

**Position of the BLL
of 12 September 2006**

regarding the dossier of the BfR on
Use of Vitamins and Minerals in Foods – Toxicological and
Nutritional-Physiological Aspects
Parts 1 and 2, 2004

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I. Background

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, and the "Proposal for a Regulation of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to foods", call for setting of standards for maximum levels of vitamins and minerals that may be added to food supplements and to fortified foods.

Such maximum levels are to be established in order to fulfill the aims of ensuring the free movement of goods and of protecting consumers from adverse effects on health. The standards for maximum levels are to ensure that products are safe when used normally.

To this end, the directive on food supplements, and the Proposal for a Regulation on the addition of vitamins and minerals and certain other substances to foods, define the bases and the means that are to be used in deriving maximum levels:

- upper safe levels of vitamins and minerals established by scientific risk assessment, and
- intakes of nutrients from other dietary sources (Article 5 (1) Directive 2002/46/EC and Article 6 (3) of the Proposal for a Regulation on fortification).

Reference levels for nutrient intake are also to be taken into account (Article 5 (2) of Directive 2002/46/EC and Article 6 (4) of the Proposal for a Regulation). In the opinion of the BLL, these should be used for deriving maximum levels only in cases in which they contribute to assessment of safety. This is made clear by the recitals.

In preparation for establishment of maximum levels, the European Food Safety Authority (EFSA), and the European Commission's former Scientific Committee on Food (SCF), have already carried out extensive work relative to derivation of Tolerable Upper Intake Levels (ULs), i.e. of "upper safe levels".

The UL for a nutrient refers to the amount of the nutrient that can be taken daily – i.e. chronically – from all sources, judged to be unlikely to pose a risk of adverse health effects to humans (SCF, 2000). In most cases, the UL is derived via determination of the relevant NOAEL (no observed adverse effect level), in combination with an uncertainty factor >1. In practice, this means that the risk of negative impacts does not increase as soon as the UL is exceeded once; that risk increases only when the NOAEL is chronically exceeded.

In Europe, maximum levels are established pursuant to Articles 5 and 7 of Council Decision 1999/468/EC, also with regard for that provision's Article 8. Consequently, establishment of such maximum levels is an implementational measure with which the Commission will be charged in the regulatory procedure. It must take its pertinent decisions on the basis of suitable scientific consultation, and it must take the above-

described criteria that are set forth in the Directive and in the Proposal for a Regulation (recital 16 of the Directive on food supplements).

In June 2006, the European Commission published a first relevant proposal for discussion. This paper does not contain explicit proposals relative to specific levels. Instead, it outlines the areas that, in the Commission's view, should be discussed in connection with derivation of maximum and minimum levels. In other words, the initial focus is on the basic approach that should be taken. In this regard, the Commission also notes, with regard to the question of the manner in which safety is to be guaranteed, that provisions under primary law – including the proportionality principle – are to be applied.

With respect to the discussion, which is to be carried out on a European level, in January 2005 the Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung (BfR; in Berlin) presented a comprehensive report on use of vitamins and minerals in foods. This report is to be understood as a basis for discussion and as an aid in making decisions relative to determination of maximum levels of relevant substances in food supplements and fortified foods. The relevant dossiers identify options for action and describe the advantages and disadvantages of each option. Lawmakers can choose any of the options outlined, in keeping with the level of protection they are seeking to achieve. The BfR's preferred choice, among the available options, is normally the restrictive option.

The following remarks respond to the BfR's proposal, from the perspective of the German food sector.

II. General remarks relative to the BfR's report

1. The BfR's risk-management model

The BfR's report is divided into two parts: In the first of these, the introduction, a risk-management model for calculation of maximum levels is developed. This model may be summarized as follows:

Maximum daily quantity of food supplement/ =	$\frac{UL - (\text{intake via normal diet} + \text{fortified foods})}{2}$
Quantity consumed daily	
Maximum level for =	$\frac{UL - (\text{intake via normal diet} + \text{food supplements})}{2}$
fortified foods / serving	

The intake via normal diet and via fortified foods and food supplements is deducted from the tolerable upper intake level, the UL. In principle, the difference is then available for food fortification and for intake via food supplements; it is the quantity of vitamins and minerals from fortified foods and food supplements that can be safely consumed. To estimate multiple intake of a nutrient from food supplements and fortified foods, the BfR divides the aforementioned difference, in each case, by a factor of 2.

The main section of the report then provides a risk assessment for each nutrient in question. It also includes action options relative to maximum levels. It should be noted that the BfR's proposed model is seldom used in derivation of maximum levels of the various vitamins and minerals, however. Only in a few cases (vitamin D, vitamin K, vitamin B₆, folic acid, vitamin C, potassium, zinc, magnesium) is the model used to calculate maximum levels for food supplements. And in only three of these cases (vitamin B₆, potassium and zinc) is the level calculated using the formula also the BfR's preferred option for the maximum level. What is more, the UL for potassium is a value derived by the BfR for supplements. In no instance is the model used to calculate maximum levels for fortified foods.

In sum, the model is rejected for the following reasons (Domke et al., 2004 p. 22; BfR, 2006; Großklaus 2006):

- (1) Neither the SCF nor the EFSA was able to derive a UL, or the relevant work was not completed at the time of writing (beta-carotene, Vitamin C, manganese, chromium, phosphorous, iron, sodium, chloride, B₁, B₂, B₁₂, vitamin K, pantothenic acid, biotin)

- (2) Insufficient data are seen to be available relative to alimentary intake of vitamins and minerals (fluoride, selenium, molybdenum, nicotinamide, manganese)
- (3) The therapeutic dose is considered exceeded (vitamin K) or
- (4) The BfR claims to have justified reservations about previously defined ULs of the EFSA (vitamin E, iodine).

Rejection of the model then leads to specific considerations. The recommended maximum level is normally the restrictive choice among the available options. It is often oriented to previous recommendations of the BfR. In such cases, the BfR's recommendations are based on considerations of nutrition physiology. Such considerations are central to the BfR's focus: "*Whenever the model was not applicable, maximum levels were determined on the basis of physiological and nutritional considerations*" (BfR, 2006).

In the case of **food supplements**, some of the BfR's recommendations lie below the levels that have been previously recommended, that have been permitted in the framework of general decrees or that are permissible in the framework of Annex 6 to the Ordinance on foods for special dietary purposes (DiätV). It is recommended that some nutrients not be used in food supplements; cf. the following table:

Vitamins

		BfR 2004 (preferred option)	BgVV 1998* (three-fold rule with the exception of vitamins A and D)	General Exemption** (Hagenmeyer, et al.2003)
Vitamin A	µg	400 (adults)		800, 900, 2400
Beta-carotene	mg	2		
Vitamin D	µg	5		5; 2,5
Vitamin E	mg	15	36	58,3; 36
Vitamin K	µg	80	240	
Vitamin B ₁	mg	4	4,8	3
Vitamin B ₂	mg	4,5	5,4	3
Niacin	mg	17 (nicotinamide)	60	
Vitamin B ₆	mg	5,4	6,3	15

Folic acid	µg	400	900	300
Pantothenic acid	mg	18	18	
Biotin	µg	180	300	100
Vitamin B ₁₂	µg	3 - 9	9	
Vitamin C	mg	225	225	

*Federal Institute for Health Protection of Consumers and Veterinary Medicine (precursor of BfR)

**"Allgemeinverfügungen" according to § 54 LFGB; general exemption of permission for the import of food legally produced in the EU member states

Minerals

		BfR 2004	BgVV 1998* Simple rule, trace elements: special rule	General Exemption** (Hagenmeyer, et al.2003)
Sodium	mg	0		
Chloride	mg	0		
Potassium	mg	500		
Calcium	mg	500		800
Phosphate	mg	250		
Magnesium	mg	250		400
Iron	mg	0	5	6
Iodine	µg	100	100	100
Fluoride	mg	0		
Zinc	mg	2,25	5	13,2
Selenium	µg	25 - 30	30	30
Copper	mg	0	1	1
Manganese	mg	0	2	1,44
Chromium	µg	60	60	60
Molybdenum	µg	80	80	80

*Federal Institute for Health Protection of Consumers and Veterinary Medicine

**"Allgemeinverfügungen" according to § 54 LFGB; general exemption of permission for the import of food legally produced in the EU member states

As to **fortification**, in many cases it is recommended that no vitamins and minerals whatsoever be added – in a position that contrasts with the basic permissibility of fortified foods in the Proposal for a Regulation. This applies to

- **Vitamin A** (with the exception of margarine and mixed-fat products), beta-carotene
- **Vitamin D** (with the exception of margarine and mixed-fat products and cooking oils)
- Sodium (with the exception of beverages designed especially to replenish the substance in healthy consumers who lose considerable amounts of it), potassium (with the exception of use for replenishment), **chloride, phosphate**
- **Calcium** (with the exception of foods serving as dairy substitutes)
- **Iron, zinc, selenium, copper, manganese and chromium and molybdenum.**
- **Iodine** (with the exception of iodized salt) and **fluoride** (with the exception of table salt).

