessment of US-FNB that there is no scope for additional manganese intake from food supplements. In this respect there is no disagreement with the European opinion that intake which goes beyond what can normally be ingested from beverages and solid foods may lead to adverse effects.

The Expert Group on Vitamins and Minerals of the United Kingdom is also of the opinion that the data are not sufficient in order to derive a safe upper level for manganese intake. However this body was prepared to indicate a guidance level based on several assumptions. It assumes that using the NOAEL from the Vieregge et al. study (1995), it can reasonably be assumed that additional manganese intake of 4 mg/day in addition to what is ingested from a normal diet will not have any adverse effects on the normal population. Using the NOAEL from the Kondakis et al. study (1989) an additional 0.5 mg/day could be ingested without any risk by older people. Based on further assumption that normal dietary manganese intake

amounts to 8.2 mg/day, this leads to an acceptable total manganese intake of 12.2 mg/day for the normal population and 8.7 mg/day for older people for the national Expert Group of the United Kingdom (Food Standards Agency, 2003).

16.4.1 Derivation of a maximum level for manganese in food supplements and fortified foods

In its opinion on manganese SCF expressly states that the margin between the range of action in human beings and the amounts of manganese ingested from foods is very small and that given the neurotoxicity and the possibly higher sensitivity of specific sub-groups, manganese intake which goes beyond what can normally be ingested from beverages and solid foods could carry the risk of possible adverse effects which is not countered by any recognisable benefit from additional manganese intake (SCF, 2000).

The former Federal Institute for Consumer Health Protection and Veterinary Medicine (BgVV), therefore, recommended that no general dispositions or exemptions should be issued any more for products to which manganese has been added. This recommendation is supported by its successor institute, the Federal Institute for Risk Assessment (BfR), and continues to apply.

As long as SCF is of the opinion that manganese intake beyond what is normally ingested from beverages and solid foods, may carry a risk of adverse effects, there is currently no alternative - in the opinion of BfR from the angle of precautionary consumer protection - to the recommendation of a ban on the addition of manganese to food supplements and other foods.

Because of the small margin between estimated intake and the levels at which adverse effects have already been observed, manganese is assigned to the highest risk category. BfR recommends that, on the grounds of preventive health protection, manganese should not be added to food supplements or fortified foods.

16.5 Gaps in knowledge

The gaps in knowledge and questions touched on by the above-mentioned evaluatory bodies should be taken up by scientific circles with a view to finding reasonable answers. For fundamental research what are required first and foremost are studies which indicate toxicological thresholds of action for manganese and its relevant compounds and studies which can identify reliable minimum levels to cover requirements. Furthermore, market analyses are urgently required in order to provide quantitative information on additional manganese intake from food supplements and/or from correspondingly fortified foods.

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17 Risk Assessment of Chromium

17.1 Summary

For the Federal Republic of Germany there are no reports of inadequate chromium intake (supply category 2). However, no representative consumption data are available.

Only trivalent chromium compounds can be added to foods.

BfR considers the health risk from the use of chromium (with the exception of chromium picolinate) in foods to be low. The EU Scientific Committee on Food (SCF) was not able to derive a UL because of the inadequate data situation but did not definitely rule out any risk. Hence and for reasons of continuity in the practice up to now, BfR is of the opinion that the previous upper level of 60 µg in the daily dose of a food supplement should be maintained and that there should be no addition of chromium for the purposes of food fortification. Chromium picolinate should not be used.

Estimated values for adequate intake	30-100 µg/day
Intake [µg/day] (Anke et al., 1998)	**m** **f**
Mean	61 * 84? *
	* No representative intake data for the Federal Republic of Germany
Tolerable Upper Intake Level	Not defined Database not sufficient
Proposal for **maximum levels** in:	
Food supplements	60 µg/daily portion (No chromium picolinate)
Fortified foods	No fortification

17.2 Nutrient description

17.2.1 Characterisation and identification

The transition metal chromium (Cr) exists in the oxidation levels Cr^{0} up to Cr^{+6} whereby elemental chromium (Cr^{0}) does not occur in nature. Chromium compounds in the oxidation levels below +3 have a reducing effect and those in the oxidation levels above +3 have an oxidising effect. The chromium compounds that occur in nature are almost always Cr^{+3} compounds. Hexavalent chromium compounds (Cr^{+6}) only rarely occur in nature and can be attributed to human actions.

The high energy required to oxidise trivalent chromium into hexavalent chromium means that chromium(VI) compounds are practically not created at all in biological systems. Because of their highly oxidising properties chromium(VI) compounds are not stable independently of their solubility and are spontaneously reduced. That is why they are scarcely found at all as natural ingredients in foods.

