

EXPERT GROUP ON VITAMINS AND MINERALS

REVISED REVIEW OF BORON

The attached review of boron is a revised version of the paper presented to the Expert Group at the meeting on 24 September 1999. The 1995 ECETOC Report no 63 was circulated with the original paper and has not been attached with this revised review. The reference has been included only in Annex 1. This paper has been amended to take account of some of the comments made by members and to correct a number of minor inaccuracies..

The following annex is included with this paper:

Annex 1. 1995 ECETOC Report no 63 – reference only

Expert Group on Vitamins and Minerals
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BORON

Chemistry and geochemistry

1. Boron is a naturally occurring element that is found in the form of borates in the oceans, sedimentary rocks, coal, shale and some soils (IPCS, 1998). It is non-metallic, with an atomic number of 5 and a relative atomic mass of 10.811. In nature it is found only in compounds, as with sodium and oxygen in borax ($\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$). It exists in two allotropic forms, a brown amorphous powder and very hard brilliant crystals. At the low concentrations and near-neutral pH found in most biological fluids, monomeric $\text{B}(\text{OH})_3$ is the most common species present [with some $\text{B}(\text{OH})_4^-$], regardless of whether the boron source is boric acid (H_3BO_3) or borate. This is because boric acid is a very weak acid ($\text{p}K_a$ 9.15).
2. The octanol/water partition coefficient of boric acid has been measured as 0.175, indicating a low bio-accumulation potential.

Natural occurrence

3. Boron is widely distributed in nature, with concentrations of around 10 mg/kg in the Earth's crust (5 mg/kg in basalts to 100 mg/kg in shales) and around 4.5 mg/l in the ocean. The most important commercial borate products and minerals are borax pentahydrate, borax, sodium perborate, boric acid, colemanite and ulexite. Economic borate deposits are rare, occurring in Turkey, the USA, Argentina, Chile, Russia, China and Peru. Total world production of boron minerals such as colemanite, ulexite, tincal and kernite, was approximately 2,750,000 tonnes in 1994 (IPCS, 1998). About 800,000 tonnes of commercial borate products were manufactured from boron minerals.
4. Atmospheric emissions of borates and boric acid in particulate and vapour form occur as a result of volatilization from the sea, volcanic activity, and, to a lesser extent, mining operations, glass and ceramics manufacturing, the application of agricultural chemicals, and coal-fired power plants. Boron is not present in the atmosphere at significant concentrations, but the total amount present in the atmosphere at any one time is significant because of the huge volume of the atmosphere. Based on their water solubility, borates would not be expected to persist to a significant degree in the atmosphere.
5. Boron can be released into water supplies and soil water through weathering processes and, to a much smaller extent, through anthropogenic discharges such as sewage outfalls. Adsorption-desorption reactions are likely to be the only significant mechanism influencing the fate of boron in water. The extent of boron adsorption depends on the pH of the water and the concentration of boron in solution.
6. Boron is adsorbed onto soil particles, with the degree of adsorption depending on the type of soil, pH, salinity, organic matter content, iron and aluminium oxide content, iron- and aluminium-hydroxy content, and clay content. Boron adsorption can vary from being fully reversible to irreversible, depending on the soil type and condition.

7. Borate ions present in aqueous solution are essentially in their fully oxidized state. No aerobic processes are likely to affect their speciation, and no biotransformation processes are reported. Therefore, biotransformation is unlikely to play any role in changing the predominant boron species.

Occurrence in food, food supplements and medicines

8. Boron accumulates in aquatic and terrestrial plants but does not magnify through the food-chain. Interest in boron as a naturally occurring trace element nutrient from the food supply is increasing. Mounting evidence suggests that boron is essential to human beings.

Dietary intake

9. The greatest exposure to boron for most populations comes from food. The daily intake of boron by humans can vary widely depending on the proportions of various food groups in the diet (Nielsen, 1988). Foods of plant origin, especially fruits, leafy vegetables, nuts and legumes are rich in boron, as are wine, cider and beer. Meat, fish and dairy products are poor sources. Coffee and milk are low in boron, but make up 12% of the total boron intake by virtue of the volume consumed. Peanut butter, avocado, wine, raisins, peanuts, and other nuts are high in boron (Rainey *et al.*, 1999). Boric acid (E284) and sodium tetraborate (E285) are permitted preservatives in sturgeons' eggs (caviar) only. The maximum permitted level is 4g/kg expressed as boric acid.

Intakes of boron from food

10. Information on dietary intakes of boron is extremely limited. Boron is not included in the nutrient databanks for dietary surveys. The most up to date information available is from analysis of samples from the 1994 Total Diet Study (TDS)^{1,2}. This showed that the population average intake of boron was 1.5 mg/day. This was lower than the intake from the 1991 TDS (1.8 mg/day). Table 1 shows the concentration of boron in each of the Total Diet Study food groups in 1994 and the intake from each group.

11. Mean and upper level (97.5 percentile) boron intake for adults has been estimated at 1.4 mg/day and 2.6 mg/day respectively using the Total Diet Study

¹The Total Diet Study is a model of the average domestic diet in the UK. A total of 119 categories of food and drink are specified for inclusion in the Total Diet. These are assigned to one of twenty broad food groups. The quantities and relative proportions of each food that make up the Total Diet are largely based on data from the National Food Survey (NFS) and are updated annually. Food samples are purchased fortnightly from different locations representative of the UK as a whole and prepared and cooked according to normal consumer practice. The constituents of each group are then homogenised and frozen. Samples can be analysed for a range of food constituents. The population average intake of a particular food constituent can be estimated from its concentration in each food group and consumption of each group as determined by the NFS.

²MAFF (1997) 1994 Total Diet Study: Metals and other elements. Food Surveillance Information Sheet No. 131.

concentrations combined with consumption data from the 1986/87 Dietary and Nutritional Survey of British Adults³.

12. The Total Diet Study shows that the highest concentration of boron is in the food group nuts, followed by fresh fruit, fruit products and green vegetables. The main contributors to dietary intake were beverages, fresh fruit and potatoes.