With regard to beta-carotene and calcium, nutrients are thus affected that have heretofore been permitted in fortified foods.

Conclusion 1:

In principle, the BfR's model is welcomed, since it conforms to the Directive's requirements. The BLL regrets that this model is rejected in the great majority of cases, however: for only a few nutrients is the formula used to calculate a possible maximum level, and for only three nutrients (vitamin B₆, potassium and zinc) has the resulting quantity been presented as the preferred option for maximum levels in food supplements. In those cases in which the model is not used, nutritional and physiological aspects are placed at the center of considerations – in contravention of the provisions of the Directive and of the Proposal for a Regulation. The resulting levels are restrictive in nature. From the perspective of the BLL, it is not always clear why the model was rejected and, thus, why derivation on the basis of other considerations was recommended. The following remarks comment on these aspects.

2. The lack of a Tolerable Upper Intake Level (UL) of the SCF or of the EFSA

One of the reasons advanced for rejecting the risk-management model is that neither the SCF nor the EFSA has derived a UL, or work for such derivation has not yet been completed.

The background to this argument is that over five years ago the European Commission commissioned the Scientific Committee on Food (SCF) to derive tolerable upper limits for daily intake of vitamins and minerals (ULs). In 2002, the European Food Safety Authority (EFSA) assumed responsibility for continuing the SCF's work. At the time the BfR's report was prepared, the great majority of nutrients had already been assessed; in the meantime, the planned assessments have been completed, and a compendium has been published (SCF/NDA, 2006). In a range of cases, no UL was derived. The reasons for such failure to derive a UL vary:

- No adverse effect was identified (thiamine, riboflavin, biotin).
- No adverse effects were observed at certain levels (vitamin K, 10 mg; Vitamin B₁₂, 1-5 mg; chromium, 1 mg), but overall the available data did not support derivation of a UL.
- While an adverse effect was considered possible, not enough pertinent data was available to substantiate this presumption (pantothenic acid in gram doses).
- An adverse effect was identified, but the available data was inadequate with regard to dose-effects relationships (manganese, beta-carotene, vitamin C, sodium, potassium, chloride, phosphate, iron).

In the BLL's view, all of the EFSA's findings relative to a nutrient must be taken into account in deriving maximum levels for that nutrient. The lack of a UL does not directly justify the nutritional approach taken by the BfR.

For example, for nutrients for which no adverse effects were observed, even though sufficient data was available, it may well be asked – also in light of the recitals of Directive 2002/46/EC and of the Proposal for a Regulation, with their focus on protecting consumers from adverse effects – whether it is even necessary to establish a daily maximum level (thiamine riboflavin, biotin). In any case, it seems ill-advised to propose that these nutrients be managed restrictively, simply because it was not possible to establish pertinent ULs – even though adequate data was available. What is more, recital 13 of the Directive and recital 15 of the Proposal for a Regulation do not provide for maximum and minimum levels for all nutrients as such: levels are to be derived "as/where appropriate" – namely, whenever protection against adverse effects is required.

For the same reason, it does not seem absolutely necessary to derive daily maximum levels for – and, thus, to apply a relevant formula to – nutrients for which the SCF / the EFSA have observed no adverse effects even at very high doses far in excess of current consumption levels and of levels currently found in fortified foods and in food supplements (chromium, vitamin K, pantothenic acid, vitamin B₁₂).

Furthermore, internationally, scientific bodies in addition to the SCF and the EFSA – such as the U.S. Food and Nutrition Board (FNB) - have concerned themselves with risk assessment relative to vitamins and minerals. For this reason, in those cases in which the EFSA's assessment was still pending at the time when the BfR's proposal was prepared, it could be useful, in principle, to use the ULs from such other assessment within the BfR's model. This could apply, for example, to

- Iron UL (FNB) = 45 mg
- Fluoride UL (FNB) = 10 mg
- Manganese UL (FNB) = 11 mg
- Vitamin C UL (FNB) = 2000 mg.

After all, the Directive does not explicitly refer to the EFSA; it simply states that the outset basis should consist of scientific risk assessment on the basis of generally accepted data.

Conclusion 2:

From a legal standpoint, the automatism applied by the BfR (lack of ULs from the EFSA = nutritional approach) cannot be justified. The totality of all findings from scientific risk assessment is relevant. And even the recitals of the Directive on food supplements and of the Proposal for a Regulation do not require that maximum levels be derived for every nutrient. For a range of different nutrients, the SCF/EFSA provide sufficient evidence that no adverse effects are to be expected. What is more, ULs of other scientific bodies – such as the U.S. Food and Nutrition Board (FNB) – may be used in a relevant model in cases in which a UL of the SCF / the EFSA is lacking. This holds, since Directive 2002/46/EC does not refer explicitly to the EFSA; instead, it speaks of "upper safe levels of ... vitamins and minerals, as established by scientific risk assessment based on generally acceptable scientific data", that are to be used in derivation.

3. Data on alimentary intake of vitamins and minerals

The BfR also justifies its approach by emphasising the lack of available data on alimentary intake of certain nutrients. There is indeed a lack of representative data, for the population of Germany, on each of the nutrients listed in the Annexes to the Directive, especially of data that

- are differentiated by sources (foods, fortified foods, food supplements),
- provide information about various different age groups, and
- include information about distribution (for example, 90th/95th/97.5th percentile).

Future surveys will have to take such aspects into account. Needless to say, common methodology throughout all of Europe would be useful (Pan European Survey).

With regard to the data available in Germany (GNHIES 1998, NVS 1985-1988, EPIC, MONICA, nutrition surveys of Saxony and Bavaria, DONALD), we refer to the BLL's position of 18 August 2006 regarding the Commission's discussion paper.

It is correct that there is a lack of representative data on **food fortification** in Germany. Information on intake of fortified foods and food supplements, by children and adolescents living in Dortmund, is available – from the Research Institute of Child Nutrition (Forschungsinstitut für Kinderernährung; in Dortmund, DONALD-Studie).

To estimate intake of beta-carotene from beverages, the Association of the German Fruit Juice Industry (Verband der deutschen Fruchtsaft-Industrie e. V.; VdF), the Association of German Mineral Water Producers (Verband Deutscher Mineralbrunnen e. V.), the Association of the German Non-alcoholic Beverage Industry (Wirtschaftsvereinigung Alkoholfreie Getränke e.V.; wafg) and a number of relevant raw-material producers took the initiative and evaluated pertinent data in cooperation with GfK Marketing Services' retail and household panels. The question they were exploring involved the levels of beta-carotene consumed via non-alcoholic beverages – the product group of greatest relevance for beta-carotene intake. In their investigation, they applied a "worst-case" scenario: Firstly, it was assumed that relevant purchased beverages were consumed to a degree of 100% by their purchasers. Secondly, it was assumed that 5.2 % of all non-alcoholic beverages – the highest conceivable share - is actually fortified with beta-carotene. Thirdly, it was assumed that the maximum level of 2 mg/100 ml (voluntary commitment by industry; BLL 2001) was attained in every beverage. The group of households with the highest intake levels was studied.

The result was as follows: The theoretical average maximum intake of isolated beta-carotene from beverages, for the "heavy buyers" group, was 3.5 mg/day. This result showed that 98.4 % of the population was consuming less than 2 mg/day from such

products. A total of 1.37 % of the population (1.13 million people) was consuming more than 2 mg/day – if the conservative assumptions underlying the worst-case scenario are actually correct (AGV-V, 2004). The result shows that the amounts in question would not be relevant even for heavy smokers. These data were presented to the BfR in fall 2004. The BfR's recommendation that all addition of beta-carotene to fortified foods be discontinued should thus be reconsidered. With regard to the safety of beta-carotene, we call attention to the relevant BLL information sheet (BLL, 2006).