Only trivalent compounds may be added to food supplements. EC Directive 2002/46/EC only lists chromium(III) chloride and chromium(III) sulphate as permissible chromium compounds for addition to food supplements. This list does not include any organic chromium compounds which are already used in practice for instance as chromium picolinate.

In 2001 all existing general dispositions and exemptions granted in Germany for the use of chromium picolinate in food supplements were withdrawn on the grounds that adverse ef-

fects on the health of consumers cannot be ruled out according to more recent findings (BMVEL, 2001).

17.2.2 Metabolism, functions, requirements

The absorption rate of orally administered chromium is influenced by several factors. They include the chemical properties of the ingested chromium compound, the intake level and the type and amount of other parallel food components. Hence, the bioavailability of chromium can be positively influenced by ascorbic acid or the presence of natural chelating agents. The absorption of chromium from chromium picolinate is far more effective than, for instance, from chromium chloride. Overall the absorption of chromium from food is very low and is between 0.5 and 2% (Anderson et al., 1997a; Anderson and Kozlovsky, 1985; Offenbacher, 1994; Stoecker, 2001). Most of the orally ingested chromium is not absorbed and is excreted in faeces (Stoecker, 1999; 2001). In the blood chromium is transported bound to transferrin to tissues. Chromium accumulates in the liver, spleen, soft tissue and bones although the concentrations are very low, for instance in the liver 8 ng/g and in the spleen 15 ng/g (Lim et al., 1983; Vuori and Kumpulainen, 1987). Chromium is excreted via the kidneys. The half life of chromium for urinary excretion is 1.51 days in healthy test subjects and 0.97 days in diabetics (do Canto et al., 1995).

Chromium is an essential trace element and influences carbohydrate, fat and protein metabolism by impacting insulin activity. The exact mechanism of action has not yet been fully clarified nor has the exact structure of the glucose tolerance factor (GTF), the biologically active form of chromium. GTF has been approximately defined as a chromium nicotinic acid complex. It is assumed that it impacts on mammals by activating a specific enzyme (Davis et al., 1996; Mertz, 1993). More recently a chromium-binding oligopeptide with a low molecular weight of 1500 was isolated from various tissues consisting of glutamate, aspartate, glycine and cysteine. This substance, which was described by Vincent as "chromomodulin", is said to be responsible for the activation of the tyrosine kinase activity of the insulin receptor (Davis and Vincent, 1997; Vincent, 2000a; b).

Favourable effects of chromium intake were demonstrated in diabetics where it was assumed that they suffer from a chromium deficiency. Dietary chromium supplementation improved glucose tolerance, raised (fasting) blood sugar values, lowered the insulin level, total cholesterol and triglyceride values whereas the HDL cholesterol values increased (Mooradian et al., 1994; Stoecker, 2001). However a more recent meta analysis of 15 randomised clinical trials in non-diabetics could not detect any influence of chromium supplementation on glucose or insulin concentrations. A corresponding effect in diabetics in China was not deemed to have been sufficiently proven (Althuis et al., 2002).

In Germany, Austria and Switzerland adequate daily chromium intake levels of between 30 and 100 µg are given for adults (D-A-CH, 2000). WHO recommends that chromium supplementation of 250 µg/day should not be exceeded (WHO, 1996). The US National Research Council (NRC) gives an estimated safe and adequate chromium intake (ESADDI) of 50-200 µg/day for adults (US-NRC, 1989). The US Food and Nutrition Board (FNB) derived adequate chromium intakes for various age groups: e.g. 35 µg/day for men aged between 19-50 and 25 µg/day for women of the same age (US-FNB, 2001).

The UK Committee on Medical Aspects of Food Policy (COMA) pointed out that the adequate intake for trivalent chromium is more than 0.025 mg/day for adults and between 0.0001 and 0.001 mg/kg body weight and day for children (COMA, 1991).

17.2.3 Exposure (dietary and other sources, nutritional status)

Chromium is ubiquitous and very differing amounts can be detected in water, soil and air. Hence various concentrations are encountered in biological media as well as in foods. In a British Total Diet Study the highest chromium contents were found in meat products (230 µg/kg), followed by fats and oils (170 µg/kg), bread (150 µg/kg), nuts and various cereals (140 µg/kg), fish, sugar and food preserves (130 µg/kg). The lowest levels were measured in milk (10 µg/kg), fresh fruit and green vegetables (20 µg/kg) and in eggs (40 µg/kg). In the USA the highest levels were measured in seafood (120-470 µg/kg), followed by meat and fish (110-230 µg/kg), grains and cereals (40-220 µg/kg), fresh fruit (90-190 µg/kg) and fresh vegetables (30-140 µg/kg). Non-contaminated drinking water normally contains less than 1 µg/l (UK-EVM 2002a).

