Risiken erkennen – Gesundheit schützen

Addition of boric acid or borax to food supplements

BfR Health Assessment No. 005/2006, 16 November 2005

Food supplements are foods containing one or more nutrients like vitamins, minerals or trace elements in concentrated form that are sold as tablets, capsules or coated tablets. They are governed by the valid provisions of the Food and Feed Code (LFBG) and Regulation (EC) No. 178/2002. According to them, foods may not be harmful.

In Germany the addition of the trace element boron as boric acid or borax to food supplements was not permitted up to now. However, this situation could soon change since the laws in the EU Member States are to be approximated and its addition is permitted in other European countries. If this happens, boron could also go on the market in Germany as an ingredient in food supplements. Against this backdrop, the Federal Institute for Risk Assessment (BfR) evaluated the risk to health which boric acid or borax could entail in food supplements.

Boron is constantly ingested by human beings from drinking water, mineral water and food. Other sources of exposure of consumers to boron are products like medicinal products, cosmetics, consumer products in contact with food, toys, detergents, adhesives or carpets containing boron compounds for their antiseptic, preserving, plasticising or flame-retardant properties. The tolerable upper intake level (UL) established by the European Food Safety Authority (EFSA) from all sources that does not lead to any health risks in conjunction with ongoing ingestion, is 10 mg for an adult per day.

BfR has estimated how much boron consumers take up from different diets and other sources. According to this, the intake of 1 mg boron per day from food supplements would not lead to the UL being exceeded. However, already in the case of higher supplementation a health risk can not anymore be ruled out. Given the uncertainty caused by the sparse data situation, the Institute recommends that boric acid or borax should not be used in food supplements. What are missing particularly for a definitive health assessment are reliable studies on total intake by consumers (exposure) and on the toxicology of boron. There is a need for research here.

Signs of possible reproduction toxic and hormone-influencing effects, that may be relevant for man, should be followed up. According to the current level of knowledge children, pregnant and lactating women, menopausal women undergoing HRT (Hormone Replacement Therapy) and sub-fertile men are to be considered as special risk groups in conjunction with additional boron ingestion from food supplements.

1 Subject matter of the assessment

Based on company dossiers and other scientific findings, the Federal Institute for Risk Assessment (BfR) has examined whether there are compelling health protection reasons which oppose the addition of boron in the form of boric acid or borax to food supplements within the intendment of § 54 LFGB)[1]. The examination is undertaken within the context of Directive

[1] Up to 31 August 2005 § 47 a para 1 No. 2 LMBG (Food and Other Consumer Products Act). § 54 LFGB stipulates that foods, cosmetics or consumer products may, in principle, be imported and placed on the market even if they do not comply with the valid provisions for foods, cosmetics or consumer products in the Federal Republic of Germany as long as they have been lawfully placed on the market in another EU Member State. Exemptions are possible to the extent that compelling reasons of health protection oppose such a procedure. When assessing the health risk of a product, international research findings are to be taken into account as are eating habits in the case of foods in the Federal Republic of Germany. The application of the company is to be accompanied by an exact description of the product and all available documents required for the decision.

2002/46/EC on the approximation of laws of the Member States relating to food supplements and the application of a company seeking to place boron-containing food supplements on the market in Germany. Up to now the addition of the trace element to food supplements was not permitted.

The company dossier was passed on to the Federal Ministry of Consumer Protection, Food and Agriculture (BMELV) for submission to the European Commission in conjunction with § 7 of the Food Supplements Ordinance (NemV)[2] and/or Directive 2002/46/EC on food supplements, Article 4 (6 - 8). If the European Commission does not raise any objections after obtaining an opinion on the dossiers from the European Food Safety Authority (EFSA) then, under the given circumstances, boric acid and borax may be used as sources of boron in food supplements up to 31 December 2009. This will not mean that boron and/or its compounds will have to be listed in Annexes I and/or II to Directive 2002/46/EC or in Annexes 1 and/or 2 to the Food Supplements Ordinance (NemV) (Lists of mineral compounds which may be used in the production of food supplements).

In the dossiers the applicant companies propose the inclusion of boric acid and borax as sources of boron in Annex II to Directive 2002/46/EC. They state that boric acid and borax had been placed on the market as components of food supplements in the EU since 12 July 2002.

The applicants indicate that boric acid and borax were used in tablets, capsules, chewable tablets, effervescent powders and liquid formulations as food supplements. As far as the doses are concerned, the applicants state that the amounts of boron contained in food supplements as borax or boric acid were determined by the individual manufacturers. Daily intake was normally in the range of 1 - 3 mg boron (up to 3 mg/day for an unlimited duration as the normal recommended dose of boron for self-selection). However, products were available over the counter in EU Member States leading to daily intakes of up to 9 mg boron (higher daily quantities are prescribed by nutritional practitioners to consumers under supervision at levels of up to 9 mg/day). Since the amounts of boron contained in food supplements are determined by the individual manufacturers, it cannot be ruled out that food supplements are also sold containing daily boron doses above the tolerable upper intake levels (UL) of 10 mg boron/adult/day established by EFSA (1).

In this context literature references seem to be important indicating that regular consumption of certain supplemental mineral products could even lead to additional boron intake of up to 30 mg per day and person (21). Two sources indicate that food supplements for bodybuilders contain boron levels of 1.5 - 10 mg boron per dose (22). If taken three times a day, this could possibly lead to daily boron intakes of up to 30 mg (1, 14).

Attention must be drawn here, as mentioned in the dossiers, to the fact that the maximum levels for minerals in food supplements (cf. Directive 2002/46/EC, Whereases (13), (14) and (16) and Article 5) have still to be established.

The dossiers submitted were prepared on the basis of the “Guidance on submission for safety evaluation of sources of nutrients or other ingredients proposed for use in the manufacture of foods of the Scientific Committee on Food” (SCF) (2).

[2] This paragraph contains information on the transitional arrangement concerning the approximation of EU-wide laws on food supplements.

2 Result

Given the gaps in knowledge above all about current exposure to boron from the most diverse sources and its impact on and interaction in the human organism, BfR advises against using boron in the form of boric acid or borax in food supplements until corresponding data are available. This applies in particular to children, pregnant and lactating women, breastfed children, menopausal women undergoing HRT (Hormone Replacement Therapy) and subfertile men who may be more sensitive to boron-induced effects.

In purely formal terms, supplementation with 1 mg boron/person/day would not already lead to an exceeding of the tolerable upper intake level (UL) of 10 mg/adult/day. It is concluded that in the case of higher supplementation levels there are compelling health protection reasons within the intendment of § 47a LMBG and § 54 LFBG for not using boron in this way.

3 Reasons

3.1 Risk assessment

3.1.1 Agent

3.1.1.1 Boric acid

The dossier submitted refers to boric acid ($H_3 BO_3$, CAS No. 10043–35-3, molecular weight 61.8) of the quality standard in the European Pharmacopoeia (3). In order to calculate the boron equivalents of a boric acid dose, a boron content of 17.48% is to be used for boric acid because of the stoichiometric preconditions in the case of boric acid.

Boric acid occurs naturally in a free form in hot sources and as a mineral (sassoline) in Tuscany (4). Boric acid has a relatively low acidity (pKs=9.14); it forms complexes with numerous hydroxyl-containing substances (e.g. carbohydrates) and proteins and only has low water solubility at ambient temperature that can be considerably increased through alkali halides (5, 7, 8).

3.1.1.2 Borax

The submitted dossier refers to borax (disodium tetraborate decahydrate, $Na_2 B_4 O_7 \cdot 10 H_2O$, CAS No. 1303-96-4, molecular weight: 381.4) of the quality standard in the European Pharmacopoeia (3). In order to calculate the boron equivalents of a borax dose, a boron content of 11.34% is assumed because of the stoichiometric preconditions in the case of borax.

Disodium tetraborate decahydrate occurs in nature as the mineral tincal and as a component of saline in salt lakes (USA) (4, 5). Tetraboric acid, on which borax is based, is not known to occur in a free form. In crystals the boron atoms of the tetraborate anion are linked in a ring-shaped manner. It is readily hydrolytically cleaved in solution (5).

3.1.1.3 Application areas for inorganic boron compounds

The fact that inorganic boron compounds and, more particularly, boric acid and borax are used in many different commercial applications because of, for instance, their pH-buffering, antiseptic, preserving, plasticising or flame-retardant properties, is of particular relevance in this context. In some cases, this can lead to by no means insignificant boron uptakes in con-

junction with complex exposure situations for consumers, private users or employees at their workplace (18, 19) (cf. 3.1.3).