Table 1 - Concentrations of boron in 1994 Total Diet samples and estimated average intake

Food group (TDS)	Mean Boron concentrations⁴ (mg/kg fresh weight)	Intake of Boron mg/day⁵
Bread	0.5	0.055
Misc. cereals	0.9	0.090
Carcase meat	<0.4	0.0104
Offal	<0.4	0.0004
Meat products	0.4	0.018
Poultry	<0.4	0.0072
Fish	0.5	0.0065
Oils & fats	0.4	0.012
Eggs	<0.4	0.0064
Sugars & preserves	0.8	0.054
Green vegetables	2.0	0.074
Potatoes	1.4	0.186
Other vegetables	1.4	0.102
Canned vegetables	1.2	0.042
Fresh fruit	3.4	0.221
Fruit products	2.4	0.103
Beverages	0.4	0.345
Milk	<0.4	0.114
Dairy produce	0.4	0.023
Nuts	14.0	0.028
Total intake (mg/day)		1.5 mg/day

13. An older study by Hamilton *et al* (1972/73) reported the calculated average daily boron intake of British people as being relatively high and variable, at 2.8 ± 1.5 mg/day.. Only one paper has been found that quotes the likely daily boron intake in the diet of vegetarians (Rainey *et al.*, 1999). The paper quotes the weighted 5th percentile, median, mean, and 95th percentile boron intakes, respectively, as 0.43, 1.02, 1.17 and 2.42 mg/day for men; 0.33, 0.83, 0.96 and 1.94 mg/day for women; and

³ This estimate should be used with caution because of differences between the Total Diet Study and Adults survey food groups.

⁴ upper-bound means across the 20 TDS towns, i.e. concentrations below limit of detection taken as the limit of detection

⁵ upper-bound intake, i.e. concentrations below limit of detection taken as the limit of detection

0.40, 0.86, 1.01 and 2.18 mg/day for pregnant women. For vegetarian adults, these intakes are generally higher, being 0.46, 1.30, 1.47 and 2.74 mg/day for men and 0.33, 1.00, 1.29 and 4.18 mg/day for women. These figures are in agreement with the study of Gormican (1970), who reported a daily intake of 1.15-1.58 mg/day on a general diet (intake was greater in summer than in winter, presumably because more salads and vegetable dishes are consumed in summer than in winter). Anderson *et al.* (1994) determined the intake to be 1.21 mg/day. More recently, Meacham and Hunt (1998) analysed the boron content of the 234 most commonly consumed American foods and applied the data to food intake information collected for the Total Diet Study Program. Boron intakes were 0.69 and 0.89 mg/d in adult women and men respectively, coming predominantly from beverages, vegetables and fruit. The IPCS report (1998) gives an average intake of boron for humans as 0.44 µg/day from ambient air, 0.2–0.6 mg/day from drinking water, and 1.2 mg/day from the diet. Average boron intake from the soil is considered to be 0.5 µg/day.

14. Body building supplements have been reported to contain 1.5-10 mg boron/serving, resulting in possible daily exposures of 1.5-30 mg boron. Bottled water can contain up to 4.35 mg boron/litre, with an average boron content of 0.75 mg/litre (Moore *et al.*, 1997).

Drinking water

15. WHO (1998) have introduced a guideline value of 0.5 mg/l for boron in water. This guideline value was derived from a no-observed-adverse-effect-level (NOAEL) of 9.6 mg boron/kg body weight daily in a developmental study in rats, an uncertainty factor of 60, and allocation of 10% of the total daily intake (TDI) to drinking water. The current regulatory limit in England and Wales is 2 mg/l (annual average), and actual concentrations in drinking water are generally much lower than this. Council Directive 98/83/EC “On the Quality of Water Intended for Human Consumption” requires a limit of 1 mg/l maximum.

Consumer products

16. Boron compounds can be found in the form of boric acid, borax and other borates in a wide range of consumer products, including borosilicate glass, soaps and detergents, preservatives, adhesives, porcelain, enamel, leathers, carpets, artificial gemstones, high-contrast photographic materials, wicks, electric condensers, fertilizers, insecticides and herbicides (Moore *et al.*, 1997). A reasonable estimate of boron exposure from consumer products is 0.1 mg/day (EU Technical Guidance Document, 1995).

Licensed medicinal products for oral use

17. Currently no medicinal products containing boron are authorised.

Cosmetics

18. Boron compounds are widely used in cosmetic products such as makeup, skin and hair care preparations, deodorants, moisturising creams, breath fresheners and

shaving creams, in concentrations up to 5% (US FDA, 1981; Beyer *et al.*, 1983). In the UK and the EU, boric acid, borates and tetraborates are permitted in cosmetic products at a maximum of 5% in powders, 0.1% in oral hygiene products and 3% in other products (excluding bath and hair waving products). Tetraborates are permitted at maximum levels of 18% in bath products and 8% in hair waving hair products. Oral hygiene products have been estimated by the European Union Scientific Committee for Cosmetology to contain up to 0.09 mg boric acid/kg body weight. Deodorants contained up to 0.25 mg boric acid/kg/ bw per day and eye products up to 0.03 mg/kg/bw. The total maximum exposure to boric acid from cosmetics has been estimated to be 0.47 mg/kg bw/day. Boric acid is also used in vaginal products and contraceptives (Beyer *et al.*, 1983).

Environmental/occupational exposure

19. Concentrations of boron in surface water are dependent on such factors as the geochemical nature of the drainage area, proximity to marine coastal regions, and inputs from industrial and municipal effluent discharges. Concentrations of boron in surface water range widely, from 0.001 to as much as 360 mg/l. However, mean boron concentrations for waters of Europe (including the UK), Pakistan, Russia, and Turkey are usually well below 0.6 mg/l. Concentrations of boron in water in Japan, South Africa, and South America are generally below 0.3 mg/l. Typical boron concentrations in North American waters are below 0.1 mg/l, with about 90% at or below 0.4 mg/l. Close similarity of boron concentrations in groundwater, fresh surface water, and drinking water indicates that boron is not removed in the treatment of groundwater and fresh surface water used for drinking-water.