Information on dietary chromium intake prior to 1980 is questionable because it is based on inexact analytics (WHO, 1996). Later information indicates that, for instance, in the USA less than 50 µg chromium per day is ingested from food (Anderson and Kozlovsky, 1986; Offenbacher et al., 1985).

In Germany duplicate studies identified daily dietary chromium intakes of 61 µg for men and 84 µg for women (D-A-CH, 2000). In the United Kingdom, Sweden and Spain dietary chromium intake is given as slightly higher and in the USA as slightly lower (cf. Table 42).

Table 42: Dietary chromium intake in *µg*/day

Country	Study method	Range	Mean
Germany [1]	Duplicate study	? ?	(M)* 61 (F)* 84
UK [2]	Food (total diet study in 1997) Food supplements Drinking water	up to 170 [a] up to 100 [b] up to 2 [c]	100 ? ?
Sweden [3]	Randomly selected 24-hour diets	50-580	160
Spain [4]	Calculated from mid-day meal by extrapolation to 100%	?	120
Spain [5]	Duplicate study, Southern Spain	9,4-205	100
USA [6]	7-day self-selected diets	(M)* 22-48 (F)* 13-36	(M)* 33 (F)* 25
	From supplements [e]	(M)* 3.2-100 [d] (F)* 4.4-127 [d]	(M)* 29.5 (F)* 30.0

According to SCF, 2003

* (M) = Males, (F) = Females

[1] D-A-CH, 2000; [2] EGVM, 2002; [3] Abdulla et al., 1989; [4] Barberá et al., 1989; [5] Garcia et al., 2001; [6] FNB, 2001 (Ap C table C14);

[a] UK-EVM: 97.5 percentile as the "maximum estimated daily intake"

[b] Related to the daily portion

[c] Estimated intake from 2 litres of water containing <1µg Cr/l

[d] Ranges from the 5 to the 95 percentile

[e] Third National Health and Nutrition Examination Survey, 1988-1994

17.3 Risk characterisation

17.3.1 Hazard characterisation (NOAEL, LOAEL)

Chromium toxicity is extensively described in numerous reports and overviews of various international institutions and bodies (ATSDR, 2000; EGVM, 2002a; b; EPA, 1998a; b; c; d; FNB, 2001; IARC, 1990; IPCS, 1988; WHO, 1996). The trivalent chromium compounds under discussion here have very low toxicity compared with the hexavalent compounds.

The oral LD_{50} for trivalent chromium in rats is 2365 mg/kg body weight for chromium acetate (ATSDR, 2000) and 3250 mg/kg body weight for chromium nitrate nonahydrate (Registry of

Toxic Effects, 1980). The oral LD_{50} values for trivalent water-soluble chromium compounds vary for rats and mice between 140 mg/kg and 422 mg/kg (UK-EVM, 2002).

In several studies in which test subjects were mostly given up to 1 mg chromium per day over several months, no adverse effects were observed. However, these studies were designed in order to record nutrient effects and not to determine toxic effects (Anderson et al., 1997b; Campbell et al., 1999; Clancy et al., 1994; Hallmark et al., 1996; Hasten et al., 1992; Kato, et al., 1998; Lukaski et al., 1996; Pasman et al., 1997; Thomas and Gropper, 1996; Walker et al., 1998; Wilson and Gondy, 1995). Here, too, the data obtained from animal experiments indicate that relatively high oral doses of trivalent chromium compounds are tolerated without any adverse effects.

In the Ivankovic and Preussmann Study (1975) frequently used in the past for toxicological assessments of chromium, doses of up to 1500 mg Cr per kilogram body weight were tolerated over 840 days, 5 days a week, in rats without any adverse effects. However, no reasonable NOAEL can be derived from this study because the chromium compound administered was a pigment which was not soluble in water (Cr_2O_3). The competent bodies have not derived a NOAEL from other studies either up to now for trivalent chromium compounds.

The studies available so far on kidney, liver and reproduction toxicity of chromium III and on interactions with DNA do not permit the derivation of a LOAEL or NOAEL either. This was reason enough for the US Food and Nutrition Board (FNB) to refrain from deriving an upper intake level for soluble chromium III salts. FNB explicitly calls for more research on the health assessment of high chromium intakes because of the widespread use of chromium supplements. It advises caution when adding chromium to supplements until corresponding data are available (US-FNB, 2001).