In foods boric acid (E 284) and borax (E 285) may only be used for the preservation of sturgeon roe (caviar) pursuant to the Additives Approval Ordinance (ZZulV) of 29 January 1998 Annex 5, Part C, List 2 whereby the maximum level of 4g/kg (calculated as boric acid) may not be exceeded. This corresponds to the general disposition mentioned in Annex 1 to the reference decree in accordance with § 47a LMBG of 9 May 1995 (10). Reference should be made in this context to the fact that the former Federal Health Office (BGA) already voiced its opposition to this application in 1983 on the basis of a health risk assessment.

In pharmaceutical preparations boric acid has been used in the past as a skin and mucosa antiseptic. This application is now obsolete because of its low efficacy and comparatively high toxicity particularly in conjunction with the risk of resorptive intoxications in children (4, 5). In the graduated plan notice from the Institute for Medicinal Products of the Federal Health Office of 25 July 1983, marketing authorisation was withdrawn for boric acid, its esters and salts in human medicinal products with effect from 1 January 1984 with the exception of:

- healing waters and salts produced from them;
- ophthalmological preparations containing contain boric acid or its salts as a buffer and/or isotonisation;
- homeopathic dilutions with boric acid or its esters or salts;
- medicinal products with phenyl mercury borate or phenyl mercuric(II) dihydrogen borate.

Here the precondition applies that "in conjunction with proper use the ingested amounts of boric acid may not exceed the guidance values for drinking water (limit 2.5 mg boron from 2.5 litre daily drinking amount)".

According to the literature boric acid is also used in vaginal products and contraceptives in concentrations of < 1% (14, 22).

In accordance with the Cosmetics Ordinance of 7 October 997, Annex 2, Part A, tetraborates may be used in concentrations of up to 18% in bath products and up to 8% in wave setting products. Furthermore, the use of boric acid, borates and tetraborates in powders, oral hygiene products and other products is restricted to maximum concentrations of 5%, 0.1 % and 3% (calculated as boric acid). Applications in children under the age of three or to damaged or irritated skin (at levels above 1.5% calculated as boric acid) are not permitted. There are no concentration limits for use in denture cleaning products.

Furthermore, it must be borne in mind that boric acid (PM/REF No. 13620 and 40320), anhydrous sodium tetraborate (PM/REF No. 87040) and barium tetraborate (PM/REF No. 36840) are authorised for the production of plastic consumer products that come into contact with foods (Consumer Products Ordinance of 23 December 1997, Annex 3). It gives a specific migration limit (SML (T)) of 6 mg B/kg food as the total of the above-mentioned three substances. This limit value was derived from the group TDI (Tolerable Daily Intake) of 0.1 mg/kg body weight/day established by SCF (calculated as boron) (11, 42). It is based on the assumption that a person weighing 60 kg ingests 1 kg food daily containing these substances (12). There are no analytical data indicating the degree to which the SML(T) is exhausted.

Various concentrations of sodium tetraborate (maximum 0.005% for presevation, 0.42% for stabilisation of liquid glass as a dewatering accelerator or maximum 2 mg/dm^2 for the vul-

canisation of natural starch) may also be contained in paper, boxes and cardboard that come into contact with food (BfR Recommendation XXXVI[3]), in special paper for specific applications like paper for boiling bags and teabags (BfR Recommendation XXXVI/1)[4], in grease-proof paper, baking boxes and cardboard (BfR Recommendation XXXVI/2)[5] and in suction inserts (BfR Recommendation XXXVI/3)[6]. Only sparse information is available to BfR from application documentation on the resulting migration to food. For instance when used for preservation purposes migration of < 0.008 mg boron/kg food was measured. For the purposes of stabilising liquid glass there are no analytical data but only a theoretical worse case assessment according to which full migration would lead to levels < 0.033 mg boron/kg food.

Furthermore, the anhydride of boric acid, diboron trioxide (B_20_3), is used as a wetting agent in the production of specific types of glass for contact with food, i.e. boron silicate glass (pyrex) and lead crystal. Maximum 0.06 mg B/kg food migrate from lead crystal to food. At a detection limit of 0.01 ppm no migration could be detected from boron silicate glass (13). Boric acid and borax are used in the production of porcelain enamels, ceramic glazes and metal alloys, too (8).

No detailed information is available about the extent to which boric acid and borax are used in other consumer products within the intendment of § 2 para 6 LFGB. However, attention should be drawn to the data available on the use of boric acid in toys and the expert opinion of the BfR predecessor institute, BgVV, of 1 February 1995 (detection of up to 1.3% boric acid in "slimy eggs"[7]) and to the BfR expert opinion of 27 October 2004 (detection of up to 8.5% boric acid in bouncing playdough[8]). For instance, according to the migration studies, correct use of the bouncing playdough would mean that the above-mentioned TDI of 0.1 mg B/kg body weight would be almost fully exhausted. BfR and its predecessor institute, therefore, recommended that the boric acid levels in toys be minimised or safe alternatives used.

Reference can merely be made here to other consumer-relevant applications of boric acid and disodium tetraborate as flame-retardants, detergent additives and to their use in adhesives, various paper products, cigarette paper, boxes, fibrous materials, water-resistant and fireproof textiles, carpets, leather goods, artificial gemstones, wicks and photographic materials (1, 4, 6 - 8, 19, 22).

Furthermore, mention should be made of numerous technical applications of boric acid and/or disodium tetraborates for instance in the electrical, paint, vanish, metal working and chemical industries (18, 19).

Furthermore, aside from sodium orthoborate and disodium octaborate, boric acid and borax are used on a large-scale in biocides as fungicides and insecticides but not in the DIY sector. They are used in wood preservatives in 0.1 - 10% solutions to impregnate timber and in dry rot treatment in 10 - 15% solutions. No significant exposure of consumers to boron has been observed from these applications; however, workplace exposure is to be expected. In arable land, grasslands and in forestry as well as in horticulture or foliar fertilisation, the use of boron compounds in fertilizers with trace nutrients is of importance whereby a minimum content of 0.01% boron is prescribed (Fertiliser Ordinance, as at 16 February 2005). Furthermore,

[3] http://bfr.zadi.de/SEARCH/BASIS/KSE1/ALL/blob_dt/DDD/360DEUTSCH.pdf
[4] http://bfr.zadi.de/SEARCH/BASIS/KSE1/ALL/blob_dt/DDD/361DEUTSCH.pdf
[5] http://bfr.zadi.de/SEARCH/BASIS/KSE1/ALL/blob_dt/DDD/362DEUTSCH.pdf
[6] http://bfr.zadi.de/SEARCH/BASIS/KSE1/ALL/blob_dt/DDD/363DEUTSCH.pdf
[7] http://www.bfr.bund.de/cm/216/borsaeuregehalte_in_slimys_zu_hoch.pdf
[8] http://www.bfr.bund.de/cm/216/borsaeure_in_huepfknete.pdf

inorganic boron compounds like borax are used in plant strengthening agents (Pesticides Act of 14 May 1998, § 31).

Finally, it should be borne in mind that boron is also used as perborates above all as bleaching agents in detergents (concentration: 15 - 31%), in dishwasher detergents (concentration: 4 - 18%) and in stain removers (concentration: 50 %) whereby metaborate, inter alia, is formed from the reaction with water (21, 38, 41). In 2000 as much as 283,849 tonnes of sodium perborate tetrahydrate reached consumers in Western Europe in detergent-containing products (38). Furthermore, sodium perborate is used, for instance, in teeth-whitening and denture cleaning products (41).

3.1.1.4 Boron: natural occurrence, levels in food and water

The element boron (molecular weight: 10.8; third main group in the periodic system) is widely distributed in nature in low concentrations of inorganic borates. It is found in rocks and soil (< 10 - 300 mg B/kg), fresh water (< 0.01 – 1.5 mg/l) and seawater (0.5 – 9.6 mg B/l) (6 - 8). Boron accumulates in aquatic and terrestrial plants but does not accumulate along the food chain. The boron content in terrestrial plants is between 2.3 and 94.7 mg/kg referred to dry weight. The boron content in marine invertebrate animals and fish is between 0.5 and 4 mg/kg referred to wet weight (6). The boron concentration in the air is <0.5 up to 80 ng/m^3 (6). Boron is naturally ingested by human beings from higly diverse foods whereby nuts, dry fruit, fruit, vegetables, wine and beer are particularly rich in boron and meat, fish and dairy products are poor sources. Referred to the ingested amount of a food, beverages with a low boron content like coffee and milk - besides other beverages, fresh fruit and potatoes - are also major contributors to boron intake (1, 6, 7, 14 - 16). A table presenting an overview of this situation can be accessed on the Internet on http://www.food.gov.uk/multimedia/pdfs/boron.pdf (14).