In contrast to the situation relative to fortified foods, representative data on intake of vitamins and minerals from **food supplements** were available at the time the BfR prepared its recommendations. Beitz et al. 2002 studied intake from supplements on the basis of data from the representative 1998 German National Health Interview and Examination Survey (GNHIES, Bundesgesundheitsurvey) (with reporting of the median, but no percentiles). The same raw data were used in an early evaluation by Mensink et al., 1999. That evaluation also gives the median for those consumers who regularly consume food supplements. Schellhorn et al., 1998 present medians for the MONICA study's data on intake of vitamins and minerals from food supplements, but also provide the highest and lowest measured values. The BfR cites the aforementioned literature without itself examining the relevant raw data.

At the BLL's initiative, the Robert Koch Institute evaluated the primary data from the German National Health Interview and Examination Survey (GNHIES, Bundesgesundheitsurvey) relative to intake of vitamins and minerals from supplements. This work focussed especially on the questions of intake of the same nutrient from more than one supplement ("multiple exposure") and of the total resulting intake of a relevant nutrient from regular diets and from food supplements for the population group with the highest intake (90th percentile). The results were published in November 2004 in the Federal Health Gazette (Bundesgesundheitsblatt) (Beitz et al., 2004). The data obtained is suitable for replacing the multiple exposure factor of "2", for food supplements, that the BfR applies on a general basis. Here we also refer to our remarks on p. 16 ff.

Conclusion 3: By no means are complete data available on intake of vitamins and minerals from all sources in Germany. Nonetheless, representative data are available on intake from food supplements that provide information about both intake quantity and multiple exposure. The industry has taken action also with regard to intake of beta-carotene from beverages. This model calculation, under the assumption of a worst-case scenario, shows – as does the evaluation carried out by the Robert Koch Institute – that intake of beta-carotene from fortified foods and multiple exposure to nutrients via food supplements are overestimated. These data should thus be taken into account. Generalizations are not justified – even with regard to European legislation.

4. Consideration of therapeutic doses

Exceeding of an (assumed) therapeutic dose is not a suitable criterion for establishing a maximum level permissible in food supplements in terms of the aspect of "safety": within a certain range, the quantity of a nutrient found in a product can be suitable both for supplementing a general diet and for serving as a medication – while still meeting criteria of "safety". Such overlapping between food supplements and medications was well-known when the Directive was issued. The solution chosen was to leave it up to producers themselves to determine the intended purposes for their products. This approach was taken in Art. 1 (1) No. 1 of the Food Supplements Ordinance (Nahrungsergänzungsmittel-Verordnung, NemV). The BfR's efforts to keep permissible levels of nutrients in food supplements below therapeutic-dose levels run counter to this legislative intent. In principle, as long as a product is safe, it may conceivably also be used as a food.

This assessment was confirmed by the European Court of Justice in its ruling of 9 June 2005 on the associated cases C-211/05, C-299/03, C-316/03 through C-318/03. Pursuant to the ECJ, the term "maximum safe levels" is of no relevance in classifying a product as either a food or a medication. No. 63 of the ruling states:

It must be noted that this term (maximum safe levels) as such plays no role in differentiation between medications and foods. On the one hand, it can be necessary to establish maximum safe levels for certain foods that cannot be considered medications. On the other hand, a product dispensed in quantities below the level of a possible maximum safe level could be a medication, in terms either of its function or of its designation."

Conclusion 4: Safety - and not the exceeding of an (assumed) therapeutic dose - is the key criterion for establishing maximum levels. Within certain ranges, some products can be both food supplements and medications – and such possibilities depend on the usage intended by the producer, as has been confirmed by the European Court of Justice. Where use of the BfR's model results in a quantity that is also used for therapeutic purposes, such a result cannot serve as justification for rejecting maximum levels that result from use of the model.

5. The BfR's reservation about the Tolerable Upper Intake Levels of the SCF / the EFSA

Another reason given for rejecting the risk-management model in the majority of cases is that some of the ULs of the SCF and of the EFSA are subject to doubt (p. 22 of the BfR's report). The ULs to which this applies include those for vitamin E and iodine.

From the perspective of the BLL, recourse to a national solution is unacceptable in cases in which the EFSA has carried out assessment via consensus – at a given time and with the available data. If revision of the EFSA's ULs is called for – for example, because of significant changes in the available data - we would urge that the Federal Republic of Germany present its pertinent concerns to the EFSA's bodies, in the interest of attaining a common approach for all of Europe.

With regard to iodine, the BfR rejects both the UL of the SCF (600 µg) and the UL of the FNB (1 100 µg), justifying this move by noting that the values were set without taking account of the vulnerable group of senior citizens who have not yet overcome the consequences of chronic iodine deficiency (p. 222). As an alternative, it proposes a value of 500 µg.

It is difficult to understand why inconsistencies in the positions of a national authority should have led to rejection of the developed risk-management model, as they did in the case of vitamin E. In the case of iodine, it is even more difficult to understand why even an alternative, developed value, 500 µg, should not be introduced into the model. This situation creates the impression that relatively little effort is being made to pursue a safety-oriented approach for derivation of maximum levels.

Conclusion 5: Where new scientific findings indicate that the ULs of the SCF and of the EFSA need to be re-assessed, then a European solution should be sought. It makes little sense for one nation to act alone in this matter, which ultimately has to do with the basis for regulatory action at the European level.

6. Substantiation of a multiple exposure factor of 4

In each case, the difference between a UL and pertinent dietary intake is available for food supplements and fortified foods, in the context of safe intake. The BLL agrees with the BfR in that, in principle, "multiple exposure", i.e. daily intake of a nutrient from more than one food supplement or fortified food, has to be taken into account. On the other hand, we maintain that such consideration must take place on the basis of reliable data.

On p. 20 ff., the BfR writes that no figures are available on multiple exposure via food supplements and fortified foods. It thus proposes the introduction of a factor of 4; i.e. the difference between a UL and pertinent alimentary intake would be divided by 4. This approach is thus based on the assumption that consumers, on a daily basis and for prolonged periods, take 4 fortified foods or food supplements with the same fortified nutrient. With this assumption, the BfR is referring to a hypothetical group of consumers who, on a daily basis, for a prolonged period (i.e. chronically) and in addition to their regular diets, take 2 food supplements and 2 fortified foods that all contain the same nutrient. This assumption seems rather far-fetched:

Firstly, representative data are available on daily intake of a nutrient from more than one food supplement. Such data certainly do not justify a general factor of 2 for the great majority of nutrients.

For example, a pertinent evaluation carried out by the Robert Koch Institute, on the basis of the representative German National Health Interview and Examination Survey (GNHIES, Bundesgesundheitsurvey) (cf. p. 12), shows that only a small portion of the population takes several supplements, on a daily basis, that contain the same nutrient (Beitz et al. 2004). Such multiple exposure, which was highest for vitamins C and E, was still quite low: 0.5 % of the population take two or more daily supplements that contain vitamin C and/or vitamin E; for magnesium, the corresponding percentage is 0.4 %. No use of more than 3 supplements was reported. In addition, no multiple exposure whatsoever from supplements was found for vitamins A and D and for iodine and selenium (cf. the table). The decisive point, however, is that such multiple exposure seen in random samples normally does not lead to the UL's being exceeded (Beitz et al., 2004). Furthermore, this evaluation could also be covering over-the-counter medications, i.e. the aforementioned evaluation would tend to overestimate, rather than underestimate, actual intake of nutrients from food supplements.

Share of the population that consumes the same nutrient from 2 or 3 different supplements on a daily basis (table modified in accordance with Beitz et al., 2004)

Nutrient	Multiple exposure ^{a)}			
	2 supplements daily		3 supplements daily	
	n	[%] ^{b)}	n	[%] ^{b)}
Vitamin C	17	0.4	4	0.07
Vitamin E	16	0.4	4	0.07
Vitamin B ₆	9	0.2	3	0.04
Vitamin B ₁	8	0.2	3	0.04
Vitamin B ₂	8	0.2	3	0.04
Niacin	8	0.2	3	0.04
Pantothenic acid	8	0.2	3	0.04
Vitamin B ₁₂	7	0.1	3	0.04
Folic acid	5	0.08	3	0.04
Beta-carotene	4	0.06		
Biotin	1	0.02		
Magnesium	10	0.4		
Calcium	10	0.3		
Iron	2	0.06		

^{a)} Defined here as intake of a nutrient from several different supplements on the same day

^{b)} Of the total population.