17.3.2 Deficiency, possible risk groups

17.3.2.1 Deficiency

Up to now, a chromium deficiency has only been observed in patients with persistent parenteral nutrition without chromium supplementation. The deficiency symptoms (impaired glucose tolerance and glucose utilisation, weight loss, neuropathy and abnormalities in nitrogen metabolism) were reversible and disappeared rapidly after the administration of 250 µg chromium in the form of chromium(III) chloride ($CrCl_3$) (Freund et al., 1979; Jeejeebhoy et al., 1977). In animal experiments a chromium deficiency led to a glucose intolerance, similar to diabetes mellitus. Other symptoms included delayed growth and elevated serum cholesterol levels (Anderson, 1988).

17.3.3 Possible risk groups for insufficient dietary intake

Aside from the above-mentioned patients on parenteral nutrition, no other risk groups are known.

For the Federal Republic of Germany there are no signs of inadequate chromium intake. However, no representative food consumption data are available (supply category 2).

17.4 Tolerable upper intake level for chromium

Chromium(III) compounds have been shown to have low toxicity even after repeated oral administration. However, in the opinion of the international evaluatory bodies the data available up to now for human beings and from animal experiments are not sufficient in order to set a UL as the safe upper level for total intake. Instead, there is a series of recommendati-

ons for the range of chromium intake where it is assumed that it does not lead to any adverse effects (SCF, 2003; US-FNB, 2001).

From the rat study by Anderson et al. (1997a) the UK EVM derives a total intake of approximately 0.15 mg/kg body weight (or 10 mg/person) that is assumed to have no adverse effects. It uses this value as a guidance level for the safe intake of trivalent chromium, whilst, again at the same time, expressly excluding chromium picolinate (UK EVM, 2003).

Only recently after evaluating various studies in human beings, SCF came to the conclusion that chromium doses of up to 1 mg/day from supplements can be considered safe and have no adverse effects. Because of the ongoing gaps in knowledge about the toxicity of chromium picolinates, this assessment explicitly does not apply to these organic chromium compounds (SCF, 2003).

By contrast, WHO assumes that chromium supplementation of 250 µg/day should not be exceeded (WHO, 1996).

17.4.1 Derivation of a maximum level for trivalent chromium (not including chromium picolinate) in food supplements.

The derivation of a maximum level is not based on quantitative risk assessment because corresponding data are not available. BfR, therefore, proposes maintaining the upper level of **60 µg/daily portion** recommended in 1996 by its precursor institute (BgVV).

> **Advantages**: The advantages of this option are firstly continuity in practice, secondly compliance with the range indicated by WHO in 1996 which should not be exceeded and thirdly the guarantee of sufficient nutritional-physiological covering of requirements. No increase in positive effects is to be expected from higher doses.
>
> **Disadvantages**: None

17.4.2 Derivation of a maximum level for trivalent chromium (not including chromium picolinate) in fortified foods

As outlined at the beginning of the Chapter, there is scientific agreement that the results from previous studies on the toxicity of chromium III do not permit the derivation of a LOAEL or a NOAEL. This means that neither the EU SCF, the US FNB nor the UK EVM was able to indicate a UL for chromium. For that reason and because of the ongoing uncertainty about the assessment of longer-term chromium supplementation, a change to existing practice that does not envisage the addition of chromium to conventional foods, cannot be advocated.

17.4.2.1 Chromium picolinate

By contrast, the increasingly observed use of chromium as chromium picolinate in food supplements must be assessed differently. There are several case studies in human beings which draw attention to a series of adverse effects (Cerulli et al., 1998; Huszonek,1993; Martin and Fuller, 1998; Reading und Wecker, 1996; Wasser et al., 1997; Young et al., 1999). Several *in vitro* studies also point to toxic effects of chromium picolinate (Speetjens et al., 1999; Stearns et al., 1995b; Stearns et al., 2002; Vincent, 2000b; 2003; Voelker, 1999). Furthermore, they stress that chromium is likely to accumulate in individual tissues (Stearns et al., 1995a).

The EU Scientific Committee on Food (SCF) states that data on the bioavailability of organically bound chromium are of decisive importance for the assessment of chromium picolinate. They go on to comment that as long as no adequate data are available, a statement on the

admissibility of the use of these chromium compounds in foods for special nutritional purposes (PARNUTS) is not possible (SCF, 1999).