20. Boron concentrations in ambient air range from <0.5 to approximately 80 ng/m³, with an average over the continents of 20 ng/m³. However, in industrial situations, airborne concentrations can be much higher. Culver *et al.* (1994) compared daily dietary boron intake and on-the-job inspired boron with blood and urine boron concentrations in workers engaged in packaging and shipping borax. Fourteen workers handling borax at jobs of low, medium, and high dust exposures were sampled throughout full shifts for 5 consecutive days each. Airborne borax concentrations ranged from means of 3.3 to 18 mg/m³, measured gravimetrically. End-of-shift mean blood boron concentrations ranged from 0.11 to 0.26 µg/g; end-of-shift mean urine concentrations ranged from 3.12 to 10.7 µg/mg creatinine.

21. Woskie *et al.* (1994) assessed short-term and daily dust and boron exposures of workers in a sodium borate production facility. The average concentration of boron relative to total dust ranged from 5.6 to 10.1%.

22. Whorton *et al.* (1994), in a study of male employees exposed to borate dusts at a borate mine over a period of 30 years, found an average exposure to sodium borate dust of 203 mg/day, assuming 7 h/day of actual exposure at an average concentration of 23.2 mg/m³.

Recommended amounts

23. The International Programme on Chemical Safety (IPCS) Report (1998) has made some recommendations regarding acceptable boron intake. They considered

that boron was a necessary trace element in the human diet, but that there was a lack of sufficient toxicity data for humans. The tolerable intake (TI) of boron was set as 0.4 mg/kg body weight per day; for a 70 kg man in the UK, this would be 28 mg/day. The allocation of the TI in various media should be based on the exposure data of individual countries. The Committee on Medical Aspects of Food and Nutrition Policy (COMA) concluded that the role of boron in humans is unknown and the essentiality of boron for humans remains to be demonstrated (DH, 1991). Therefore, there is no Reference Nutrient Intake for boron. WHO (1996) stated that an acceptable safe range of population mean intakes for adults could well be 1-13 mg/day. In 2001, the Food and Nutrition Board of the Institute of Medicine released new dietary reference values for Americans and Canadians (Trumbo *et al.*, 2001). Although they reviewed the evidence, they were unable to recommend an intake for boron.

Analysis of boron intake

24. Because boron is not a particularly toxic element, indicators of chronic excessive boron intake are not well defined. However, elevated boron concentrations (i.e. significantly greater than the accepted values of 0.05-0.6 µg/g tissue) are indicators of acute and possibly chronic excessive intake of boron by both animals and humans (Nielsen, 1986). WHO (1996) note that blood and urinary boron can be used.

25. The preferred method for analysis of boron in bone, plasma and food is inductively coupled plasma atomic emission spectroscopy (Hunt, 1989). Detection limits range from 0.005 to 0.05 mg boron/l in the solution analysed. This method can also be used to measure boron in water supplies, sewage, soils and plant samples.

26. Colorimetric/spectrophotometric methods can also be used, but are subject to interference; if used, the method should be calibrated against inductively coupled plasma atomic emission spectroscopy. A recently developed technique (Garcia-Campana *et al.*, 1992) uses Alizarin Red S. Flow injection analysis utilizing the sorbitol/borate complex and Methyl Orange indicator for eye lotion samples has a detection limit of 0.02 mg/l (Nose and Zenki, 1991).

27. The normal concentration of boron in blood appears to lie between 0.1 and 0.2 µg/ml.

Interactions

28. Boron appears to interact with other nutrients and plays a regulatory role in the metabolism of minerals, such as calcium, and subsequently bone metabolism (Naghii and Samman, 1993). The review by Naghii and Samman contains a table of interactions between boron and other dietary constituents; the data relating to the interaction of boron with calcium are reproduced in Table 2 below. A study by Elliot and Edwards (1992) found no interaction of boron with calcium or cholecalciferol in broiler chickens fed with a diet containing boron and calcium or cholecalciferol. A study by Armstrong *et al.* (1994) in weanling pigs found that boron supplementation of a low-boron diet improved bone strength characteristics, but boron

supplementation of a diet containing "normal" levels of boron (6.7 mg/kg diet) had no effect.

Table 2: Interaction between boron and calcium (taken from Naghii and Samman, 1993)

<i>Species</i>	<i>Dietary manipulation</i>	<i>Comment</i>	<i>Reference</i>
Men >45 years and postmenopausal women	Low Mg and Cu, 3.23 mg boron/day	Boron supplementation results in an increase in plasma ionized Ca and vitamin D ₂ and a decrease in serum calcitonin and osteocalcin	Nielsen <i>et al.</i> (1990)
Postmenopausal women	Low Mg, 3.25 mg boron/day	Boron supplementation results in a reduction in Ca and P excretion	Nielsen <i>et al.</i> (1987)
Rabbits	High F, 38 mg boron/day	Boron supplementation counteracts F toxicity and restores Ca and P balance	Elsair <i>et al.</i> (1980)
Rats	Low vitamin D, 2.72 mg boron/g diet	Boron supplementation improves Ca and P absorption and balance by alleviating vitamin D deficiency	Hegsted <i>et al.</i> (1991)
Chickens	0.5 mg boron, <i>in ovo</i> injection	Boron injections enhance hatchability and bone formation by extending the half-life of vitamin D	King <i>et al.</i> (1991)
Chickens	Low Mg and Mo, 4 mg boron/g diet	Boron supplementation results in elevated plasma Ca, Mg and Mo levels by alleviating vitamin D deficiency	Hunt (1989)

29. Ultimate shear force, shear stress and shear fracture energy of the tibia, humerus and radius from White Leghorn layers was not increased by dietary boron at levels of up to 56 mg/kg bw (Wilson and Ruszler, 1995).