According to the current WHO Guidelines for Drinking-Water Quality, the "Provisional Guideline Value" for boron levels in drinking water is 0.5 mg B/l (9). The provisional nature of this value is due to the fact that in areas with naturally high boron levels there are difficulties in complying with the value using the technologically available treatment methods. The boron levels in drinking water around the world are normally between 0.1 mg and 0.3 mg B/l. They depend on the natural boron concentration in groundwater and the boron levels in wastewater stemming from specific detergents (9, 21).

According to the Drinking Water Ordinance of 21 May 2001 Annex 2, Part 1, No. 3 which transposes Directive 98/83/EC, the limit value of 1 mg/l for boron in water for human consumption must be complied with in Germany. The relevant literature indicates that drinking water from public water supplies in Germany only rarely contains more than 0.3 mg B/l (21).

By contrast, mineral waters could contain considerably more boron than drinking water. For bottled mineral water 0.75 mg B/l is given as the average level and 4.35 mg B/l as the maximum known level (22). The latter value was also taken into account in the current opinion of the EFSA "Scientific Panel on Contaminants in the Food Chain“ (CONTAM-Panel) (17). According to this, it is very unlikely that the general population, including children over the age of 14, would have boron intakes from food and bottled natural mineral water (consumption of 1938 ml/day) that exceed the UL of 10 mg/person/day or, in the case of over 14 to17 year-olds, 9 mg/person/day. For children aged between 1-14 a maximum value of 1.5 mg boron/l for mineral water was recommended based on a similar fluid intake to that of adults (1938 ml/day).

Annex 4 No. 5 to the Ordinance on natural mineral water, spring water and table water of 1 August 1984 in the version of 24 May 2004 envisages a maximum borate level of 30 mg/l in natural mineral waters whereby for boron the instructions concerning the analytical method in Annex 5 have still to be formulated. If one refers the maximum levels of 30 mg/l to the borate anion BO_3^{3-} (molecular weight: 58.8), then this corresponds to a maximum level of 5.5 mg boron/l. In an older study from Germany (24) 25 mineral waters, which were purchased in the retail trade, were found to have boron levels of between <0.02 and 3.23 mg /l, the mean value being approximately 0.5 mg B/l.

3.1.1.5 Physiological relevance of boron

The question about the physiological relevance of boron and related topics can only be touched on briefly here by referring to the corresponding literature and expert opinions (1, 14-16, 23, 27). The dossiers submitted do not contain any information on this subject. Whereas boron is an essential element for plants (6 - 8), no analogue importance for man could be determined. According to a current announcement by the German-speaking Societies for Nutrition and Nutritional Research (27), boron is classified in the group of ultratrace elements. For these elements deficiency symptoms were observed in animal experiments under extreme conditions without, however, anything being known about their specific functions. Their dietary uptake covers the requirements of animals and human beings according to the current level of knowledge since no relevant deficiency symptoms have occurred up to now. In line with the data available, the Food and Nutrition Board of the Institute of Medicine (USA) did not define an "Estimated Average Requirement“ (EAR), a "Recommended Dietary Allowance“ or an "Adequate Intake“ for boron (15).

There are signs that the function of boron in human beings could be linked, amongst other things, to the metabolism of vitamin D and oestrogen and the metabolism and utilisation of calcium, copper, magnesium, glucose and triglycerides (14, 15, 23). The mechanisms behind the interactions between boron and nutrients are uncertain and have not been sufficiently researched (15, 23). The effects observed in tests in higher animals do not permit any sufficiently clear conclusions about the physiological functions of boron (15). There are reports of embryonal defects in conjunction with a boron deficiency in experiments with zebra fish, frogs and trout. These findings would seem to indicate that boron plays a role in reproduction and development. However, tests in rodents did not consistently confirm any boron-related developmental defects (15).

In order to record boron status in bones, plasma, blood and urine, use was made of inductively coupled plasma atomic (or mass) emission spectrometry (14, 23). The normal boron concentration in blood appears to be between 0.1 and 0.2 µg/ml (14).

As far as possible pharmaceutical applications are concerned, there are reports of claims that boron alleviates some symptoms of osteoarthritis and rheumatoid arthritis (14, 23).

3.1.2 Hazard potential

As boric acid is a weak acid, undissociated boric acid is the main form found in aqueous solutions of boric acid or borax with a physiological pH. Hence boric acid and borax more or less have the same toxicity, referred to boron equivalents. This does not apply to sodium perborate (6 - 8).

Several summaries of international bodies (1, 6-8, 14, 15, 22, 23) are available on the toxicology and toxicokinetics of boric acid and borates in addition to the reports of BfR and its

predecessor institutes already mentioned. In some cases they were added to the company dossiers (1, 15, 23). Reference is, therefore, made more particularly below to the report of the EFSA "Panels on Dietetic Products, Nutrition and Allergies“ (NDA-Panel) (1) and only an overview is given of toxicology and toxicokinetics aside from the data directly related to the risk assessment.

3.1.2.1 Toxicokinetics

We know from several studies in human beings, too, that boric acid and borax can be absorbed from the gastrointestinal tract and after inhalation. Values of approximately 95% are given for boron resorption after oral administration of borate in human beings and rats (6). A human study in which diet was supplemented with 10 mg boron/day, led to a recovery of 84% of the administered boron in urine (1, 8).

In vitro data (e.g. 28) and *in vivo* findings (8, 14, 22) are available which indicate that the dermal resorption of boron, administered for instance as boric acid or borax in various preparations, through intact skin is negligible. However, it may be toxicologically relevant in the case of more damaged skin and mucosa (4, 5, 29). This is indicated by animal experiments (rabbits, rats) and human studies (neonates, infants, adults).

According to the results available from animal experiments, undissociated boric acid is evenly distributed, following the administration of boric acid or borates, from the blood compartment to the various soft tissues, with the exception of lower levels in fatty tissue and an accumulation of boric acid in bones. For instance, following the 7-day oral administration of boric acid in rats (equivalent to 93 - 96 mg B/kg body weight/day), a two to three times higher value (47.4 µg B/g) was measured in the bone tissue than the boron concentration in plasma that roughly corresponded to the boron contents in the other organs (8, 22).

Only limited data are available on boron distribution in the human organism. After workplace exposure no signs were found of boron accumulation in blood. From older studies it is known that boron also accumulates in the human skeleton (6, 8, 22).

Boron compounds do cross the human placenta (1, 23) and migrate to breast milk although only limited data are available on this (6).

As far as biotransformation is concerned, it is assumed – on the basis of well-known data and thermodynamic considerations - that inorganic boron compounds are present in the mammal organism as boric acid which is not metabolised (6, 8). As already indicated in section 3.1.1.1, boric acid can form complexes with hydroxyl, amino and/or thiol groups from diverse biomolecules. This complex formation depends on the concentration and is reversible (8, 22).

Studies in rats and rodents are available on the elimination and excretion of boric acid and borate. They show that most of the orally ingested boron is excreted relatively quickly in urine (8, 22). For instance, 60-75% of 750 mg boric acid, equivalent to 131 mg boron, administered orally to test persons, was excreted within the first 24 hours and 93% within the first 96 hours of ingestion in urine (8).

Concerning risk assessment it is of interest that renal boron clearance in rats is higher than in man (1, 8, 15) and that gestating rats and pregnant women had slightly higher boron clearance rates than non-gestating rats and non-pregnant women (8).

Results in rats showing that boron elimination from bones has a different timeline from that in serum or soft tissue are also of relevance. For instance, the boron concentrations in bones in one test, in which rats were fed about 1.4-6.8 mg B/kg body weight/day for nine weeks, only fell gradually in the post-observation phase and were still higher than the controls 32 weeks after treatment. The IPCS (International Programme on Chemical Safety) believes there is a need for research into longer post-observation phases and the factors that influence the accumulation and mobilisation rates of boron in bones (6). Given these findings EPA (Environmental Protection Agency) uses a two-compartment steady state model for its risk assessment of boron compounds (8).