The remaining uncertainty about the assessment of chromium picolinates also prompted BfR to continue to reject the use of these compounds in foods. In this context "compelling reasons of health protection" must also be enforced not only in the case of proven health damage or risks but also in terms of the fundamental principle of risk minimisation in cases of suspicion in which health risks cannot necessarily be proven but are described as possible in scientific discussions. In Germany therefore, all general dispositions issued in accordance with § 47a Foods and other Commodities Act (LMBG) for the use of chromium picolinate in food supplements have been revoked (BMVEL, 2001).

BfR estimates the health risk from the use of chromium (with the exception of chromium picolinate) in foods to be low. Given the inadequate data situation a risk cannot, however, be reliably ruled out. For reasons of preventive health protection, BfR is of the opinion that the current upper level of 60 µg per daily dose of a food supplement should be maintained and that no chromium should be added for the purposes of food fortification.

17.5 Gaps in knowledge

- Through its effect on insulin activity, chromium III intervenes in the metabolism of carbohydrates, lipids and proteins. Further studies are needed to clarify the exact mechanism of action of the chromium-binding substance and its physiological functions.
- Studies to clarify the toxicological questions which have still to be answered about chromium picolinate should be encouraged and supported.
- There are no adequate, representative data available on chromium intake, particularly intake which includes the consumption of food supplements and fortified foods within various groups in the population. The development of methods to record chromium nutritional status would be helpful in this respect.

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18 Risk Assessment of Molybdenum

18.1 Summary

For the population of the Federal Republic of Germany there are no indications of inadequate molybdenum intake. However, it is still unclear which levels of daily intake are needed to meet human requirements (that is why only estimated ranges of adequate intake are given). And additionally, no representative data on daily molybdenum intake of the German population are available.

Deviating tolerable upper intake levels derived by three renowned scientific bodies (SCF, FNB, EVM) highlight uncertainties concerning the risk assessment of nutrients. In line with the precautionary principle, the lowest numerical UL derived by the above-mentioned bodies for adults is taken as the basis for the derivation of maximum levels of molybdenum in food supplements and fortified foods, that is the UL set by SCF of 600 µg/day. According to the risk classification of nutrients taken over by BfR, molybdenum is therefore to be assigned to the risk class "moderate risk".

As no representative data are available in Germany about molybdenum intakes in the upper percentile range (95 and 97.5 percentiles), the proposed formula-based derivation of maximum levels in food supplements and fortified food is not applicable here. Concomitantly, there is uncertainty about whether and, if so, on what scale current molybdenum intake in the 95 or 97.5 percentile can be elevated without exceeding the UL. Given this uncertainty maximum levels in food supplements and fortifications modes of foods that would lead to increases in the current daily intakes cannot be advocated. It is, therefore, proposed that the addition of molybdenum to food supplements be restricted to a daily maximum level of 80 µg. However, products of this kind should be labelled as unsuitable for children up to the age of 10. As in the past, it should be abstained from molybdenum addition to conventional foods.

Estimated values for adequate intake	50-100 µg/day
Intake [µg/day]	**m** **w**
Median	? * ? *
P 2.5	? * ? *
P 97.5	? * ? *
	* No representative intake data for the Federal Republic of Germany
Tolerable Upper Intake Level	600 µg/day
Proposals for **maximum levels** in:	
Food supplements	80 µg/daily dose (not for children up to age 10)
Fortified foods	No fortification

18.2 Nutrient description

18.2.1 Characterisation and identification

Molybdenum (CAS No. 7439-98-7) is one of the transition elements and occurs in various oxidation levels whereby Mo^{IV+} and Mo^{VI+} are the main ones. Molybdenum compounds, which may be added to foods for special dietary purposes and food supplements and that have been proposed for the fortification of foods include: sodium molybdate (dihydrate: CAS No. 10102-40-6) and ammonium molybdate (anhydrate: CAS No. 13106-76-8; tetrahydrate: CAS No. 12054-85-2) (Ordinance on Foods for Special Dietary Uses; Ordinance on Food Supplements and Amendment to the Ordinance on Vitaminised Foods; Commission of the European Communities, 2003).

18.2.2 Metabolism, functions, requirements

Molybdenum is absorbed in the small intestine where, depending on the molybdenum source, absorption rates of around 35% up to 90% were observed in human beings (Turnlund et al., 1995; 1999; Werner et al., 1998). Excretion is related to dietary intake and mainly occurs by kidney, less by gallbladder and gastro-intestinal tract (Food Standards Agency, 2002).