30. In the study of Beattie and Peace (1993), postmenopausal women were given a low-boron diet (0.33 mg/day) for 3 weeks and took a boron supplement of 3 mg/day

in addition to the low boron diet for a further 3 weeks. The low boron diet appeared to induce hyperabsorption of Ca since positive Ca balances were found in combination with elevated urinary Ca excretion.

31. In a double-blind placebo controlled crossover study, 43 peri-menopausal women were given supplements of 2.5 mg/day boron in the form of sodium borate (Nielsen and Penland, 1999). Nineteen of the women were given the supplement for 60 days followed by a lactose placebo for 90 days. Twenty four of the women received the placebo first. Boron supplementation resulted in more severe hot flushes and night sweats in 21 women. However, 10 women reported a reduction in symptoms with the remaining women experiencing no change. Boron supplementation increased white blood cell numbers with a decreased percentage of lymphocytes and an increased percentage of polymorphonuclear leukocytes. Supplementation altered 17β -oestradiol levels, alkaline phosphatase and thyroxine levels, however, the effect was influenced by the sequence in which boron was given. Increases in alkaline phosphatase and triiodothyronine were noticeably increased when boron was given first, whereas the increase on 17β -oestradiol was more marked when the placebo was given first.

32. Naghii and Samman (1993) suggest that boron may induce changes in calcium homeostasis by interaction with vitamin D and magnesium metabolism, through an effect of boron on cell membranes. The study by Nielsen and Shuler (1992), quoted in the original report, supports this hypothesis. However, this effect may only be apparent when the normal balance of minerals involved in bone formation is disturbed.

33. Although the mechanism of action has not been defined, it has been shown that boron supplementation after depletion enhances the elevation in serum 17β -oestradiol and plasma copper caused by oestrogen therapy (Nielsen *et al.*, 1992). Additionally, boron supplementation in post-menopausal women reduced total plasma concentration of calcium and the urinary excretion of calcium and magnesium in addition to elevating serum concentrations of oestradiol and testosterone (Nielsen, 1987). The elevation of endogenous oestrogen as a result of boron supplementation suggests a protective role for boron in atherosclerosis (Naghii and Samman, 1997).

34. Experiments in rats (Nielsen and Shuler, 1992) have confirmed that boron interacts with calcium, and that this interaction may be modified by dietary magnesium and potassium. Boron and calcium deprivation can cause an elevation in plasma alkaline phosphatase activity and depression of femur calcium concentration. Under some dietary conditions, both boron and calcium deprivation affected some variables related to iron metabolism. However, the effects of dietary boron and calcium on spleen weight/bodyweight ratio, haematocrit and femur iron concentration generally were not similar. Femur copper, magnesium, phosphorus and zinc were also affected by an interaction between boron and calcium under some dietary conditions. The authors concluded that their findings showed a relationship between boron and calcium, but did not clearly indicate the nature of the relationship. However, the data do suggest that boron and calcium act on similar systems in the rat.

Absorption

35. Boron in foods, and the compounds sodium borate and boric acid are rapidly absorbed and excreted largely in the urine (Nielsen, 1986; 1988). Absorption appears to be virtually complete (95% in humans and rats), and boron appears rapidly in the blood and body tissues of several mammalian species following ingestion.

Oral

36. Boron is absorbed rapidly and virtually completely from the human gastrointestinal tract. The urinary excretion of boron ingested solely from dietary sources indicates 83-94% absorption (Kent and McCance, 1941). Oral absorption in animals appears to be similar to that in humans. The mechanism by which boron absorption occurs has not been reported.

37. In a study by Barr *et al.* (1993), in which the concentrations of naturally occurring boron in the water supplies ranged from 0.31 to 15.2 mg/l, blood boron concentrations for residents from seven geographical regions showed a positive correlation with boron levels in the local drinking water supplies. In three regions with boron levels in drinking water below 2.5 mg/l, blood boron levels were <0.1 µg/g blood. In the region with the highest boron concentration in drinking water (15.2 mg boron/l), average blood levels were approximately 0.7 µg boron/g blood.

Inhalation

38. Inhalation exposure to borax in the range of 3.3-18 mg/m³ produces increases in human blood and urine boron levels (Culver *et al.*, 1994). Animal studies have shown similar results. Swallowing of particles cleared from the respiratory tract by coughing, with subsequent absorption from the gastrointestinal tract, may have contributed to systemic uptake, but it appears that boron can nevertheless be absorbed from the respiratory tract.

Dermal

39. Dermal absorption across intact skin is negligible in all species evaluated, including human infants, human adults, rabbits and rats. However, when boric acid is applied to broken or damaged skin, absorption of boric acid through the damaged skin can be demonstrated (Draize and Kelley, 1959; Nielsen, 1970). In one report (Vignec and Ellis, 1954), infants received applications of a talcum powder containing 5% boric acid 7-10 times/day for at least 1 month, resulting in an estimated dose of 2.33 g boric acid/day (408 mg boron/day). The boron concentrations in a test group of 12 infants were 0.04 ± 0.04 mg/100 ml in blood and 0.16 ± 0.14 mg/100 ml in urine. An additional group of 12 treated infants who had developed a mild to moderate nappy rash had an average blood boron concentration of 0.03 ± 0.04 mg/100 ml, suggesting that even in infants with moderate nappy rash, only traces of boric acid penetrated the skin.

40. In a study by Wester *et al.* (1998), human volunteers were administered percutaneously ¹⁰B-enriched boric acid, 5.0%, borax, 5.0%, or disodium octaborate tetrahydrate (DOT), 10% in aqueous solutions. Urinalysis for boron and changes in boron isotope ratios were used to measure absorption. Percutaneous absorption of

boric acid was 0.226 (SD = 0.125) mean percent dose, with flux and permeability constant (K_p) calculated at $0.009 \mu/\text{cm}^2/\text{h}$ and $1.9 \times 10^{-7} \text{ cm}/\text{h}$, respectively. Borax absorption was 0.210 (SD = 0.194) mean percent dose, with flux and K_p calculated at $0.009 \mu/\text{cm}^2/\text{h}$ and $1.8 \times 10^{-7} \text{ cm}/\text{h}$, respectively. DOT absorption was 0.122 (SD = 0.108) mean percent, with flux and K_p calculated at $0.01 \mu/\text{cm}^2/\text{h}$ and $1.0 \times 10^{-7} \text{ cm}/\text{h}$, respectively. Pre-treatment with the potential skin irritant 2% sodium lauryl sulphate had no effect on boron skin absorption. These *in vivo* results show that percutaneous absorption of boron, as boric acid, borax, and DOT, through intact human skin is low and is significantly less than the average daily dietary intake.