3.1.2.2 Toxicology

3.1.2.2.1 Human data

No consistent data are available on the lethal dose of boric acid and borax in man (7). The pharmaceutical literature indicates 0.8 to 3.0 g for infants, 5-6 g for small children, 12 to 30 g for adults as the lethal doses after oral intoxication (4, 5). It lists intoxication symptoms like gastrointestinal disorders, granular degeneration of tubular cells, cardiovascular collapse, exfoliative dermatitis, alopecia, menstruation disorders and effects on the central nervous system like epilepsy, oedemas and cerebral hyperaemia, anorexia, debility and confusion (1, 29). From case studies in which toxic effects occurred after 4-10 weeks administration, an average daily oral dose of 0.143-0.429 g boric acid/kg body weight/day is calculated. This is equivalent to 25-76 mg boron/kg body weight/day (1).

Some studies examined the endocrine effects of boron supplementation. In one study in 18 men, supplementation of 10 mg boron/day over four weeks led to a significant increase in the plasma-oestradiol concentration and a tendency towards higher testosterone values. The clinical relevance of these findings is uncertain. Their reproducibility in larger numbers of test persons is considered to be necessary (14, 23).

In other studies in perimenopausal or postmenopausal women, contradictory results were obtained concerning the impact on oestradiol plasma values. Whereas supplementation with 2.5 mg boron/day for 60 days led to an increase in oestradiol plasma values during perimenopause (23, 39), the steroid hormone values in plasma in a second study were not affected by the administration of 3 mg boron/day over three weeks to women in postmenopause when this was coupled with parallel and prior administration of a low boron diet (1, 14, 40).

In view of the current reassessment of Hormone Replacement Therapy concerning the causation of a higher risk of breast cancer (on the Internet on http://www.bfarm.de/de/vigilanz/am_sicher_asi/ index.php?more=asi024.php), the findings of Nielsen et al. (37) seem to be important which were not taken into account in the expert opinion of the EFSA NDA Panel (1). In postmenopausal women treated with oestrogen, dietary supplementation of 3 mg boron/day led to a major additional increase in the 17ß-oestradiol serum level. Four men and nine postmenopausal women, of whom five were given oestrogen therapy, and one women prior to menopause ate a diet with a boron content of 0.25 mg over 63 days. They were then given the same diet for 49 days which had been supplemented with 3 mg boron/day as sodium borate. Only in the case of the women who were undergoing hormone treatment, did the 17ß-oestradiol serum contents of 99 ± 15 pg/ml prior to boron supplementation increase to 157 ± 27 pg/ml (p=0.02) after supplementation. The copper concentration in plasma rose from 146 ± 9 µg/dl to 159 ± 11 µg/dl (p=0.04). The authors suspect that the elevated 17ß-oestradiol values could be due to greater resorption of 17ß-oestradiol or reduced degradation

or excretion caused by boron. It is a well-known fact that oestrogen administration leads to an increase in the copper plasma concentration. The study also reveals that the administration of oestrogens raises the serum concentrations of the immunoreactive ceruloplasmin and triglycerides and that the concentrations of these compounds in serum, as a consequence of boron supplementation, increased in all test persons. From this the authors conclude that boron not only amplifies some oestrogen effects but also imitates them. The reproducibility of the results in larger patient groups has still to beexamined.

These findings reveal a need for research into the effect of boron on the endocrine system (23).

Given the positive findings of numerous animal experiments on developmental and reproduction toxicology, a study in employees involved in borax mining in the USA and an ecological study in Turkish population groups with differing boron uptakes from drinking water (up to 29 mg B/l) are important. They provided no indications of fertility impairments through exposure to boron. Both studies did, however, show a lower, albeit not significant, excess of female births (1, 6, 14, 23). The validity of these studies must be deemed to be very limited as, in some cases, they do not contain any statistical analyses and the more sensitive parameters of reproduction toxicity like weight at birth or sperm quality were not examined(1, 6, 23). IPCS (6) and Moore (22) criticise the lack of reliable human studies on reproduction toxicology and express a need for research. For instance, there are no studies on the periods of time involved up to the achievement of pregnancy, on delays in conceiving, spontaneous abortions, testicular function or sperm analyses (6). The possible impairment of sperm quality (cf. 3.1.2.2.2) could be relevant for sub-fertile men (23).

3.1.2.2.2 Data from animal experiments

With reference to the existing above-mentioned expert opinions (e.g. 1, 6-8), the studies involving inorganic boron compounds on acute, sub-acute, sub-chronic and chronic toxicity and on mutagenicity cannot be addressed here. The evaluations revealed that there were no signs of carcinogenic or genotoxic effects of boric acid or borates; however, the data do not permit any classification in this respect for human beings.

The decisive factors for the assessment of the hazard potential of inorganic boron compounds are their developmental and reproduction toxic effects which are compiled below by on a dose basis. More details on the individual studies can be found in the literature (1, 6-8, 14, 15, 22, 23).

The most important developmental toxicological study is the feed study in rats by Price et al. (30). They observed, amongst other things, an increased incidence of rib shortening and reduced foetal weight in the offspring of animals fed boric acid with a LOAEL (Lowest observed adverse effect level) of 13.3 mg B/kg body weight/day and a NOAEL (No observed adverse effect level) of 9.6 mg/kg body weight/day.

Rib malformations and reduced body weight were also observed in the litters of mice in a feed study with boric acid (31). It led to a LOAEL of 79 mg B/kg body weight/day and a NOAEL of 43 mg B/kg body weight/day.

In a study in rabbits fed a boric acid solution by gavage, there were reports of reduced foetal weight, an elevated incidence of cardiovascular malformations in the offspring and maternal toxicity with a LOAEL of 43.7 mg B/kg body weight/day and a NOAEL of 21.9 mg B/kg body weight/day (32).

A NOAEL of 4.4 mg B/kg body weight/day was derived from a reproduction toxicological study in dogs given boric acid or borax in feed over 90 days in which severe testicular atrophy was observed at a dose of 44 mg B/kg body weight/day. (33, 14, 23). The study is only considered to have limited validity because of the low number of animals (23).

From a multigeneration feed study in rats by the same authors, 58.8 mg B/kg body weight/day was established as the effect level for adverse effects on female and male reproduction (sterility, lack of spermatozoa, testicular atrophy, decreased ovulation) and 17.5 mg B/kg body weight/day is given as the NOAEL (33).

In a rat feeding study with boric acid inhibited sperm release from a dose of 26 mg B/kg body weight/day on and testicular atrophies from 52 mg B/kg body weight/day on is reported (34).

In a multigeneration study in mice in which boric acid was administered in feed (doses in mg B/kg body weight/day: for females 31.8; 147.9; 290.2; for males 19.2; 104.5; 220.2), the fertility of the two genders was reduced in the highest dose group and the fertility index was decreased at the middle dosage. Cross-mating experiments showed that boric acid primarily affected the male reproductive system. From the study no NOAEL could be derived for male animals as, at 19.2 mg B/kg body weight/day, reduced sperm motility could still be observed in the F_0 generation and a lower sperm concentration in the F_1 generation. 31.8 mg B/kg body weight/day is deemed to be the NOAEL for female animals (14, 22, 35, 36).

Furthermore, endocrine effects of boron were also detected in animal experiments. After the administration of 2 mg boron/animal(?)/day in drinking water, elevated testicular and plasma testosterone values were observed in rats as well as elevated plasma values in the luteinising hormone. The administration of 25 mg boron/animal(?)/day led to elevated plasma values for the follicle-stimulating hormone (14).

Given these findings, according to which boron intakes led to an increase in testosterone and vitamin D coupled with a decrease in HDL cholesterol in plasma, it is assumed that boron could influence hydroxylation reactions at the steroid rings by forming bridges (14).

3.1.2.2.3 Classification in the framework of the assessment of chemical substances

As far as we know the Technical Committee on Classification and Labelling of Dangerous Substances (TC C&L) of the European Commission approved a proposal at its meeting on 8 September 2005 to classify boric acid and sodium borates with regard to their developmental toxic and fertility toxic properties in category 2 in the 30th (ATP) (Adaptation to Technical Progress of Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances).