In human organisms molybdenum is part of the enzymes sulphite oxidase, xanthine oxidase/dehydrogenase and aldehyde oxidase by forming "molybdenum cofactor" a complex of molybdenum and molybdopterin. It is involved for instance in the degradation of sulphur-containing amino acids and detoxification of sulphite to sulphate or purine degradation to uric acid (Food Standards Agency, 2002; Rajagoplan, 1988).

Interactions between molybdenum and copper and sulphate ions with adverse effects on molybdenum and copper absorption have been reported (Food Standards Agency, 2002).

It is still not clear which levels of daily molybdenum intakes are really needed to met human requirements. For that reason only D-A-CH estimated ranges for adequate intake can be given. For adolescents and adults the estimated range of adequate intake is 50-100 µg/day, for children (1-15 years of age) the ranges depending on age are between 25-50 µg/day (1-4 years of age) and 50-100 µg/day (10-15 years of age). No special estimated ranges are given for pregnant or lactating women (D-A-CH, 2000).

18.2.3 Exposure (dietary and other sources, nutritional status)

Sources: Molybdenum-rich food groups are pulses, nuts and cereals (Pennington and Jones, 1987). According to studies from Germany and USA bread and bakery groups, with more than 40% (Germany) and cereal products with more than 30% (USA) contribute most to the molybdenum intake of adults (Glei et al., 1994; Pennington and Jones, 1987).

Nutritional status: With regard to current intake levels, reference is made to a five-country study (not including Germany) from 1991. Standardised to an energy intake of 10 MJ/day, median molybdenum intakes of 80-250 µg/day were reported. With 83 µg/day they were lowest in Italy and Spain and highest in Iran with 247 µg/day (Parr et al., 1991). Insight into the situation in Germany can only be gained from a regional study with a small number of subjects from 1996. In this study conducted in Thuringia mean intakes of 89 and 100 µg/day were measured for women and men on a mixed diet (n=62) and 179 and 170 µg/day for female and male vegetarians (n=20) (Holzinger et al., 1997; 1998).

There are no indications of inadequate molybdenum intake for the German population. However, valid and adequately evaluated biomarkers to record molybdenum status are not yet available (IOM, 2002).

There are no representative data concerning the molybdenum intakes achieved in Germany in the upper ranges of intake (95 and 97.5 percentiles of intake). For the United Kingdom a value of 210 µg/day is given for the 97.5 percentile without taking into account intake by drinking water (230 µg/day included calculated intake from drinking water) (Food Standards Agency, 2003). There are also some indications from WHO data based on data reported in literature according to which the 90 percentile of human intake was 260 µg/day. Maximum intake was given as 520 µg/day (WHO, 1996)

There are no indications of inadequate molybdenum intake for the population of the Federal Republic of Germany. However, it is still unclear which molybdenum intakes are actually needed to meet human requirements. Nor are any representative data available on the level of molybdenum intake (supply category 2).

18.3 Risk characterisation

18.3.1 Hazard characterisation (NOAEL, LOAEL)

Overall there are no systematic or adequately designed studies on the impact of long-term elevated molybdenum intakes in human beings which can be used for risk assessment (SCF, 2000). Hence, studies in animals are of particular importance.

Gout-like symptoms with arthralgia of the knee and certain joints in the hands and feet as well as hepatomegaly were observed in human beings in Armenia in an area with high molybdenum intake (10-15 mg/day molybdenum, 5-10 mg/day copper). Compared with individuals who showed no symptoms or compared to a control group from another region, the affected individuals had elevated serum uric acid levels, hyperuricosuria and elevated molybdenum blood levels. For regions outside the area concerned, the authors indicated daily molybdenum intakes of 1-2 mg and copper intakes of 10-15 mg (Kovalsky et al., 1961). However, the validity of this study is challenged by FNB and SCF on the grounds of methodological shortcomings (IOM, 2002; SCF, 2000).

In conjunction with the short-term intake of 1.5 mg molybdenum/day, Deosthale and Gopalan (7 days, 4 subjects) did not observe any elevated renal uric acid excretions nor did Turnlund et al. (24 days, 4 subjects) observe any effects on serum uric acid levels (Deosthale and Gopalan, 1974; Turnlund et al., 1995). In conjunction with increasing molybdenum intake (160 µg molybdenum/day versus 540 µg molybdenum/day), Deosthale and Gopalan observed effects on copper metabolism with elevated serum levels and elevated renal copper excretion whereas Turnlund and Keyes did not observe any impact on copper metabolism from higher molybdenum intakes (1.5 mg/day) (Deosthale and Goplan, 1974; Turnlund and Keyes, 2000).