Distribution

41. Distribution of boron appears to take place through passive diffusion through the body fluids. Boron is distributed throughout the tissues and organs of animals and humans at concentrations normally between 0.05 and 0.6 mg/kg fresh weight, and several times these concentrations in bones (Nielsen, 1986). Boron distributes evenly throughout the body fluids (Ku *et al.*, 1991), but appears to accumulate in bone. In a study of boron distribution in rats fed a control diet or a diet containing 9000 mg boric acid/kg for 7 days, boron concentrations after 7 days were 47.4 mg/kg in bone, versus 20-30 mg/kg for most other tissues. Elimination kinetics from bone also differ from those from soft tissue and body fluids (Chapin *et al.*, 1997), suggesting the existence of a second kinetic compartment in which a small percentage of absorbed boron is sequestered.

42. Blood boron levels generally increase with dose in rats and humans.

Metabolism and excretion

43. Borate compounds are not metabolised by biological systems, because of the considerable energy required to break the boron-oxygen bond (Emsley, 1989). At low concentrations, inorganic borates can convert to boric acid at physiological pH in the aqueous layer overlying mucosal surfaces prior to absorption.

44. Boron appears to be eliminated largely in the urine (Nielsen, 1986; 1988). More than 90% of the administered dose of borate is excreted as boric acid. Elimination kinetics, including route of elimination and terminal half-life, appear to be similar in humans and rats. Murray (1998) noted that the half life of boron in rats (14-19 hours) was slightly shorter than that in humans (21 hours), which was attributed to their higher glomerular filtration rate. Litovitz *et al.* (1988) found an elimination half-life of 13.4 h (range 4-27.8 h) in 800 patients accidentally or intentionally poisoned with boric acid. A study by Culver *et al.* (1994) has confirmed that boron does not accumulate in the blood or urine of regularly exposed workers, thus confirming its relatively short half-life. Samman *et al.* (1998) have shown that the urinary excretion of boron is 1.9 mg/day, and there appears to be little intra-individual variation. Sutherland *et al.* (1998) measured boron intake (by composite diet) and urinary excretion in 7 healthy men participating in a metabolic study. There were 3 dietary periods where boron intakes were 4.56, 1.87 and 4.75 mg/d. Although urinary excretion of boron mirrored the changes in dietary intake, the fluctuations were smaller (30% lower in the second period rather than 60% lower). The authors

concluded that the kidney may be the primary tissue for regulating homeostasis, and urinary boron was a sensitive indicator of intake at these levels of intake. It should be noted, however, that this study was designed and conducted to investigate zinc homeostasis and had few subjects.

Function

45. Boron appears to be an essential nutrient for humans, in that dietary deprivation of boron consistently results in changed biological functions that are detrimental and that can be corrected by increasing boron intake (Nielsen *et al.*, 1987). Similar effects have been shown in animal models. However, as yet, no specific biochemical function for boron has been discovered. In plants, boron has been shown necessary for the plant life cycle, but its precise action is unknown.

46. In humans, boron can affect the metabolism and utilisation of calcium, copper, magnesium, nitrogen, glucose, triglycerides, reactive oxygen and oestrogen. In this way, boron can have positive effects on the function of several body systems, including blood, brain and bone. In a short series of brain electrical activity, cognitive and psychomotor function tests, Penland (1998) reported that relatively short periods of restricted boron intake can affect brain function and cognitive performance in healthy men and women.

47. Nielsen (1991) has suggested that boron has a role in cell membrane function, stability or structure such that it influences the response to hormone action, transmembrane signalling or transmembrane movement of regulatory cations or anions. Alternatively (Hunt, 1994; 1998), boron may be a negative regulator that influences a number of metabolic pathways (energy metabolism, insulin release, and the immune system, particularly the respiratory burst) by competitively inhibiting some key enzyme reactions.

Deficiency

48. The signs of boron deficiency in animals are variable in nature and severity, being dependent on dietary intake of aluminium, calcium, cholecalciferol, magnesium, methionine and potassium (Hunt and Nielsen, 1981; Hunt, 1988; Nielsen *et al.*, 1988 a,b). Variables affected by dietary boron include plasma and organ calcium and magnesium concentrations, plasma alkaline phosphatase and bone calcification. Consistent signs of deficiency include depressed growth and a reduction in some blood indices, particularly steroid hormone concentrations. Consumption of foods of plant origin, which are high in boron, is often higher in countries with a lower incidence of osteoporosis, although this relationship, if it exists, has yet to be established. It has been suggested that boron could be a contributing factor in Kashin-Beck disease (KBD). KBD is an osteo-arthritic condition affecting children in China and the former Soviet Union which causes severe joint deformity and has been linked to selenium deficiency. A cross-sectional survey in China assessed boron status from scalp hair and found significantly lower hair boron levels in children with KBD compared to local children without KBD (Peng *et al.*, 2000).