3.1.2.2.4 Tolerable upper intake level

Several national and international panels have looked at the establishment of tolerable daily intakes or similar parameters for boron from boric acid and borates from various aspects (1, 6-8, 15, 23). They almost all uniformly observed that the available human data are not sufficient for this purpose and that, therefore, recourse must be made to data from animal experiments particularly on developmental and reproduction toxicology. They also agree that the NOAEL of 9.6 mg B/kg body weight/day established in the study by Price et al. (30) is the

most suitable value concerning reduction of foetal weight. The lower NOAEL derived from a study in dogs of 4.4 mg B/kg body weight/day (33) is not used because of the overly low number of animals in the study and the relatively large margin between factor 10 and the effect dose (23). Based on various uncertainty factors or adjustment factors, IPCS derived for instance a TI (tolerable intake) of 0.4 mg B/kg body weight/day (6), ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) a TDI (Tolerable Daily Intake) of 19.2 mg B/day (7) for an adult weighing 60 kg for the developmental toxicological aspect and EPA a RfD (the human dose that is likely to be without an appreciable risk of deleterious non cancer effects during a lifetime) of 0.2 mg B/kg body weight/day. The EPA expert opinion gives a comprehensive comparison of the different derivation models (8). In 1996 for the assessment of boron in mineral water based on a NOAEL of 9.6 mg B/kg body weight/day and the usual uncertainty factor of 100, SCF calculated a TDI of 0.1 mg/kg body weight/day and assumed its 10% exhaustion in mineral water (11). With regard to the risk assessment to be undertaken here, reference is made to the 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) proposed by the EFSA NDA Panel in 2004. It also underlies the current expert opinion on boron levels in mineral waters (17). Based on the NOAEL of 9.6 mg B/kg body weight/day, an uncertainty factor of 60 was used to derive the UL (the usual factor 10 for the variability between animals and man; for interindividual variability 6 was used instead of 10 that takes into account the boron-specific data for the glomerular filtration rate (23)). This leads to a UL of 0.16 mg/kg body weight/day corresponding to 10 mg/person/day for adults which also applies to pregnant and lactating women. From the UL for adults the NDA Panel derived UL values in (mg/person/day) of 3, 4, 5, 7 and 9 taking into account the body surface situation of children aged 1-3, 4-6, 7-10, 11-14 and 15-17.

The UL recommended by the Food and Nutrition Board in the USA (15) of 20 mg/adult person/day was established for a body weight of 61 kg from the NOAEL of 9.6 mg B/kg body weight/day with an uncertainty factor of 30 (10 for interspecies variability, 3 for intraspecies variability taking into account the expected similarity of kinetics in various human beings). The choice of factor 3 instead of 6 was not scientifically substantiated which means that, in the opinion of BfR, preference should be given to the UL derived by the NDA Panel which is in the order of magnitude of the EPA RFD.

3.1.3 Human exposure to boron

The extremely diverse application of inorganic boron compounds (cf. 3.1.1.3) coupled with the major differences in concentrations at which boron occurs in individual food sources (cf. 3.1.1.4) leads to a highly complex exposure situation dependent on individual behaviour and belonging to specific groups in the population (e.g. children, employees with workplace exposure). The various assessments of daily boron intake by different panels mention the sparse data situation and consideration is normally restricted to specific intake fields (e.g. 1, 7). They quote as the main sources of boron exposure: food, mineral water and possible exposure at the workplace during production and the diverse industrial uses of boron compounds (cf. 3.1.1.3) (22). Applications involving medicinal products, cosmetics, consumer products and specific other products like insecticides are also considered to be further possibly significant sources of exposure (8).

3.1.3.1 Sources of exposure

Varying information is given for dietary intake (not including food supplements) depending on the population and food habits considered. In the dossiers submitted reference is made to data from the Expert Group on Vitamins on Minerals (23) and analyses of the British Total

Diet Study (1994) according to which the dietary boron intake of British adults has a mean value of 1.5 mg/day and an upper value (97.5 percentile) of 2.6 mg/day (1, 14, 23). Older British studies dating back to 1972/73 mentioned a higher mean value with greater variability: 2.82 ±1.55 mg B/day (14, 16, 22). According to more recent data the median of daily boron intake in the American population is 0.75 – 0.96 mg for school children, 0.87 – 1.35 mg for adults, 1.05 mg for pregnant women and 1.27 mg for lactating women (15). Comparison of the weighted 5th percentiles, medians, mean values and 95th percentiles for the US population on a normal diet (men: 0.43, 1.02, 1.17, 2.42 mg B/day; women: 0.33, 0.83, 0.96, 1.94 mg B/day) and on a vegetarian diet (men: 0.46, 1.30, 1.47, 2.74 mg B/day; women: 0.33, 1.00, 1.29, 4.18 mg B/day) reveals that vegetarians are to be seen as a potentially "high intake group" (1, 14, 21, 23). Moore comments that a diet rich in vegetables, fruit and other foods with a high boron concentration can lead to boron intakes of 10 mg/day (22).

The company dossiers indicate boron uptake from drinking water of 0.2 – 0.6 mg/day (1, 2, 3) whereby reference is made to the IPCS assessment (6). ECETOC assumes that less than 1 mg B/day is normally ingested from drinking water (7).

Hence, an exhaustion of the limit value of 1 mg boron/l (cf. 3.1.1.4 and 14) currently in place in the EU is not to be expected. This would entail exposure of 2 mg boron/day in conjunction with the amount of water normally assumed to be consumed by adults of 2 l/day (22).

With regard to boron uptake from mineral water, it is hypothetically assumed in the literature that a quarter of the daily water consumption of adults, which is set at 2 l, is replaced by mineral water. If one assumes mineral water with the highest boron level of 4.35 mg B/l, this would lead to a boron intake of 2.18 mg B/day (22).

In view of the data that the daily consumption of bottled mineral water by adults (indication of mean value, 95th percentile and 99th percentile) is for instance in France 408 ml, 1109 ml and 1672 ml and in Italy 487 ml, 1000 ml and 1938 ml (17), it is possible that individuals, who under certain circumstances drink the same brand of bottled mineral water over longer periods with far higher than average boron contents, should be considered as a potential "high intake group“ (21).

Not enough information is available on just how high additional human exposure to boron from other sources actually is. It is probably governed by differences in behaviour and life situation and, therefore, subject to major fluctuations. The company dossiers assume exposure through cosmetics and consumer products of up to 0.47 mg B/day (23, 1). It is unknown how this value has been established, in view of the many diverse uses in cosmetics and consumer products. It does, however, appear to be very low given that the specific migration limit value alone for plastic consumer products that come into contact with food is 6 mg/kg food and that intake of 0.17 mg boron could only be achieved by ingesting 1 g of a cosmetic oral hygiene product containing 0.1% boric acid. Another example from the area of consumer products is the possibly high exposure to boron in toys. As explained in the BfR report of 27 October 2004, it was assumed, for instance, in conjunction with the proper use of bouncing playdough based on the measured migration value in welding simulations that, assuming a dermal resorption rate of 10% for a child weighing 20 kg, there may be an uptake of 1.75 mg boron. Consequently, children must also be included in the groups which are possibly exposed to higher boron levels.

No data are available either in the dossiers or in the literature on boron exposure through medicinal products like ophthalmics which are often used regularly and over long periods. Hence, it can merely be stated here that, in accordance with the comments in Chapter

3.1.1.3, the daily maximum exposure of 2.5 mg boron/day must not be exceeded in pharmaceutical products as this additional boron source can also lead to higher boron exposure.

According to information in a HERA (Human and Environmental Risk Assessment on Ingredients of European Household Cleaning Products) report (38) referred to kg body weight/day, the boron intakes of the consumer from possible dermal, inhalational or oral exposure in consequence of the proper use of perborate-containing household products (detergents and dishwasher detergents) are considerably lower than 1µg or are described as negligible. No exposure data are provided on this or any other perborate applications in the company dossiers.

At the workplace exposure to boron-containing compounds can occur mainly through inhalation during mining, manufacturing and processing stages. According to Moore et al. (22) boron exposure at the workplace varied in women (assumed body weight: 60 kg) in the USA by three orders of magnitude from < 0.065 mg up to 130 mg B/day with a mean value of 6.5 mg B/day. Another source indicates total boron intakes of 5 - 24 mg/person/dayas a consequence of workplace exposure (including dietary boron intakes) (7). According to estimates from the USA from 1993 some 420,000 workers may possibly have been exposed to borates at the workplace (22). Comparisons of production figures (which can also be deemed to be a sign of possible consumer exposure) indicate that in Europe, too, numerous workplaces are affected by boron exposure. For instance in 1989 in the USA 750,000 tonnes sodium borates and 195,000 tonnes boric acid , and in Western Europe 30,000 tonnes sodium borates and 56,000 tonnes boric acid were utilised (calculation as diboron trioxide B_2O_3) for the production of the main boron compounds (7). In this context it should be pointed out that the "Senate Commission for the Testing of Harmful Working Materials" of the German Research Society (DFG) is also currently involved in drawing up MWC (maximum workplace concentration) values for boron and its inorganic compounds (25). On this basis individuals exposed to boron-containing compounds at the workplace are deemed to be a group with potentially high boron intakes.