Respiratory intake of molybdenum-containing dust (calculated intake approximately 10 mg/day) in workers in a molybdenum-processing factory was linked to elevated serum ceruloplasmin levels as well as slightly elevated serum uric acid levels. The employees were found to be suffering from medical complaints. Corresponding epidemiological assessment was not, however, possible because of the high turnover rate of workers (Walravens et al., 1979).

In animal experiments reproduction and development disturbances were found to be the most critical and most sensitive indicators of elevated molybdenum intakes. In rats which were given increasing doses of molybdenum in drinking water (0, 5, 10, 50, 100 mg/l), Fungwe et al. observed prolonged estrus cycles, decreased body weight gains during gestation, lower weights of litter, increased rate of fetal resorption and delayed fetal developments with levels of = 10 mg/l (Fungwe et al., 1990). From data on the level of molybdenum intake from drinking water and based on some assumptions Vyskocil and Viau (1999) calculated daily intakes of 0.91, 1.6, 8.3 and 16.7 mg molybdenum/kg body weight/day for the above-mentioned drinking water levels. They derived a NOAEL of 0.9 mg molybdenum/kg body weight/day and a LOAEL of 1.6 mg molybdenum/kg body weight/day. In conjunction with the administration of feed with a molybdenum content of 20 mg/kg and 5 mg/kg copper Jeter and Davis (1954) observed significant growth depression in male rats. Molybdenum levels of 80 mg/kg feed led in some male animals to infertility and testicular degeneration and in female animals to growth depression. From these results and based on some assumptions Vyskocil and Viau (1999) derived a LOAEL for growth depression in male rats of 2 mg molybdenum/kg body weight/day. For female rats the NOAEL for growth depression was 2 mg molybdenum/kg body weight/day. In mice fed 10 mg/l molybdenum in drinking water Schroeder and Mitchener (1971) observed early deaths in offsprings, dead litters, maternal deaths and, in some cases, failure to breed. According to calculations by Vyskocil and Viau (1999) the

administered amount of molybdenum corresponds to approximately 1.5 mg molybdenum/kg body weight/day.

By way of summary, both SCF and the American Food and Nutrition Board (FNB) come to the conclusion that no adequate human data are available for the derivation of a tolerable upper intake level for molybdenum. Both bodies consider reproductive disturbances in rats to be the most sensitive indicator of elevated molybdenum intakes and both derive a NOAEL of 0.9 mg molybdenum/kg body weight/day based on the study by Fungwe et al. (IOM, 2002; SCF, 2000).

18.3.2 Deficiency, possible risk groups

There have been no reports of a molybdenum deficiency in healthy individuals. For humans deficiency symptoms have been reported in individual cases in conjunction with total parenteral nutrition and in children with rare congenital metabolic disorders (Abumrad et al., 1981; Food Standards Agency, 2002).

18.3.3 Excessive intake, possible risk groups

Elevated molybdenum intakes resulting from the consumption of conventional foods have only been reported in a limited regional way up to now (Kovalsky et al., 1961). For more information on the adverse effects observed, please refer to Chapter 18.3.1 "Hazard characterisation (NOAEL, LOAEL)".

18.4 Tolerable upper intake level for molybdenum

Based on a NOAEL (0.9 mg molybdenum/kg body weight/day) derived from a study in rats, SCF, applying an uncertainty factor of 100, derived a tolerable upper intake level (UL) of 0.01 mg molybdenum/kg body weight/day corresponding to an intake of 600 µg/day for adults. The uncertainty factor encompasses a factor 10 in order to protect possible risk groups with inadequate copper intakes or deficient copper metabolism in view of the species-dependent differences in the antagonism of molybdenum and copper. A further factor 10 seeks to reflect the gaps in knowledge about the reproductive effects of molybdenum and about toxicokinetic data (SCF, 2000).

Particular tolerable upper intake levels have been derived for children and adolescents as adverse effects on growth were observed in young animals (Jeter and Davis, 1954; SCF, 2000). On a body weight basis and applying the UL for adults, the following ULs broken down into age groups were extrapolated: 1-3 years = 0.1 mg/day, 4-6 years = 0.2 mg/day, 7-10 years = 0.25 mg/day, 11-14 years = 0.4 mg/day and 15-17 years = 0.5 mg/day (SCF, 2000).

In contrast to SCF the American Food and Nutrition Board (FNB) derived a UL for adults of 2 mg/day based on the same NOAEL (0.9 mg molybdenum/kg body weight/day) but with an uncertainty factor of 30 (factor 10 for the extrapolation animal-human being, factor 3 for intraspecies variations) (IOM, 2002).