Secondly, the degree to which fortified foods account for intake of vitamins and minerals is regularly overestimated. In a conservative view, over 50 % of foods (measured in energy %) are simply not available for fortification. This group of foods includes unprocessed, unpackaged, unlabelled and traditional foods (Flynn et al, 2002). A model calculation carried out by Godfrey et al. using data from France, Germany, Italy, Spain and the UK (Godfrey et al., 2004), showed that 75 % of foods are almost never fortified. The authors of this work also summarise as follows:

“Overall about 75% of food and drink in European diets is never fortified. Where fortification is permitted, such foods rarely contribute more than 3 % of the total diet on a per capita basis. The exception is the UK where restoration of bread to replace losses in milling is mandatory.

Significant consumption of fortified foods by high level consumers is limited to foods where vitamins are used to restore those lost in processing, such as milk and bread. Excluding those foods, a consumer could have a theoretical

diet that comprised up to 10 % fortified foods. However, this is unlikely to be achieved in practice because it would require a consumer to consistently select foods that were fortified from a group of foods that included a wide range of brands and varieties. In reality, the majority of high level food consumers are unlikely to obtain more than 4 % of their diet from fortified food. If consumers were high level consumers of more than one type of fortified food then the overall proportion could be higher. When foods are considered in groups the proportion could apparently be as high as 17% but the high level consumer would need to select only fortified foods out of this group (carbonates, juices, fruit drinks, milk) to achieve this.

An average consumer is unlikely to obtain more than 3% of their diet in a fortified form (excluding situations where fortification is mandatory) even in those markets where fortification has been practised across a wide variety of foods for several decades" (Godfrey et al., 2004).

With regard to the aforementioned fortification data in general, it must also be taken into account that the foods in question certainly do not all contain the same nutrients, and this factor is of key relevance in the context of multiple exposure. It must also be remembered that most fortified foods tend to contain rather small amounts of the nutrients they are fortified with: In general, they tend to contain only a small share of a person's daily requirements.

In discussions, the concern is often voiced that the market could be "flooded" with fortified foods and food supplements. The BLL does not share this concern. Even after the Regulation of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to foods enters into force, the share of food products that are fortified will not increase significantly. This is indicated, for example, by the fact that in Germany many types of options for fortification are not being made use of. The reasons for this include technological aspects, reasons related to taste, smell and appearance, cost aspects, and issues of stability and shelf life. In a comparison of data from nutrition studies of 1986/1987 and 2000/2001, data from the UK, a highly liberalised market, show that intake of nutrients from all foods, including fortified foods (but not food supplements), increased relevantly (> 20%) in only two cases: that of vitamin C and that of vitamin B₆ (UK Office for National Statistics, 2003).

And thirdly, it must be noted that occasional intake in excess of the UL does not present an increased risk, since the Tolerable Upper Intake Level (UL) refers to the quantity of a nutrient that can be consumed daily and chronically without presenting a likelihood of adverse effects on health. Occasional intake of nutrient quantities above the UL presents no direct risk. What is more, in most cases, the UL is derived via determination of the

relevant NOAEL (no observed adverse effect level), in combination with an uncertainty factor >1 . In practice, this means that the risk of adverse effects does not increase as soon as the UL is exceeded; that risk increases only when the NOAEL is chronically exceeded. As a result, risk assessment need not consider the case of the consumer who, on a few days of the year, consumes 4 food supplements or fortified foods that all contain the same nutrient (for example, vitamin C); instead, it must consider the consumers who have such intakes regularly and over very long periods of time.

Conclusion 6: Use of a multiple exposure factor must take place on the basis of reliable data. The BfR proposes a multiple exposure factor of 4. The assumption underlying this proposal does not seem realistic: Firstly, representative data are available on daily intake of a nutrient from more than one food supplement. Such data certainly do not justify a factor of 2 for the great majority of nutrients. Results of analysis of data from the 1998 German National Health Interview and Examination Survey (GNHIES, Bundesgesundheitsurvey) show that multiple exposure via food supplements is normally overestimated. A multiple exposure factor of 4 cannot justifiably be applied in an undifferentiated manner to food supplements and fortified foods, and to all vitamins and minerals, within the BfR's model. Secondly, the share of foods that are fortified is regularly overestimated. Thirdly, it must be noted that occasional intake in excess of the UL does not present an increased risk. Only chronic intake increases the risk of adverse effects. For this reason, for each relevant nutrient, chronic intake of the nutrient must also be deducted from the UL for that nutrient. The assumption that significant groups of consumers consume 4 fortified foods and food supplements that contain the same nutrient and do so on a daily basis and chronically – i.e. over long periods of time - is unrealistic.

7. Nutrition status / benefits of supplements

At various points, the BfR justifies its low maximum levels by noting that higher intake levels do not provide any benefits: Most consumers receive an adequate supply of nutrients (such as vitamins B₁, B₂, B₆, and B₁₂, and pantothenic acid), so the BfR. However, the argument that a defined quantity greater than the recommended daily allowance provides no benefits, or that the majority of the population receives an adequate supply of nutrients, will not hold up to legal scrutiny on the basis of Directive 2002/46/EC and of the Proposal for a Regulation:

The criteria for deriving maximum levels are set forth in Article 5 of the Directive and in Article 6 of the Proposal for a Regulation. These criteria include the upper safe levels as determined by scientific risk assessment and the quantities consumed, as part of diets, via other sources. Furthermore, the reference quantities for nutrient intake should be taken into account properly. In its recital 13, Directive 2002/46/EC justifies the setting of maximum levels solely with the need to protect consumers from adverse effects on health. "Safety" is the key criterion for setting maximum levels, not considerations regarding benefits. In the BLL's opinion, reference quantities for nutrient intake should be taken into account primarily when they play a key role in determining safe intake levels. At a November 2004 meeting, the Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Purposes expressed the position that orientation to reference levels must not lead to basing of most maximum levels on the reference levels (Alinorm 05/28/26).

Surely, risk assessment relative to nutrients must consider not only the risk of excessive intake, it must also consider the risk of insufficient intake. Consequently, it is only logical that the BfR's developed risk-management model must be rejected in some cases; subtraction of intake quantities from the UL, for the 90th / 95th or 97th percentile, can result in negative values. Such results are always possible when a few segments of the population consume very high amounts in excess of the relevant ULs. Vitamin A provides a case in point. Relevant cases of this type must really be considered individually, since significant parts of the population are exposed to a certain risk via inadequate nutrient intake. In the EPIC study, for example, 10 % of the studied population failed to attain the SCF's defined lowest intake threshold for Retinol - 300 µg (men) or 250 µg (women) (cited from Domke et al., 2004). This group of persons would thus profit from foods fortified with, or from supplements containing, vitamin A or beta-carotene. Any general orientation to such deficiencies, and any use of such an orientation to justify low maximum levels, would run counter to the sense of the Directive, however.

Conclusion 7: The focus on benefits

The argument for generally low maximum levels to the effect that a defined quantity greater than the recommended daily allowance provides no benefits, or that the majority of the population receives an adequate supply of nutrients, will not hold up to legal scrutiny on the basis of Directive 2002/46/EC and of the Proposal for a Regulation. In addition, the Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Purposes expressed the position that orientation to reference levels must not lead to basing of most maximum levels on the reference levels. On the other hand, reference levels for nutrient intake certainly can play a useful role in assessing safety.

III. Special remarks regarding assessment of the risks of vitamin C

In each case, the BfR provides two options for maximum levels for vitamin C for discussion:

- **Food supplements:**
430 mg, on the basis of the formula presented in the introduction:

$$\text{Maximum level, food supp./daily serving} = \frac{2000 \text{ mg (UL of the FNB)} - 282 \text{ mg (intake, DINF)}}{4 \text{ (multiple exposure factor)}} = 430 \text{ mg}$$

and **225 mg** (= retention of existing practice. Advantages mentioned: no side effects, facilitation of differentiation from medications that contain vitamin C, no warnings or cautions are required; disadvantages mentioned: the maximum level is not based on a quantitative risk assessment)

- **Fortified foods:**
100 mg / quantity consumed daily (orientation to the recommended daily dose and to precautionary health protection) and **no maximum level** (= retention of existing practice).