Overview of reported beneficial effects

49. Nielsen's group (Nielsen, 1989; 1994; Nielsen *et al.*, 1990; 1991; 1992) have carried out two studies in which men over the age of 45, postmenopausal women and postmenopausal women on oestrogen replacement therapy were fed a low-boron diet (0.25 mg/2000 kcal) for 63 days and then fed the same diet supplemented with 3 mg boron/day for 49 days. Regardless of copper and magnesium intake, boron deprivation had several effects, while marginal or inadequate copper and magnesium caused apparent detrimental changes that were more marked during boron deprivation than during boron repletion. Boron supplementation following 63 days of boron depletion caused increased serum 25-hydroxycholecalciferol and a decrease in elevated calcitonin caused by inadequate copper and magnesium, decreased serum glucose and increased serum triglycerides, decreased blood urea nitrogen and serum creatinine and increased urinary hydroxyproline excretion, increased serum erythrocyte superoxide dismutase and serum caeruloplasmin, increased blood haemoglobin and mean corpuscular haemoglobin content. Boron supplementation also enhanced the elevated serum 17 β -oestradiol and copper concentrations caused by oestrogen therapy, altered EEG and improvements in attention and memory. It has also been reported that boron supplementation may improve symptoms in those with osteoarthritis and rheumatoid arthritis (Travers *et al* 1990; Newnham 1979, Newnham 1991). There is an emerging boron-inflammation hypothesis that boron reduces the risk of inflammatory disease by down-regulating enzymes of the inflammatory response (Hunt and Idso, 1999).

Toxicity

50. Boric acid and borax have a low acute oral toxicity; LD₅₀ values for mice, rats and dogs range from 2000 to >6000 mg/kg body weight (see below). Signs of acute toxicity for both borax and boric acid include depression, ataxia, convulsions and death; kidney degeneration and testicular toxicity are also observed. Pentaborane is the most toxic boron hydride, all of which are highly toxic; its 4-h LC₅₀ value for mice and rats is 6 and 12 mg/m³, respectively (American Conference of Governmental and Industrial Hygienists, 1981). Additional information on the toxicology of borates is contained in the 1994 ECETOC report.

Human toxicity

Short-term toxicity and poisoning

51. The available human exposure data on boron compounds for routes other than inhalation are generally refer to boric acid and borax. Stokinger (1981) found the lowest lethal dose for humans exposed to boric acid to be 640 mg/kg/bw by oral exposure, 8600 mg/kg/bw by dermal exposure, and 29 mg/kg body weight by intravenous injection. However, deaths have been reported at doses between 5 and 20 g of boric acid for adults and below 5 g for infants. Potential lethal doses are usually cited as 3-6 g total for infants and 15-20 g total for adults (Litovitz *et al.*, 1988). A case-series report of seven infants aged 6-16 weeks who used pacifiers coated with a borax and honey mixture for 4-10 weeks reported that exposures ranged from 4 to 30 g, with an estimated average daily ingestion of 0.143-0.429g (O'Sullivan and Taylor,

1983). Toxicity was manifested by generalised or alternating focal seizure disorders, irritability, and gastrointestinal disturbances. Other findings included inflammation, congestion, oedema, exfoliation of the mucosa, cloudy swelling and granular degeneration of tubular cells, and exfoliative dermatitis.

52. Teshima *et al.* (1992) reported a 26-year-old woman who had ingested 21 g of boric acid. The elimination of boric acid was about 4 times faster with haemodialysis than with conventional medical treatment. Grella *et al.* (1976) described a case of apparent transplacental poisoning. A pregnant woman with diabetes was accidentally given 70 g of boric acid instead of 70 g of glucose for the glucose tolerance test at 33 weeks gestation. She was immediately treated with gastric lavage and intravenous sodium bicarbonate fructose. The woman developed contractions, and an emergency Caesarean delivery was conducted. The infant was born alive weighing 2.5 kg and had spontaneous respirations, but later developed cardiac arrest, was resuscitated, but died. Cause of death was attributed to cardiocirculatory collapse.

53. Kliegel (1980) has described mild to severe responses to boron compounds. Nineteen patients with epilepsy or infections developed body hair loss as a response to boron compound treatment. Stein *et al.* (1973) described a 32-year-old woman with pancreatitis who ingested and swallowed several bottles of mouthwash containing boric acid daily for a minimum of 1 year. She lost almost all of her body and scalp hair and also developed erythema on the palms of her hands, severe fatigue, anorexia, and mental confusion. Her blood boric acid level was 32 µg/ml, corresponding to 5.6 µg boron/ml (the normal value has been reported as 3 µg boric acid/ml). Upon cessation of mouthwash consumption, hair growth returned, suggesting that the effect was reversible.

54. Goldbloom and Goldbloom (1953) reported four cases of boric acid poisoning and reviewed an additional 109 cases in the literature. The four cases were infants exposed to boric acid by repeated topical applications of baby powder. The infants developed cutaneous lesions (erythema over the entire body, excoriation of the buttocks, and desquamation), gastrointestinal disturbances and seizures. One infant died, but cause of death was not specifically attributed to boric acid. Approximately 35% of the 109 other case reports involved children under 1 year of age. The mortality rate was higher in the children, at 70.2% compared with 55.0% for all cases combined. Death occurred in 53% of patients exposed by ingestion, in 75% of patients subjected to gastric lavage with boric acid, in 68% of patients exposed by dermal application for treating burns, wounds and skin eruptions, and in 54% of patients exposed by other routes. Gastrointestinal disturbances were prevalent (73%), followed by central nervous system (CNS) effects (67%). Cutaneous lesions were observed in 76% of the cases and in 88% of cases involving children under 2 years of age. Gross and microscopic findings were reported for 27/60 (45%) fatal cases. In general, boric acid caused chemical irritation primarily at sites of application and excretion and in organs with maximum boron concentrations. The most common CNS findings were oedema and congestion of the brain and meninges. Other common findings included liver enlargement, vascular congestion, fatty changes, swelling, and granular degeneration.

55. Two infants whose pacifiers had been dipped in a preparation of borax and honey over a period of several weeks exhibited scanty hair, patchy dry erythema, anaemia and seizure disorders (Gordon *et al.*, 1973). The seizures stopped and the other abnormalities were alleviated when the use of the borax and honey preparation was discontinued.