Unlike the above-mentioned scientific bodies the British Expert Group on Vitamins and Minerals (EVM) did not derive a safe upper level for molybdenum or a scientifically less secured guidance value given the inadequate data. This Group does, however, assume that the maximum dietary intake observed in the United Kingdom (0.23 mg/day) does not constitute a risk to health (Food Standards Agency, 2003).

The deviating derivations of tolerable upper intake levels by three renowned scientific bodies (SCF, FNB and EVM) despite the same data balance, highlight the degree of uncertainty

concerning the risk assessment of molybdenum. BfR upholds the precautionary principle and takes the lowest numerical UL for adults, derived by the above-mentioned bodies, as the basis for its considerations on the derivation of maximum levels for molybdenum in food supplements and fortified foods, i.e. the SCF value of 600 µg/day.

18.4.1 Derivation of a maximum level for molybdenum in food supplements and fortified foods

Very little information, which is not representative either, is available on molybdenum intakes in Germany. Mean intakes of 90-100 µg/day from a conventional diet and 170-180 µg from a vegetarian diet are quoted. Study results on molybdenum intakes in Germany in the upper percentile range (95 and 97.5 percentile intake) are not available (see Nutritional status, Chapter 18.2.3). For this reason the proposed formula-based procedure for the derivation of maximum levels in food supplements and fortified foods is not applicable here. Concomitantly, there is uncertainty about whether and, if so, on what scale the current molybdenum intake in the 95 or 97.5 percentile can be increased without exceeding the UL. Given the uncertainty, maximum levels in food supplements and modes of food fortification leading to increases in current daily molybdenum intakes cannot be advocated. There are no scientifically backed reasons for extending the current practice of molybdenum addition to food supplements and conventional foods.

The uncertainties described above concerning daily molybdenum intakes also apply to children and adolescents. For precautionary reasons, particularly as growth depressions were observed in animal experiments, we consider it is necessary to establish at least alternatively some basic calculations in order to be able to roughly estimate for these age groups possible exceedences of the UL through proposed daily maximum levels of molybdenum in food supplements. These calculations are based – for want of a better calculation basis – on the median daily molybdenum intakes (83 µg/10 MJ) obtained by Parr et al. (1991) for two European countries (Italy, Spain) using a dupliate method and the daily energy intakes detected in the National Food Consumption Study (in each case 97.5 percentile of male subjects) [*)] (Adolf et al., 1995).

18.4.1.1 Possible management options

18.4.1.1.1 Food supplements

a) Adherence to the current maximum levels

   At present, 80 µg molybdenum per recommended daily portion are accepted in food supplements (BgVV, 1999; 2002). Experience is already available with this maximum level. Despite the lack of corresponding studies it can be assumed that no health risks are to be expected for adults with this molybdenum levels.

   However, with this maximum level in children of various ages it cannot be ruled out that the additional consumption of molybdenum-containing food supplements can lead to an exceeding of the relevant tolerable upper intake level (see below).

b) Adherence to the current maximum levels for adults and a label advisory statement regarding children up to age 10

   For adult consumers the same applies as in Option a.

With regard to children and adolescents it should be noted that when using the above-mentioned calculation and assuming additional intake of up to 2 molybdenum-containing

[*)] 4-6 years: 11.9 MJ/day; 7-9 years: 13.6 MJ/day; 10-12 years: 16.2 MJ/day; 13-14 years: 19.5 MJ/day; 15-18 years: 20.0 MJ/day

food supplements per day with maximum levels of 80 µg, the tolerable upper intake level for 4-10 year-old children will be exceeded (children aged up to 3 were not taken into account).

For precautionary reasons food supplements with a recommended daily intake of 80 µg molybdenum should be labelled as unsuitable for children up to age of 10.

18.4.1.1.2 Fortified foods

Because of the uncertainties outlined above, an extension of the current practice of adding molybdenum to conventional foods cannot be advocated. Hence, as in the past, it should be abstained from the addition of molybdenum to conventional foods for fortification purposes.

In line with the risk classification of nutrients taken over by BfR, molybdenum is to be assigned to the risk class "moderate risk". Because of the existing uncertainties there is no scientific justification for extending the current practice of molybdenum addition to food supplements and fortified foods. BfR continues to recommend restricting molybdenum addition to food supplements to 80 µg per recommended daily portion. However, products of this kind should be labelled as unsuitable for children up to age of 10 (Option b). As in the past, it should be abstained from fortification of conventional foods with molybdenum.

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