In each case, the **recommended** maximum level for vitamin C, among these options, is the **restrictive** option, obtained without any use of the formula: 225 mg for food supplements, and 100 mg per daily serving for fortified foods.

The BfR justifies its restrictive position regarding assessment of the risks of vitamin C as follows:

- The **EFSA** was **unable to derive a UL** because insufficient data was available.
- For a certain, unknown percentage of the population with increased oxalate excretion, increases in such excretion could increase the risk of **kidney-stone formation**.
- Vitamin intake in excess of actual requirements does not provide **any additional benefits** in terms of nutrition physiology.

From the perspective of the BLL, these views, and the BfR's rejection of its own formula for derivation of maximum levels for Vitamin C, are rather questionable.

Regarding the BfR's three objections in detail:

1. Risk assessment of the EFSA and the FNB

The BfR justifies its restrictive approach by arguing that the EFSA was unable to derive a UL. Nonetheless, **risk assessment practice** provides indications of the quantities that may be considered safe and that can be inserted into the formula.

For example, the authority concluded that supplementary vitamin C doses of up to **1 g daily**, taken in addition to normal daily intake via the diet, are not associated with gastrointestinal side effects, and that habitual intake of **1.5 g of vitamin C** would not present an increased risk of kidney stones (EFSA, 2004, page 13). In this light, the BfR's statement on p. 225, to the effect that the EFSA "considers a daily total intake of 1 g vitamin C to be safe", while not wrong, is the result of an incomplete citation.

Furthermore, Directive 2002/46/EC on food supplements does not refer explicitly to the Tolerable Upper Intake Level (UL), nor does it refer to the EFSA as the sole authority for assessing safety; instead, it refers to "upper safe levels of vitamins and minerals established by scientific risk assessment based on generally acceptable scientific data (Article 5 (1)). In this light, the lack of a UL from the EFSA does not have to lead to rejection of risk-management models that – like the BfR's model – are based on determining a difference between the upper safe level and intake via the regular diet.

For example, in 2000 the U.S. Food and Nutrition Board (FNB) concluded that prolonged daily intake of **2000 mg of vitamin C** would very likely have no adverse effects on the health of virtually any healthy adult. For adults, therefore, a UL of 2 g for vitamin C has been established. Separate ULs have been established for children and adolescents and for pregnant and lactating women. The UL of 2 g for adults is used in one of the BfR's options. For the above reason, we welcome this. The BfR's concerns regarding use of the FNB's UL, to the effect that this UL was derived without taking account of the group of persons with certain congenital metabolic defects and with secondary hyperoxaluria, are puzzling, from the perspective of the BLL:

2. Vitamin C and kidney stones

Unlike the FNB and the SCF, the BfR maintains that the group of persons predisposed to developing kidney stones (patients with a rare primary hyperoxaluria, patients with chronic intestinal disorders and patients with extensive intestinal resections; BfR p. 229) must be taken into account in derivation of a UL or must be taken into account in derivation of a maximum level for vitamin C.

The BLL has strong doubts regarding the correctness of this assessment:

In derivation of maximum levels for the general population, it seems highly questionable to include persons who are predisposed as described above and who, in keeping with the aforementioned indications, are undergoing medical treatment. Furthermore, the planned (restrictive) risk-management recommendation, which is based on the rather vague presumption that vitamin C intake in persons so predisposed could be tied to an

increased risk of kidney-stone formation, also seems questionable. These approaches create the impression that the BfR considers the risk of excessive intake to be much more serious than that of insufficient intake. It is true that vitamin C intake levels tend to be relatively good in comparison to levels for other vitamins. At the same time, one-third of the population does not receive the daily recommended amount of 100 mg/d vitamin C (Beitz et al., 2002). Restrictive management could tend to reduce the range of available sources for this vitamin – as well as the range of available sources for other vitamins. A balanced perspective should be adopted.

a) The risk group of persons predisposed to developing kidney stones is not a sensitive consumer group that must be taken into account in UL derivation.

In principle, the UL should be applied to the general population, including sensitive consumer groups, and throughout various age groups and for both genders, so the SCF and the FNB. This does not include those persons, however, who consume relevant nutrients in the context of medical treatment (FNB 1997, cited in SCF, 2000). Specific, precisely identified sub-populations – such as those that are especially vulnerable as a result of genetic predisposition or of certain other disorders – should be excluded via suitably individualised considerations. The SCF explains its position as follows:

"The derivation of ULs for the normal healthy population, divided into various life-stage groups accounts for normally expected variability in sensitivity, but it excludes sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other considerations [...]. Sub-populations needing special protection are better served through the use of public health screening, health care providers, product labelling, or other individualised strategies. The extent to which a sub-population becomes significant enough to be assumed to be representative of a general population is an area of judgement and of risk management and will be considered for individual nutrients" (SCF, 2000, page 5).

Persons in the group to which the BfR refers ("patients with rare primary hyperoxaluria, patients with chronic intestinal disorders such as M. Crohn and patients with extensive intestinal resections", p. 229) can be expected to be in a physician's care. In most cases, genetically based formation of calcium-oxalate stones is associated with a restriction of kidney function (Coe et al., 2005; Hesse 2002a). Patients with such problems will be well aware that they should not take excessively high doses (> 2 g/d) of vitamin C. The incidence of primary hyperoxaluria is 0.1-0.2:10⁶, while prevalence is 0.8-2.9:10⁶ (Wirth 2006). In other words, both are low. The BLL thus maintains that the risk group consisting of the aforementioned patients does not have to be taken into account in UL derivation.

In light of basic considerations, the **FNB**, acting on the basis of the available scientific data, selected osmotic diarrhea and related gastrointestinal complaints as the critical end point for UL derivation. On the other hand, it did not so select potentially increased

oxalate excretion via the kidneys, which can increase the risk of kidney-stone formation. In general, the FNB found no clear correlation between extremely high vitamin C intake and kidney-stone formation (FNB, 2000, page 161). Consequently, kidney-stone formation was not chosen as the critical end point for derivation of maximum levels. The **EFSA** also concludes that acute gastrointestinal complaints are the most clearly defined adverse effect of high vitamin C intake.

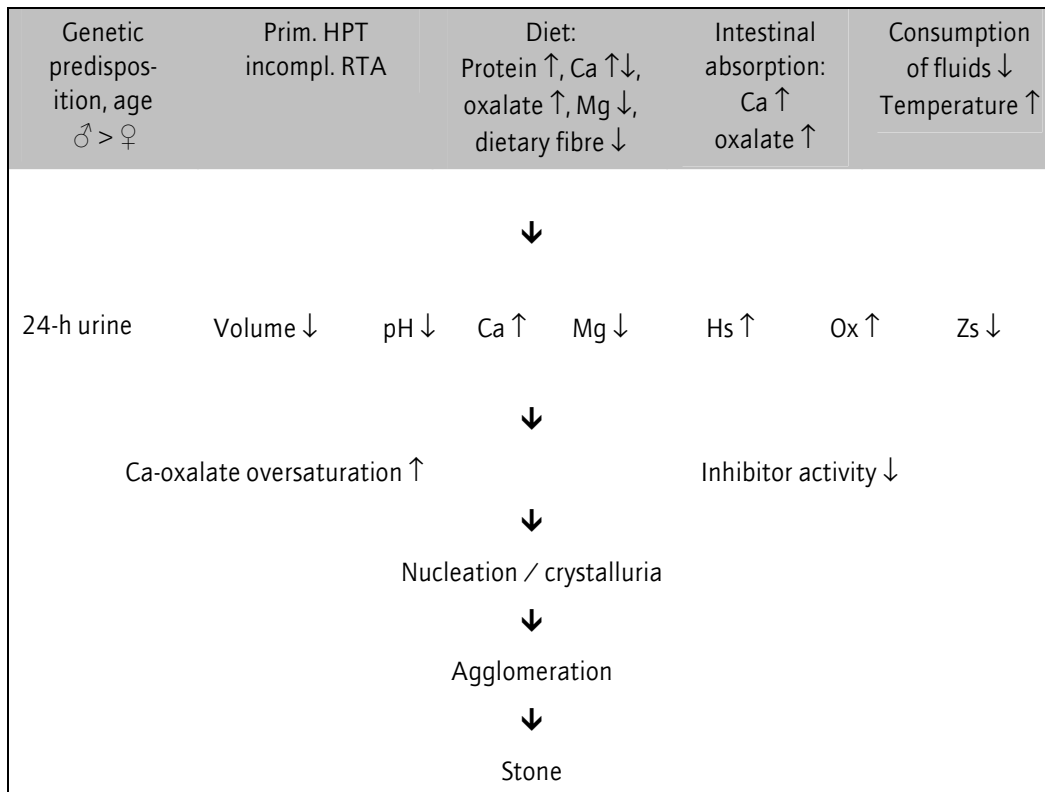
b) There is no clinically relevant correlation between vitamin C intake and kidney-stone formation.