56. More recent reports from poison centres suggest that the oral toxicity of boron in humans is less than previously thought. Litovitz *et al.* (1988) conducted a retrospective review of 784 cases of boric acid ingestion reported to the National Capital Poison Center in Washington, DC, USA, during 1981-1985 and the Maryland Poison Center in Baltimore, MD, USA, during 1984-1985. Of these, 88.3% of the cases were asymptomatic. All but two had acute (single) ingestion, and 80.2% involved children under 6 years of age. No severe toxicity or life-threatening effects were noted, although boric acid levels in blood serum ranged from 0 to 340 µg/ml. The most frequently occurring symptoms, which involved the gastrointestinal tract, included vomiting, abdominal pain, diarrhoea and nausea. Other symptoms occurred in six or fewer cases: lethargy, rash, headache, light-headedness, fever, irritability, and muscle cramps. The average dose ingested estimated from 659 cases was 1.4 g (range 0.010-88.8 g). For children under 6 years, the average dose was 0.5 g (range 0.010-22.2 g), compared with 4.1 g (range 0.030-88.8 g) for individuals aged 6 years or more. The average dose for asymptomatic cases was 0.9 g (range 0.010-88.8 g), compared with 3.2 g (range 0.10-55.3 g) for symptomatic cases. Twenty-one of the children under 6 years of age, 15 of whom were under 2 years of age, ingested the reported potential lethal dose of 3 g and eight adults ingested the reported potential lethal dose of 15 g without evidence of lethal effects.

57. Linden *et al.* (1986) published a retrospective review of 364 cases of boric acid exposure reported to the Rocky Mountain Poison and Drug Center in Denver, CO, USA, between 1983 and 1984. Vomiting, diarrhoea, and abdominal pain (incidence not reported) were the most common symptoms given by the 276 cases exposed in 1983. Of the 72 cases reported in 1984 for whom medical records were complete, 79% were asymptomatic, whereas 20% had mild gastrointestinal symptoms. One 2-year-old child died, presumably from repeated ingestion of an insecticide containing 99% boric acid.

58. The average dose of boric acid required to produce clinical symptoms is still unclear, but is presumably within the range of 100 mg to 55.5 g (see paragraph 56).

Dietary Exposure

59. 120 patients attending a nutrition clinic were assessed by questionnaire for their dietary intake of boron, alcohol or purines (Moss, 2001). The patients were seeking help with chronic health problems. Subjects with a high intake of boron, alcohol or purines were significantly more likely to have irritable bowel syndrome or frequent diarrhoea. The study group size was increased to 578 individuals and the findings were the same. A high boron diet was attributed to subjects who ate 'lots of "tomatoes, peaches, apples, apricots, peppers or pears" or who drank "a lot of" tomato or apple juice'.

Chronic toxicity and occupational exposure

60. Data regarding subchronic or chronic exposure to boron in the general population are limited. However, effects on the male reproductive system have been reported following long-term exposure.

Reproductive toxicity

61. Whorton *et al.* (1994) estimated the standardised birth ratio (SBR; ratio of the observed number of live births to the expected number) to assess fertility in 542/750 (72% participation) occupational workers in a borax mine. These workers had been employed for a mean of 18 years, and their occupational exposure to sodium borate dust was uncontaminated by other exposures. Self-administered questionnaires were used to ascertain the observed number of live births fathered by male workers following employment. The US general population adjusted for age, race, parity, and calendar time period was used to estimate the expected number of live births. An SBR >100 reflects an excess of live births in relation to the US general population, whereas an SBR below 100 reflects a deficit.

62. SBRs were significantly elevated for workers in the lowest (< 0.82 mg/m³) and highest (≥ 5.05 mg/m³) exposure categories (i.e. 151 and 125, respectively), but no significant trend between exposure and SBRs was observed. An excess percentage of female live births in comparison with male births was observed across most categories of exposure and length of employment, but this did not reflect a deficiency of male births, as an excess of births for both genders was found. None of the findings was statistically significant. The findings do not support an adverse effect of boron on demonstrated fertility for this occupational sample of male workers in comparison with the US general population.

63. Şayli *et al.* (1998a) assessed boron exposure from drinking water and fertility among residents in two geographical regions in Turkey. Region I comprised 2368 residents, whereas region II comprised 2319 residents. Boron levels in drinking water were higher in region I (range 2.05-29 mg/l) than in region II (range 0.03-0.40 mg/l). Ever-married residents from each region who could provide reproductive histories for three generations of family members represented the study sample; 159 in region I and 154 in region II. The overall percentage of couples with unresolved infertility or those without children across three generations of the extended families was comparable for the two regions (i.e. 6.0% and 4.6%, respectively). However, region I had a ratio of male to female live births of below 1 (0.89), suggesting an excess of female births and region II had a ratio slightly above 1 (1.04), suggesting a slight excess of male births. Statistical significance was not assessed. These results suggest that fertility, as measured by the ability to produce a live birth, is not adversely affected for this population. The observed reversal of the secondary sex ratio for region I requires careful interpretation, as factors reported to alter sex ratios (e.g. advancing parental age, elective abortion rates, and multiple births) were not considered. In addition, the study by Whorton *et al.* (1994; see above), which also considered male to female live births, failed to find a significant effect.

64. Şayli *et al* (1998b) provided further details of the study considered above. Three generation reproductive histories were taken from 927 subjects (proband) in three provinces of Turkey with highest boron deposits. Occupational as well as environmental exposure would have occurred in all three areas. Some differences in the infertility rate were observed but these were attributed to differences in ascertainment. A slight excess of female births was noted in parts of the three provinces compared to a boron free area but the biological significance of the finding was unclear. No matched controls were included but this was not considered to be necessary since the primary infertility rate of approximately 3% was less than found in most other countries. This was not expected to conceal any important adverse effects. The exposure data provided are limited and, as described above, other factors affecting reproduction were not considered.

65. The rates of infertility were compared in the same regions described above (Tüccar *et al*, 1998). In addition, Kirka town, a borax manufacturing site, as well as a third region was considered where no regular measurements of drinking water had been made, but where concentrations were considered to be “not too high”. Active and former borate workers lived in all three regions. There were no differences in the rates of spontaneous abortions or stillbirths in populations exposed to high or low levels of boron. Infant death rates were higher in Region II (low boron). Congenital abnormalities occurred in 4/459 conceptions in Region I and 1/325 conceptions in Kirka only. The numbers were too low to allow statistical analysis.