Boron intakes from the environment amount to 0.5 µg/day from the soil and 0.44 µg/day from the air according to IPCS and are, therefore, negligible.

3.1.3.2 Total exposure

A satisfactory assessment of total boron intake is not possible given the sparse data situation. In principle concerning the following calculations it must be suspected that actual total boron intake could be higher than assumed here because of non-recorded boron availability from the most diverse products. Additional daily boron intake from food supplements is assumed according to the dossiers to be a) 1 - 3 mg, b) 9 mg and in the literature c) 30 mg.

Scenario 1: In accordance with the data in the dossiers, the boron intakes for consumers on a normal diet who do not belong to a "high intake group“ (1, 14, 23) are given in Table 1. This would lead per person to daily total boron intakes not including food supplements of up to 3.67 mg and including food supplements up to a) 4.67 – 6.67 mg, b) 12.67 mg and c) 33.67 mg.

Table 1: Boron intakes according to Scenario 1

	Daily boron intake		
From food (97.5 percentile)	2.6 mg		
From 2 l drinking water	0.6 mg		

From cosmetics and consumer products	0.47 mg		
Total intake not including food supplements	3.67 mg		
From food supplements	a) 1- 3 mg	b) 9 mg	c) 30 mg
Total boron intake including food supplements	a) 4.67 – 6.67 mg	b) 12.67 mg	c) 33.67 mg

Scenario 2: This is based on the assumption that instead of a normal diet a diet that mainly consists of plant components or other components rich in boron is consumed (for instance 100 g nuts contain: 1.4 mg boron; 500 g fruit: 1.7 mg boron, 500 g leafy vegetables: 1 mg boron, 10 g caviar: 7 mg boron). Hence by way of example a boron intake , is presumed that is 2 mg higher than in Scenario 1. Per person this can, therefore, lead to permanent total daily boron intakes, not including food supplements, of 5.67 mg and including supplements of a) 6.67 – 8.67 mg, b) 14.67 mg and c) 35.67 mg.

Scenario 3: If, in addition to the assumption of the normal diet in Scenario 1, we regardpartial or complete substitution of drinking water with boron-rich mineral water (2 l contain maximum 8.7 mg boron, cf. 3.1.1.4 and 3.1.3), then a possible additional boron intake of 4 mg boron could be assumed by way of example. This would lead per person to total daily boron intakes not including food supplements of up to 7.67 mg and including food supplements of up to a) 8.67 – 10.67 mg, b) 16.67 mg and c) 37.67 mg.

If one extends Scenario 1 to include the administration of a medicinal product containing a boron compound like e.g. eye drops, this would lead in **Scenario 4** to a possible increase in daily boron intake by maximum 2.5 mg boron per person (cf. 3.1.1.3). This would result per person in total daily boron intakes not including food supplements of up to 6.17 mg and including food supplements of up to a) 7.17 – 9.17 mg, b) 15.17 mg and c) 36.17 mg.

In **Scenario 5** it is assumed by way of example that in addition to the exposure in Scenario 1 there is a further boron intake of 5 mg/day/person as a consequence of workplace exposure (cf. 3.1.3.1). This would lead per person to a total daily boron intake not including food supplements of 8.67 mg and including food supplements of a) 9.67 – 11.67 mg, b) 17.67 mg and c) 38.67 mg.

Just one example is used in **Scenario 6** to illustrate the exposure that would result for a consumer belonging to two high intake groups. The combination of Scenarios 2 and 3 does not seem to be unrealistic (intake of boron-rich foods and a specific boron-rich mineral water). Per person this would result in total daily boron intakes not including food supplements of 9.67 mg and including food supplements of a) 10.67 – 12.67 mg, b) 18.67 mg and c) 39.67 mg.

These scenarios presented here for adults are intended as examples and can only be seen as a rough estimate for the assessment of daily boron intakes which in reality are likely to be mixtures of the above scenarios. Furthermore, it should be borne in mind that the exposure values calculated could be exceeded in reality. This is not just because, as mentioned already, on the one hand the scale of possible boron exposure sources could not be recorded here owing to inadequate data and, on the other, we did not assume the exhaustion of existing limit values (e.g. for drinking water and plastic consumer products that come into contact with foods) or of known maximum concentrations (e.g. in mineral water). This may also be due to the fact that there may be individuals, unlike what has been proposed here, who be-

long to more than one or two high intake groups. A worst case calculation, which would take all this into account, would exceed the values calculated in Scenario 6 theoretically by at least 10 mg boron/day/person. However, this does not seem to be very realistic in terms of the assessment to be undertaken here.

Finally, a separate exposure assessment would be needed for children but this is scarcely possible because of the inadequate data available. With regard to dietary boron intake, recourse must be made to the value of 0.75 – 0.96 mg boron/day/person indicated for American school children (no data on age) (15). Bearing in mind the high fluid intake recommended for school pupils of at least 2 l (26), 0.6 mg B/day/person is proposed, as in the first scenario, for boron uptake from drinking water. Furthermore, regarding exposure to boron in cosmetics and consumer products, the value of 0.47 mg boron is assumed which is indicated in Table 1 for adults. This means that as the basic exposure of school children (**Scenario 1 sc**), without it being possible to specify age, the total daily boron intake per person not including supplements is 2.03 mg and including supplements is a) 3.03 – 5.03 mg and b) 11.03 mg (as the administration of 30 mg boron/day including supplements to children appears to be completely unlikely, no calculation is made on the basis of c)). For school children, too, possible additive exposure sources must be taken into account. In addition to Scenario 1 $_{SC}$ there could also possibly be a daily intake per person of for instance: as **Scenario 2 sc** 2 mg boron from nuts and foods of plant origin, as **Scenario 3 sc** 4 mg from boron-rich mineral water (cf. 3.1.1.4 for the recommended limitation of boron levels in mineral water for children aged between 1 - 14) or **Scenario 4 sc** 1.75 mg from plastic toys like bouncing playdough whereby no data are available on possible further exposures e.g. from school or handicraft materials (glues, paper, paints). **Scenario 5 sc** is a combination of Scenario 2 SC and Scenario 3 SC (intake of boron-rich food as well as boron-rich mineral water). The resulting exposure values are given in Table 2. For the reasons outlined above, the estimated values given here could be lower than boron exposure in reality at least in particularcases.

Table 2: Various scenarios for boron intake by children

	Total daily boron intake (mg/day/person)		
	Not including food supplements	Additional boron intake from food supplements	
		a) 1 - 3 mg B/day	b) 9 mg B/day
Scenario 1 $_{SC}$	2. 03	3.03 – 5.03	11.03
Scenario 2 $_{SC}$ (boron-rich plant based diet)	4.03	5.03 – 7.03	13.03
Scenario 3 $_{SC}$ (boron-rich mineral water)	6.03	7.03 – 9.03	15.03
Scenario 4 $_{SC}$ (boron intake from toys)	3.78	4.78 – 6.78	12.78
Scenario 5 $_{SC}$ (boron-rich plant diet and boron-rich mineral water)	8.03	9.03 – 11.03	17.03

The scenarios calculated for adults must be used for the exposure situation of pregnant and lactating women.

3.1.4 Discussion and assessment

3.1.4.1 General consideration

The health assessment to be undertaken concerning the addition of borax and boric acid to food supplements faces the problem of considerable gaps in knowledge about the fundamental core parameters of risk assessments. It is not just that the basic exposure derived from diverse sources can only be vaguely estimated; human toxicological data are also sparse. There is a lack of clarity about the effects and mechanisms of action in man coupled with the fact that interactions with endogenous and added active substances (e.g. steroid hormones) seem to be toxicologically relevant. The large dose range, at which boron-containing food supplements are obviously currently available on the European market, highlights the unclarified question whether daily requirements really do exist. All this makes risk assessment even more difficult. In principle, the tolerance of possible health risks of boron supplementation which have not been identified or could not be estimated up to now must be set against the fact that there have been no reports so far of damage resulting from a boron deficiency. This also seems to be of importance against the backdrop that, for instance, boron supplementation was not permitted in Germany up to now.