First, some background information: kidney-stone formation is a multifactorial process (Coe et al., 2005). Along with pathological kidney morphology and disruptions of urine flow, urine composition (inadequate urine dilution, increased excretion of lithogenic substances, urine pH, inhibitor deficiency) plays a decisive role. Kidney stones form only when a number of different factors are simultaneously active (Figure 1.).

One of these factors is diet. In this context, the BfR also discusses the significance of nutritive intake of vitamin C in formation of calcium-oxalate stones, a type of kidney stones.

Calcium-oxalate stones occur primarily in the presence of the following three factors:

- Excessive calcium in the urine (hypercalciuria)
- Excessive oxalate in the urine (hyperoxaluria) and
- Inadequate levels of inhibitors (citrate, magnesium and glycosaminoglycans) in the urine (cf. the Figure).



General scheme for calcium-oxalate formation (Hesse 2002b)

Hypercalciuria can be caused by three factors: Increased intestinal absorption of calcium, increased mobilisation of calcium from bones or a disruption of tubular calcium resorption.

The term hyperoxaluria is applied to cases in which oxalate excretion > 45 mg/d (Neisius D et al. et al. 1999, Hesse 2002a) and physiological oxalate excretion via the urine is 10-55 mg/24 h (Löffler et al., 1997). A distinction is made between primary and secondary hyperoxaluria. Primary hyperoxaluria is caused by a congenital enzyme defect. The incidence of such primary hyperoxaluria is 0.1-0.2:10⁶ (i.e. 1 case in 10 million), while the **prevalence** of the disorder is **0.8-2.9:10⁶ (i.e. 8-29 cases in 10 million)** (Wirth, 2006). These statistics indicate that between 64 and 240 people in the Federal Republic of Germany suffer from this disease. The condition thus involves an extremely rare genetic defect. The secondary form can occur in connection with inflammatory intestinal disorders or intestinal resections, which can lead to increased oxalate absorption.

Both exogenic and endogenic causes of hyperoxaluria are discussed:

Exogenic: An average of 152 mg of oxalate are consumed via the diet, on a daily basis (Holmes et al, 2000). Normally, 10-20 % of this amount is absorbed. In cases of high

oxalate intake (rhubarb, spinach, cocoa, black tea) and high intestinal absorption, exogenic oxalate can account for 50-80 % of urinary oxalate (Traxer et al. 2003a, Pearle 2001, Holmes and Kennedy 2000). Although it would seem only logical to reduce consumption of oxalate-rich foods, in order to prevent the formation of urine stones, the randomised, prospective studies that could show the effectiveness of a low-oxalate diet in preventing kidney stones are lacking (Coe et al. 2005, Pearle 2001, Tiselius et al. 2001).

Endogenic: The largest share of oxalate in the urine (50-70%) is a metabolic end product that results from dehydration of glyoxylate. Only very small quantities of oxalate are obtained via the amino acids tryptophane, phenylalanine, tyrosine, aspartate and via purines (Baxmann et al. 2003, Traxer et al. 2003a).

Breakdown of ascorbic acid produces oxalate to a degree of about 35-55%; this normally corresponds to about 10-20 mg of urinary oxalate (Baxmann et al. 2003, Traxer et al. 2003a, Chalmers et al. 1986). A similar quantity is reported by Massey et al. (2005). It is assumed that only a small percentage of vitamin C intake, 1.5%, is converted into oxalate and then excreted as oxalate in the urine. This means that only 15 mg of a vitamin C intake of 1000 mg would be excreted as urinary oxalate. As a result, vitamin C plays a minor role in urinary oxalate concentrations.

The question thus arises of whether such small quantities of oxalate from vitamin C are of clinical relevance in the formation of calcium-oxalate stones.

A number of studies have attempted to answer this question indirectly by focussing on the effects of different vitamin C doses on urinary oxalate levels. The results of such studies differ widely (cf. EFSA 2004, FNB 2000). Variances in urinary oxalate concentrations are explained as follows:

- Firstly, as a result of the large individual variances seen in oxalate metabolism (Massey 2005, Briggs 1976)
- Secondly, as a result of inadequate monitoring of diets during the study phase.
- A third, special problem is that of measuring urinary oxalate levels. This is significant in that in vitro, vitamin C is oxidised quickly to oxalate (Wandzilak et al. 1994, Chalmers et al. 1985). It thus cannot be ruled out that the sharp urinary oxalate increases reported in the past were due to an analytical artefact (Traxer et al. 2003a).

Clinical studies with healthy people

In more recent studies, closer attention was given to the aforementioned problems encountered in oxalate analysis. These studies did find a significant oxalate increase in 24-h urine samples, amounting to 10-15 mg, in healthy people following intake of 1000 mg Vitamin C (Levine 1996). Total oxalate excretion remained within the normal range, however (cf. p. 26). Fituri et al. (1983) reached similar conclusions. Eight healthy test persons were given 8 g ascorbic acid per day for a period of 7 days. Average oxalate excretion in 24-h urine samples increased from 22.6 mg/d to 25 mg/d. In a randomised cross-over study with 6 healthy test persons, Liebmann "und Mitarbeiter" (1997) studied the influence of vitamin C supplements, and of vitamin-C-rich orange juice, on oxalate metabolism. Over a four-day period, test persons received on a daily basis either 2 g vitamin C or orange juice with an adequate amount of vitamin C. Following the vitamin-C supplementation, oxalate concentrations in 24-h urine samples increased from 30 mg to 32 mg/d. In those persons who consumed the orange juice, oxalate concentrations in 24-h urine samples increased from 30 mg/d to 40 mg/d. The authors attributed the increases following consumption of orange juice to higher endogenic oxalate synthesis.

Epidemiological surveys of healthy people

Prospective epidemiological studies of healthy people have also failed to find any indication of a correlation between vitamin C and kidney-stone formation.

The Nurses Health Study, a prospective study, followed a total of 85,557 women with no history of kidney stones. After 14 years, no correlation between vitamin C intake and kidney-stone formation had been found (Curhan et al. 1999).

In the prospective Physicians' Health Study, Curhan et al. (1996) followed a total of 45,251 men between the ages of 45 and 75 with no history of kidney stones. After a six-year period, the relative risk of kidney-stone formation was found to be lower with vitamin C intake of 1.5 g than it was with vitamin C intake of 250 mg. Even after a period of 14 years, no increased risk of kidney-stone formation was found as a result of vitamin C intake. Only one multivariate analysis, which also covered potassium, found a positive correlation. Nonetheless, that study's authors did not think that their findings justified recommending reductions in consumption of foods rich in vitamin C (Taylor et al. 2004).

In sum, recent studies also confirm the resolution adopted relative to vitamin C at the 1987 3rd consensus conference:

" This has led to the conclusion that the practice of ingesting large quantities of ascorbic acid will not result in calcium-oxalate stones ... in healthy individuals" (Rivers 1987).

Clinical studies of persons with histories of kidney stones

Some authors considered the question of whether persons with histories of kidney stones would react to vitamin C supplements differently than would healthy persons with no histories of kidney stones. Tab. 1 lists current studies of this question.

Tab. 1: Oxalate increases in 24-h urine samples following 2 g of vitamin-C supplementation

Studies	Persons with no history of kidney stones			Persons with history of kidney stones		
	(n)	Oxalate increase (mg/d)	Difference	(n)	Oxalate increase (mg/d)	Difference
Massey et al. (2005) Chai et al. 2004)	19	45 → 49	4	29	51 → 59	8
Traxer et al. (2003b)	12	28.5 → 34.7	6.2	12	30.5 → 41.0	10,5
Baxmann et al. (2003)	20	25 → 39	14	2 4	34 → 48	1 4
Chalmers et al. (1986)	11	→ 27		1 7	→ 38.7	

In these studies, oxalate increases in 24-h urine samples were found, following supplementation with 2 g vitamin C, in both persons with no histories of kidney stones and in persons with histories of kidney stones. Both before and after vitamin C supplementation, the oxalate levels of persons with histories of kidney stones were higher than those of persons with no histories of kidney stones. At the same time, most of the levels concerned lay within the normal range of 10 – 55 mg in 24-h urine samples (cf. p. 26).

The findings of Massey and Traxer also show that kidney-stone formation is an extremely complex process: Among both persons with histories of kidney stones and persons with no such histories, Massey et al. (2005) and Traxer et al. (2003b) found so-called **responders**. These persons reacted to vitamin C supplementation with increased oxalate excretion. Such increased excretion is attributed to increased ascorbic-acid absorption and to increased endogenic oxalate synthesis.

The increases seen in oxalate excretion in 24-h urine prompted some of the authors to propound an increased risk of kidney-stone formation for persons with a predisposition for kidney-stone formation (Massey et al. 2005, Baxmann et al. 2003, Urivetzky et al. 1992). On the other hand, no studies have found a direct,

clinically relevant link between vitamin-C supplementation and kidney-stone formation (Costello 1993, Traxer et al. 2003a).

Overall, the the authors of various studies have developed the following recommendations: For healthy persons, increased vitamin C intake presents no risk (Traxer et al. 2003a). For patients with kidney stones, and for dialysis patients, a daily vitamin C intake of 100-200 mg is recommended (Gerster 1997). The recommendations for patients with risks of developing kidney stones range between 500 mg/d (Massey 2005) and < 2 g (Traxer et al. 2003b, Pearle 2001).

From the above, the following may be concluded: To date, it is still the case that no studies have found any clinical relevance of vitamin C in kidney-stone formation – in either healthy persons or in persons with a predisposition for kidney-stone formation. While some clinical studies did find increased levels of formed oxalate, the oxalate levels in question almost always lay within the normal range. As a result, any links between high levels of vitamin C intake and kidney-stone formation are of a speculative nature (Gerster 1997). From the BLL's perspective, relevant studies to date do not support the BfR's proposed restrictive approach.

Urologists at a consensus conference held on 23 January 1999 in Mannheim reached the following conclusion:

“There are no studies that have associated a high intake of vitamin C with an increased recurrence rate or that show a reduced intake of vitamin C to have been of clinical value. There is presently no convincing evidence that an intake of large doses of vitamin C (up to 4 g) has a negative influence on calcium stone recurrence” (Tiselius et al. 2001).

3. Benefits as a criterion for derivation of maximum levels

The BfR emphasises the the lack of any benefits from the levels resulting from the calculations, and it calls attention to the relationship between vitamin-C intake levels and reduced bioavailability and to the issue of saturation of immunocompetent cells in blood plasma. Without wishing to discuss the relevant nutrition-physiological data, the BLL calls attention to the legal framework for deriving maximum levels (safety) and to the basic remarks made on this issue on p. 20.

4. Additional remarks regarding assessment of the risks of vitamin C

a) Relative to classification of vitamin C as a "moderate health risk"

In its relevant summarising remarks, the BfR states that oral intake of vitamin C involves a moderate health risk, because excess amounts are excreted faecally and renally. Here, we refer to Table 2, on p. 225 of the BfR's report. There, "risk" is seen solely quantitatively, as the degree of probability that a given nutrient will lead to undesirable risks. For vitamin C, the pertinent factor ranges between the RDA and UL 20, i.e. only as of an intake of 2 g of vitamin C, over a very prolonged period, does the probability of adverse effects increase. The gravity of the adverse effects in question (light diarrhea) is irrelevant for the definition of "risk"; the term has been taken from probability mathematics.

In the BLL's view, the manner in which the term "health risk" is used on p. 225 has a qualitative component that goes beyond what is meant by the term "risk of an adverse effect". At the very least, the term can be so interpreted – depending on the recipient (such as a consumer) – and thus it can connote "real" dangers to life and health. With regard to adverse effects, it must be remembered that levels in excess of the UL solely increase the risk of adverse effects. And such an "increased risk" has nothing to do with whether the adverse effects involved are serious health impairments or are simply gastrointestinal disruptions (diarrhea, etc.), as in the case of vitamin C.

For this reason, the BLL urges that the potential effects of the BfR's reports on consumers and the media be taken into account – even where the reports are focussed on risk assessment. In our view, a good relevant example is provided by the FNB's statement to the effect that "The risk of adverse effects resulting from excess intake of vitamin C from food and supplements appears to be very low at the highest intake noted above." (FNB, 2000 p. 165). Another example is provided by the EFSA's "the vitamin is of low acute toxicity" (EFSA, 2004).

b) Other adverse effects of vitamin C

It must also be emphasised that the BfR also refers to other adverse effects from high doses of vitamin C:

"The accompanying symptoms to the consumption of very high doses are increasing oxalate excretion with the risk of kidney stones, increasing uric acid excretion, potential prooxidative effects, elevated iron absorption and acid-related dental enamel corrosion (FNB, 2000)".

The BfR's citation of the FNB does not give the relevant quotation in its original form: The FNB begins the relevant chapter by listing the accompanying symptoms studied in the publication:

„Possible adverse effects associated with very high intakes have been reviewed and include: diarrhea and other gastrointestinal disturbances, increased oxalate excretion and kidney stone formation, increased uric acid excretion, pro-oxidant effects, [...] The data on these adverse effects are reviewed below.“ (FNB, 2000, p. 156)

An evaluation of the available studies on these issues led to the following conclusion, however:

“Based on considerations of causality, relevance, and the quality and completeness of the database, osmotic diarrhea and related gastrointestinal disturbances were selected as the critical endpoints on which to base a UL. The in vivo data do not clearly show a causal relationship between excess vitamin C intake by apparently healthy individuals and other adverse effects (i.e. kidney stone formation, excess iron absorption, reduced vitamin B12 absorption and copper levels, increased oxygen-demand, systemic conditioning, pro-oxidant effects, dental enamel erosion, or allergic response) in adults and children (FNB, 2000, Seite 161).

The FNB thus concludes that the totality of the available data does not substantiate any causal relationship between high vitamin C intake and the aforementioned adverse effects (excess iron absorption, pro-oxidant effects, kidney stones, dental enamel erosion, etc.).

Conclusion 8 on assessment of the risks of vitamin C

In the BLL's view, the reasons given in the BfR's report for not applying the formula for derivation of maximum levels to vitamin C are untenable:

Firstly, the entire body of scientific risk assessment must be taken into account. For example, the FNB has adopted a UL of 2000 mg/day. The EFSA explains that excess quantities of 1 g vitamin C are not associated with gastrointestinal side effects. No increased risk of kidney-stone formation was found in persons who regularly take 1.5 g vitamin C / day, so also the EFSA. Kidney-stone formation is a multifactorial process, and diet is only one of the factors involved.

Secondly, the demand that the risk groups of "patients with a rare primary hyperoxaluria, patients with chronic intestinal disorders such as M. Crohn and patients with extensive intestinal resections" be included in UL derivation, or be taken into account for reasons of precautionary health protection, is unjustified. No actual risk has been found in clinical studies carried out to date. What is more - and this is of relevance for risk management – such persons are normally in a doctor's care and are familiar with the necessary behavioural guidelines. Furthermore, the group of persons with primary hyperoxaluria is very small in Germany (ca. 8-29 cases for every 10 million persons). Neither the FNB nor the SCF has concluded that the aforementioned risk groups have to be considered.

Thirdly, the argument that relevant benefits are lacking does not hold up to legal scrutiny.

The remarks relative to vitamin C provide an example of how the BfR's proposed options for risk management cannot be justified solely on the basis of precautionary health protection. In the BLL's view, the available scientific data do not support the restrictions planned by the BfR. The restrictions run counter to the principle of proportionality.