Boron is essential for plants and is, therefore, contained in foods of plant origin. By means of feed and drinking water uptake it also reaches animal organisms and corresponding foods. Furthermore, human beings ingest significant amounts of boron from conventional beverages (drinking water, mineral water, milk, juices, coffee, wine, beer). The risk of a boron deficiency, which would make corresponding food supplementation necessary, can scarcely be identified aside from the open question of essentiality. In this context, attention should be drawn to the paradox situation that boron intakes from numerous other sources outside the food sector (which mean additional "intake") are reduced on toxicological grounds e.g. by limit values to such an extent that they are below or on the same scale as the amounts which are now to be added for the purposes of supplementation.

3.1.4.2 Assessment of exposure data

First of all, the exposure data suffer from the deficit that insufficient information is available on the boron intakes of various groups in the population depending on their diet. More particularly, there are no age-related data for children. Furthermore, there is a lack of concrete data concerning the extent to which consumers ingest boron from other sources. Here contact with intact skin, a resorption barrier, seems to be less important than the use of boron in products which facilitate possible resorption through damaged skin or mucosa or via the inhalational or oral routes. Hence, the risk assessment for consumers focuses primarily on application areas that can lead to oral exposure. In this respect, there is not enough information on the migration of boric acid or borates from plastic consumer goods that come into contact with food (cf. 3.1.1.3 and 3.1.3.1). The same holds for all other consumer-relevant applications mentioned in Chapter 3.1.1.3, particularly consumer goods. Not enough information is available either on the concentrations used or the release of the boron compound under conditions of utilisation. This means that here, too, the resulting exposures cannot be realistically estimated. Given these gaps in knowledge the following risk assessments (3.1.4.3), that compare the exposure doses and the UL, can only be seen as a rough approximation. Attention is, therefore, drawn to the fact that the exposure scenarios presented in Chapter 3.1.3.1 are oriented towards realistic preconditions that do reflect comparatively high boron uptake from multiple sources but do not constitute a worst case situation.

3.1.4.3 Dose-related risk assessment

Adults

The exposure scenarios 1 to 6 for adults presented in Chapter 3.1.3.2 highlight the fact that in the case of food supplements leading to the intake of a daily dose of 9 or 30 mg boron, the UL of 10 mg B/person/day (1) (cf. 3.1.2.2.4) is already permanently exceeded when based on a normal diet and, to an even greater degree, when there is additional boron intake from boron-rich food, mineral water or other sources. On this basis alone it must be assumed that there are compelling health protection reasons within the intendment of § 47a LMBG and § 54 LFBG for not marketing food supplements with daily boron doses on the above-mentioned scale. Risks are seen, as can be derived from the data from animal experiments (cf. 3.1.2.2.2), particularly with regard to developmental toxicity (reduced weight of foetus, malformations) and fertility. Pregnant women and sub-fertile men are, therefore, to be considered as possibly especially sensitive groups. For instance, in the case of ingestion of 9 mg boron/day from a food supplement by an adult weighting 60 kg in Scenario 6, the Margin of Safety (MOS) (basic exposure coupled with consumption of boron-rich foods and boron-rich mineral waters) is 56.2 for reproduction toxic effects taking into account the NOAEL of 17.5 mg B/kg body weight/day (33) and is only 30.9 for developmental toxic effects taking into account the NOAEL of 9.6 mg B/kg body weight/day (30). These margins do not guarantee sufficient health protection given the gaps in knowledge about the use of boron in food supplements.

In the case of Scenarios 3 (additional consumption of boron-rich mineral water), 5 (additional workplace exposure) and 6 (see above), the taking of food supplements with daily boron doses of 3 mg would lead to a permanent exceeding of the UL of 10 mg/person/day by up to 27%. Consequently it has to be taken into account that supplementation with 3 mg/day, i.e. a dose which normally exceeds the level of dietary boron ingested, may lead for a by no means insignificant section of the population to overly low margins of safety to the NOAEL values in animal experiments. Here again pregnant women, unborn children and sub-fertile men are to be highlighted as an especially sensitive risk group.

Aside from the minor exceeding of the UL in Scenario 6, it is solely in the case of food supplements containing only 1 mg boron as the daily dose that there are total boron intakes below the UL of 10 mg in all the scenarios presented.

However, it must be pointed out that supplementation with boron levels that are also in the range of possible dietary boron intake could entail risks that have not been assessed up to now. The findings by Nielsen et al. (37) seem to be important and need to undergo further research. After supplementation with 3 mg boron/day in postmenopausal women, who were treated with oestrogen, they observed clearly elevated 17 ß-oestradiol values in serum (cf. 3.1.2.2.1). Because of the low number of test persons and limitations in the test regimen, interpretation of the findings is difficult. It should also be pointed out in this context that given the findings of the WHI (Women's Health Initiative) study, a higher breast cancer risk is assumed in postmenopausal women in consequence of HRT with oestrogen-gestagen combinations. Hence, the Federal Institute for Medicinal Products and Medical Devices (BfArM) issued the recommendation that oestrogen doses in HRT should be reduced as far as possible (in the Internet under http://www.bfarm.de/de/vigilanz/am_sicher_asi/index.php?more=asi024.php). From these facts the question arises whether the addition of boron to food supplements could increase the risk of mammary carcinomas for women on HRT by raising the oestrogen levels. This group of patients encompasses 5 million women in Germany,.

There could also be interaction between boron and oestrogen-containing oral contraceptives. There are no studies available on this or on the question of how boron intakes influence the menstruation cycle.

Furthermore there is a need for research having regard to sensitive reproductive toxicological parameters in man, above all regarding male fertility depending on boron intakes. For instance, it has not been examined whether boron can lead to delayed pregnancies, delayed conception, higher miscarriage rates and impaired testicular function. Furthermore, no sperm analyses are available either. For instance minor reductions in sperm quality may be significant for sub-fertile men, a risk group included in the patient cohort of reproductive medical counselling centres ("child wish consulting hours"). Furthermore, there is a need for clarification of findings indicating that boron supplementation led to elevated oestradiol plasma values in men.

The factors that influence boron accumulation and boron mobilisation in bones have not undergone sufficient examination.

With regard to breastfeeding no data are available which allow to draw conclusions from the boron status of the mother to the boron content of the breast milk.

In consideration of the inadequate data situation particularly on overall exposure, boron supplementation during lactation and pregnancy is advised against on precautionary grounds.

Children
No age-specific data on dietary boron intake are available for children. This means that the total exposure can only be roughly estimated for school children in Chapter 3.1.3.2. Under these circumstances an exact individual comparison with the allocated age-specific UL values is not possible (cf. 3.1.2.2.4). The total exposures calculated in Scenarios 1 $_{SC}$ to 5 $_{SC}$ do, however, illustrate that food supplements containing a daily dose of 9 mg lead, in every case, to an exceeding of the UL values for all age groups. This probably also holds in many cases for food supplements with daily doses of 1-3 mg boron. This applies in particular when there is additional intake from boron-rich food (Scenario 2 $_{SC}$) or boron-rich mineral water (Scenario 3 $_{SC}$). Since no adequate exposure data are available and it is not possible to rule out possible adverse effects on skeletal growth resulting from boron accumulation, boron supplementation even at low doses is advised against in children.

3.1.4.4 Summary and action framework

By way of summary it can be said that the current state of knowledge does not permit any risk assessment of the quality standard required for substances to be used as food supplements.

Besides the lack of exposure data, there are no studies particularly on the effects of boron on sensitive fertility parameters in man or on the endocrine system either. There is above all a need for clarification of signs of a possible elevation of oestradiol serum levels in postmenopausal women undergoing hormone replacement therapy through the administration of 3 mg boron/day and of elevated oestradiol plasma levels in men following supplementation with 10 mg boron/day. Overall, the possible adverse effects of boron supplementation cannot be estimated because of the lack of knowledge about physiological functions, mechanisms of action, toxicological effects and interactions of boron with various endogenous and exogenous substances (e.g. steroids) in man. Hence, the use of boron in food supplements is advised against until sufficient data become available. This applies above all to consumer

groups who could be particularly sensitive to possible boron-induced adverse effects, i.e. children, pregnant and lactating women, breastfed children, postmenopausal women undergoing hormone replacement therapy and sub-fertile men.