IV. Summary and conclusions

- The above remarks present the food sector's position regarding the proposals of the Federal Institute for Risk Assessment (BfR) relative to maximum levels in fortified foods and in food supplements.
- In future, the permitted maximum levels for food supplements and for fortified foods are to be harmonised throughout Europe. The food sector welcomes this aim.
- Any approach for all of Europe must be applicable in all Member States. It must be transparent and logical and it must lend itself to a flexible response to changes in the pertinent data. It is the task of the European Commission to develop such an approach. It is familiar with the pertinent risk management.
- The issue of safety is key to derivation of maximum levels (recitals 5, 13 and 14 and Article 5 of Directive 2002/46/EC, and recitals 14 and 15 and Article 6 of the Proposal for a Regulation on fortified foods). As to the manner in which safety is to be guaranteed, primary-law provisions – including the principle of proportionality – must be adhered 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, and the Proposal for a "Regulation on the addition of vitamins and minerals and of certain other substances to foods", state the criteria that are to be used in deriving daily maximum levels. In the main, such levels are the upper safe levels of vitamins and minerals, as established by scientific risk assessment based on generally acceptable scientific data, along with normal dietary intake. Furthermore, the reference values for nutrient intake should be taken into account properly.
- In its introductory section, the BfR's extensive document presents a risk-management model for calculation of maximum levels: The quantity of a relevant nutrient absorbed via food is subtracted from the Tolerable Upper Intake Level (UL). The difference is divided by 2 or 4. This factor is intended as a way of accounting for simultaneous use of fortified foods and / or food supplements that contain the same nutrient ("multiple exposure").
- In the main section of the work, the model is rejected for the great majority of relevant cases. The calculation model is used – and then recommended – for only three nutrients (vitamin B₆, potassium and zinc). And yet the model is to be welcomed, in principle, since it is based on the criteria set forth in the applicable legal provisions.

- Rejection of the model then leads to specific considerations. Most of the sub-sections conclude that the restrictive option is the best of the available options. As a rule, such options are based on considerations of nutrition physiology. Often, they are also based on previous recommendations. With regard to fortification, in many cases the recommendations specify that certain nutrients – such as beta-carotene or calcium – should not be added at all (except in a few isolated applications). The recommendations thus cover nutrients that to date have been approved for food fortification. With regard to food supplements, zero levels are recommended for iron, fluoride, copper and manganese; in other cases, the recommendations call for levels below existing customary levels (for example, 2.25 mg for zinc, 15 mg for vitamin E).
- The BfR gives a range of reasons for not applying the derived model to many of the nutrients in question. From the perspective of the BLL, these reasons are not always logical, however. One is left with the impression that too little effort is being made to apply the model:
- Reason 1: The ULs of the European Food Safety Authority (EFSA) are lacking. The BLL maintains that a lack of EFSA ULs cannot automatically justify proposals for restrictive levels – such as 4.8 mg for thiamine, 4.5 mg for riboflavin or 180 µg for biotin. The reason for this is that Directive 2002/46/EC does not expressly refer to the EFSA's ULs; instead, it refers to "upper safe levels of vitamins and minerals established by scientific risk assessment based on generally acceptable scientific data". In cases, for example, in which the EFSA concludes that no adverse effects have been identified even for high doses (as, for example, with thiamine, riboflavin and biotin), the industry maintains that no maximum levels need be defined and, therefore, that the proposed model need not be rejected (cf. also the recitals in the Directive and in the Proposal for a Regulation on fortified foods). On the other hand, the EFSA reports also provide indications of the strength and reversibility of identified adverse effects of other nutrients, and they provide information relative to safe levels (for example, supplementary intake of 1 g vitamin C is considered safe). In the cases of vitamin C, iron and manganese, the Food and Nutrition Board (FNB) has derived ULs that are worthy of use.
- Reason 2: The model cannot be applied because inadequate intake data are available. It is true that no representative data are available for Germany on intake of nutrients from fortified foods. Future national nutrition studies – such as the NVS that is currently being prepared, or research in the framework of the European Union's Seventh Framework Programme – could illuminate this area by generating data directly related to it.

- Multiple exposure: The BLL has taken the initiative and asked the Robert Koch Institute to evaluate raw data from the representative German National Health Interview and Examination Survey (GNHIES, Bundesgesundheitsurvey) in light of the issue of such intake of a single nutrient from more than one food supplement. The results indicate that levels of multiple exposure via food supplements are generally low in Germany – the highest such levels are seen with regard to vitamins C and E and magnesium: 0.5 and 0.4 % of the population, respectively. The results certainly do not justify any non-differentiated application of a multiple exposure factor of 2 for food supplements, for all vitamins and minerals. The assumption that significant groups of consumers, on a daily basis and for prolonged periods, i.e. on a chronic basis, consume 2 food supplements and 2 fortified foods, in addition to their "normal diets", that all contain the same nutrient (such as vitamin E), seems highly unrealistic. The BfR's proposed multiple exposure factor of 4 exceeds the requirements arising from precautionary consumer protection.
- Reason 3: The therapeutic dose is exceeded when the model is applied. With regard to the relevant legal basis, the BLL maintains that safety must be the decisive criterion for defining maximum levels – and not the exceeding of an (assumed) therapeutic dose. Within certain ranges, some products can be both food supplements and medications – and such possibilities depend on the usage intended by the manufacturer, so also the European Court of Justice.
- Reason 4: The BfR does not apply the model because it has reservations about the ULs of the SCF and the EFSA (iodine, vitamin E). In any necessary reassessment of a nutrient, consensus at the European level should be sought, and action on an isolated national basis should be avoided. This insight is not a reason for rejecting the model, however.
- Benefits: In the cases of many nutrients, arguments for rejecting the developed model turn on considerations of nutrition physiology. Such arguments' focuses include a supposed lack of benefits from various nutrients when taken at the levels resulting from the model (vitamin C, for example). Justifications for low levels, in cases in which no serious risks of adverse effects exist at higher levels, do not hold up to legal scrutiny, however. Safety is the deciding criterion in derivation of maximum levels. On the other hand, reference levels of nutrient intake certainly can play a useful role: Where the quotient $(UL - intake) /$ reference level for relevant nutrient intake is high, the risk of exceeding the UL is low. If the quotient is small, the risk is higher, however. By way of example, the reader is referred to the ERNA risk-management model. These considerations also make it easier to identify risks of inadequate intake. One of the special aspects of assessment of the risks of nutrients is that the risk of "too much" can

co-exist with the risk of "too little". It is true that deficiency disorders, i.e. clinically relevant disorders with characteristic deficiency symptoms, do not occur frequently in Germany (DGE, 2004). At the same time, the German National Health Interview and Examination Survey found that large portions of the population do not attain the reference levels for intake of certain nutrients (this is the case, for example, for about 90% of all women with regard to vitamin D and folic acid, for half of the population with regard to vitamin E and for about one-fourth with regard to calcium; Mensink, 2002). Furthermore, specific population segments, in special life situations, that can profit from specific types of fortification or supplementation have to be taken into account (DGE, 2004).

- The remarks relative to vitamin C provide an example of how the BfR's proposed options for risk management cannot be justified solely on the basis of precautionary health protection.

Conclusion:

For the aforementioned reasons, the German food industry has reservations about the BfR's report. At the same time, the risk-management model developed in the introduction to the BfR's report – with the exception of the multiple exposure factor of 4 – is greatly to be welcomed, in principle. It takes account of the relevant legal requirements.

The criticism is aimed primarily at the facts that, in the main part of the report, this model is not used, for the great majority of nutrients, and that considerations from nutrition physiology are applied instead. And yet, in the BLL's view, such an approach is by no means necessary, and the grounds given for using the restrictive approach and for the extensive rejection of the model are not always convincing.

The BLL urges the Federal Government to work to ensure that the pending European discussion takes place on a solid legal and scientific basis. Derivation of maximum levels must conform to the criteria set forth in recitals 13 and 14, and Article 5, of Directive 2002/46/EC and in recitals 15 – 18, and Article 7, of the Proposal for a Regulation. Safety must be the primary concern.

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About BLL:

The Bund für Lebensmittelrecht und Lebensmittelkunde e. V. (BLL) is the leading association of the German food sector. In this role, it represents the food sector throughout the entire production chain, "from farm to fork". Its membership includes some 90 associations, representing the areas of agriculture, food trades, food industry and food sellers; 100 individual members and 300 companies – ranging from mid-sized firms to international corporations.

The BLL's tasks include facilitating the development of German, European and international food laws and actively supporting the relevant scientific fields. It carries out its work on a solid scientific foundation. In addition, the BLL functions as a partner for dialogue with political, administrative and scientific sectors, with consumer organisations and with the media, relative to the areas of food, food production, quality and safety, food laws and consumer protection.

In the BLL, lawyers and scientists work together interdisciplinarily. The BLL reinforces its expertise through cooperation with scientists – in particular, the BLL's Scientific Advisory Board, which advises the BLL in both legal and scientific issues.

Further information:

www.bll.de

<http://www.bll.de/themen/nahrungsergaenzungsmittel/>

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