Estimates of total exposure in consequence of boron supplementation in amounts of 1, 3, 9 or 30 mg/person/day showed technically that the only case in which the tolerable upper intake level (UL) was not exceeded even by the high intake groups was at a dose of 1 mg/person/day. It can, therefore, be assumed within the intendment of § 54 LFGB (formerly § 47a LMBG) that there are compelling health protection reasons that oppose the uptake of boron from supplements

a) in amounts from 3 mg upwards for groups in the population with comparatively high boron intake from various sources and
b) in amounts from 9 mg upwards for all population groups.

Furthermore, it is generally to be recommended that risk assessment and the establishment of limit values for inorganic boron compounds in individual application areas should take into account the complex exposure situation. For instance, the extensive exhaustion of tolerable intake levels by just one of the many exposure areas is deemed to be problematic. In this context it is felt that there is a need for examining the extent to which the comparatively high specific migration limit value (SML (T)) of 6 mg B/kg food can be reduced for plastic consumer goods that come into contact with food (cf. 3.1.1.3). BfR will propose that the appropriate EFSA panel should examine this question.

Finally, this risk assessment shows by way of example that, in certain cases, in conjunction with the envisaged establishment of maximum levels for mineral substances, the exposure assessment outlined in Article 5 b) of Directive 2002/46/EC on food supplements of 10 June 2002, that only envisages consideration of mineral intake from other food sources, must be taken one step further. All sources of exposure must be taken into account.

4 References

1. EFSA, 2004.
Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the Commission related to the tolerable upper intake level of boron (Sodium Borate and Boric Acid), (Request No. EFSA-Q-2003-018); The EFSA Journal Vol. 80:1-22.

2. Scientific Committee on Food; 2001.
Guidance on submissions for safety evaluation of sources of nutrients or of other ingredients proposed for use in the manufacture of foods; SCF/CS/ADD/NUT/21Final 12 July.

3. European Pharmacopoeia; 2002.
Borax, Boric acid, 4th ed.

4. Hager ROM; 2003.
Natriumtetraborat Decahydrat; Springer Verlag, Heidelberg.

5. Kommentar zum DAB 10; Grundlfg. 1991.
Borsäure; B 48 (2.Lfg. 1993), Natriumtetraborat; N 48 (4. Lfg. 1994).

6. WHO; 1998.
Boron; Environmental Health Criteria 204, IPCS.

7. ECETOC; 1995.
Reproductive and general toxicology of some inorganic borates and risk assessments for human beings; Technical Report No. 63.

8. U.S. Environmental Protection Agency; 2004.
Toxicological review of boron and compounds; EPA 635/04/052.

9. WHO; 2004.
Guidelines for drinking-water quality; Vol. 1: 3rd ed.

10. Bundesministerium für Gesundheit; 1995.
Bundesanzeiger vom 23. Mai.

11. Reports of the Scientific Committee on Food; 1998.
Opinion on arsenic, barium, fluoride, boron and manganese in natural mineral waters; Expressed on 13 December 1996, 43rd series.

12. European Commission; 2005.
Synoptic Document; SANCO D3/AS D(2005) .

13. Food Standards Agency; 2002.
Investigation of the significant factors in elemental migration from glass in contact with food; Project A03029.

14. Expert Group on Vitamins and Minerals; August 2002.
Revised review of boron; EVM/99/23/P.REVISEDAUG2002.

15. Food and Nutrition Board, Institute of Medicine; 2001.
Dietary Reference Intakes; National Academy Press.

16. WHO; 1996.
Trace elements in human nutrition and health.

17. Scientific Panel on Contaminants in the Food Chain; 2005.
Opinion of the scientific panel on contaminants in the food chain on a request of the Commission related to concentration limits for boron and fluoride in natural mineral waters; The EFSA Journal, Vol. 237:1-8.

18. European Commission, European Chemicals Bureau; 2000.
Iuclid Dataset: boric acid.

19. European Commission, European Chemicals Bureau; 2000.
Iuclid Dataset: disodium tetraborate.

20. Aurand K, Lange-Asschenfeldt H, Hässelbarth U, Steuer W; 1991.
Die Trinkwasserverordnung, 3. Auflage, Erich Schmidt Verlag.

21. Grohmann A, Hässelbarth U, Schwerdtfeger W; 2003.
Die Trinkwasserverordnung, 4. Auflage; Erich Schmidt Verlag.

22. Moore JA, Expert Scientific Committee; 1997.

An assessment of boric acid and borax using the iehr evaluative process for assessing human developmental and reproductive toxicity of agents; Reproductive Toxicology, Vol. 11, No. 1: 123-160.

23. Expert Group on Vitamins and Minerals; 2003.
Safe upper levels for vitamins and minerals; Food Standards Agency.

24. Graffmann G, Kuzel P, Nösler H, Nonnenmacher G; 1974.
Spurenbestimmung von Bor in Oberflächengewässern und Trinkwässern; Chemiker-Zeitung, 98. Jahrgang, Nr. 10: 499-504.

25. Deutsche Forschungsgemeinschaft; 2005.
MAK- und BAT-Werte-Liste; Wiley-VCH Verlag.

26. Ärzte Zeitung;02.09.2005.
Bessere Noten durch Trinken im Unterricht?

27. Deutsche Gesellschaft für Ernährung; 2000.
Referenzwerte für die Nährstoffzufuhr; 1. Auflage, Umschau/Braus Verlag.

28. Dusemund B;1987.
Freisetzung und In-vitro-Hautpermeation von Borsäure aus einer Salbe; Arzneim.-Forsch./Drug Res., Vol. 37 (II).10:1197 - 1201.

29. Martindale; 2005.
The complete drug reference; Thirty-fourth edition, Parmaceutical Press.

30. Price CJ, Strong PL, Marr MC, Myers CB, Murray FJ; 1996.
Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation; Fundam. Appl. Toxicol., Vol. 32: 179 - 193.

31. Heindel JJ, Price CJ, Field EA, Marr MC, Meyers CB, Morrissey RE, Schwetz BA; 1992.
Developmental toxicity of boric acid in mice and rats; Fundam. Appl. Toxicol., Vol.18: 266 - 277.

32. Price CJ, Marr MC, Myeos CB, Seely JC, Heindel JJ, Schwetz BA; 1996.
The developmental toxicity of boric acid in rabbits; Fundam. Appl. Toxicol., Vol. 34: 176 - 187.

33. Weir RJ, Fisher RS; 1972.
Toxicologic studies on borax and boric acid; Toxicol. Appl. Pharmacol., Vol. 23: 351 - 364.

34. Ku WW, Chapin RE, Wine RN, Gladen BC; 1993.
Testicular toxicity of boric acid (BA): Relationship of dose to lesion development and recovery in the F344 rat; Reprod. Toxicol., Vol.7: 305 - 319.

35. Fail PA, George JD, Grizzle TB, Heindel JJ, Chapin RE; 1990.
Final report on the reproductive toxicity of boric acid (CAS No. 10043-35-3) in CD-1 Swiss mice; Research Triangle Park, North Carolina, US Department of Health and Human Services, National Toxicology Program (NTP Report No. 90 – 105).

36. Fail PA, George JD, Seely JC, Grizzle TB, Heindel JJ; 1991.
Reproductive toxicity of boric acid in Swiss (CD-1) mice: Assessment using the continuous breeding protocol; Fundam. Appl. Toxicol., Vol. E 17: 225 - 239.

37. Nielsen FH, Gallagher SK, Johnson LK, Nielsen EJ; 1992.
Boran enhances and mimics some effects of estrogen therapy in postmenopausal women; The Journal of Trace Elements in Experimental Medicine, Vol. 5: 237 - 246.

38. Human & Environmental Risk Assessment on ingredients of European household cleaning products – HERA; August 2002.
Perboric acid, sodium salt, mono and tetrahydrate, CAS NO.: 11138-47-9, (10332-33-9, 10486-00-7.

39. Nielsen FH, Penland JG; 1999.
Boron supplementation of peri-menopausal women affects boron metabolism and indices associated with macromineral metabolism, hormonal status and immune function; The Journal of Trace Elements in Experimental Medicine, Vol. 12: 251-261.

40. Beattie JH, Peace HS; 1993.
The influence of a low-boron diet and boron supplementation on bone, major mineral and sex steroid metabolism in postmenopausal women; British Journal of Nutrition, Vol. 69: 871-884.

41. CSTEE; 2004.
Opinion on the results of the risk assessment of sodium perborate Human Health part C7/GF/csteeop/NaPerborate/hh/ 280504 D(04)

42. Scientific Committee on Food; 2001.
Opinion on the 13th additional list of monomers and additives for food contact materials CS/PM/GEN/M85 Final, 31 May 2001