Endocrine effects

66. Naghii and Samman (1997) carried out two studies to quantify the urinary boron concentration of subjects consuming their habitual diet and the effect of supplementation. Boron excretion in 18 healthy male subjects, was found to be 0.35-3.53 mg/day. Supplementation with 10 mg boron/day for 4 weeks resulted in 84% of the supplemented dose being recovered in the urine. Plasma oestradiol concentrations increased significantly as a result of supplementation (51.9 ± 21.4 to 73.9 ± 22.2 pmol/l; $P < 0.004$) and there was a trend for plasma testosterone levels to be increased.

67. Samman *et al*. (1998) reported that in humans, supplementation with 10 mg of boron/day resulted in a significant increase in plasma oestradiol concentration, but no effect on plasma lipoproteins.

68. These findings have not been supported by other human studies, using lower doses of boron. The study of Beattie and Peace (1993) investigated the effect of a boron supplement on bone mineral absorption and excretion, plasma sex hormone levels and urinary excretion of pyridinium crosslink markers of bone turnover in healthy postmenopausal women. The women were given a low-boron diet (0.33 mg/day) for 3 weeks and took a boron supplement of 3 mg/day in addition to the low boron diet for a further 3 weeks. Changing boron intake from 0.33 to 3.33 mg/day had no effect on minerals, steroids or crosslinks. Nielsen *et al* (1992) reported that high dietary boron (3 mg/day) enhanced the increases in serum copper and β -oestradiol levels associated with oestrogen therapy in post-menopausal women. This effect was not apparent in subjects not taking estrogen therapy.

69. Ferrando and Green (1993) investigated the effect of boron supplementation in 19 male bodybuilders aged 20-27 years. Ten were given a 2.5-mg boron supplement while nine were given a placebo every day for 7 weeks. Plasma total and free testosterone, plasma boron, lean body mass, and strength measurements were determined on days 1 and 49 of the study. Plasma boron levels were 20.1 ± 7.7 ppb ($\mu\text{g/l}$) pretest and 32.6 ± 27.6 ppb post-test in the experimental group, and 15.1 ± 14.4 ppb pretest and 6.3 ± 5.5 ppb post-test in the control group. Analysis of variance indicated no significant effect of boron supplementation on any of the dependent variables. Both groups demonstrated significant increases in total testosterone, but this was thought to be due to the bodybuilding alone. The authors concluded that boron supplementation had no effect on testosterone concentrations

Inhalation exposure

70. Wegman *et al.* (1994) used sodium borate particulate exposure estimates to estimate cumulative exposure in relation to long-term pulmonary function. Of the 631 workers who originally underwent pulmonary evaluation 7 years earlier, 336 (53%) underwent a subsequent evaluation. Ninety per cent (303/336) of workers had acceptable pulmonary test results. After the expected smoking-related pulmonary abnormalities were taken into account, no relation was observed between forced expiratory volume in 1 s (FEV_1) and accumulated exposure to sodium borate.

71. With regard to occupational exposure, most toxic effects reported have been acute or short-term, resulting from the irritant effects of boron compounds. A detailed analysis of 629 (93% participation) workers in a boron mining and refining plant was carried out by Garabrant *et al.* (1985). This analysis was based on frequency of acute symptoms in four mean boron dust exposure categories (1.1, 4.0, 8.4, and 14.6 mg/m^3) and persistent symptoms in three exposure categories (0.9, 4.5, and 14.6 mg/m^3 of total particulates). The particles were composed almost entirely of borax. Acute symptoms showing a significant linear trend ($P < 0.0001$) in order of decreasing frequency were dryness of mouth, nose, throat, and eye irritation, dry cough, nosebleeds, sore throat, productive cough, shortness of breath, and chest tightness. The frequency of these symptoms in the highest exposure category ranged from 5% to 33%. The only symptom reported by $\geq 5\%$ of workers exposed to 4.0 mg/m^3 was eye irritation; no symptoms were reported by $\geq 5\%$ of workers exposed to 1.1 mg/m^3 . Pulmonary function was not significantly affected by exposure to boron and chest X-rays did not show abnormal regions indicative of boron exposure. The authors concluded that borax caused simple respiratory irritation that produces chronic bronchitis with no impairment of pulmonary function. Borax dust appeared to cause acute and persistent respiratory irritation at concentrations $\geq 4.5 \text{ mg/m}^3$.

Human supplementation studies

72. Human studies have suggested that subjects consuming about 0.25 mg/day boron can be responsive to boron supplementation (Nielsen *et al.*, 1987; 1988c; 1990). The daily requirement must therefore lie somewhere between 0.25 mg/day and 2.8 mg/day.

73. It is thought that the body probably has a storage reserve of boron, because there is evidence that more than 21 days are required to induce changes in humans by feeding a low-boron diet.

74. Meacham *et al.* (1994) studied the effects of boron supplementation on blood and urinary minerals in female college students, 17 athletes and 11 sedentary controls, over a 1-year period. The athletes had lower percent body fat and higher aerobic capacities than sedentary controls. Athletic subjects consumed more boron in their normal diets than sedentary subjects; all other dietary measures were similar between the two groups. The athletes showed a slight increase in bone mineral density, whereas the sedentary group showed a slight decrease. Serum phosphorus concentrations were lower in boron-supplemented subjects than in subjects receiving placebos, and were lower at the end of the study period than during baseline analysis. Activity depressed changes in serum phosphorus in boron-supplemented subjects. Serum magnesium concentrations were greatest in the sedentary controls whose diets were supplemented with boron, and increased with time in all subjects. In boron-supplemented subjects, exercise lowered serum magnesium. In all subjects, calcium excretion increased over time; in boron-supplemented subjects, boron excretion increased over time. In all subjects, boron supplementation affected serum phosphorus and magnesium, and the excretion of urinary boron.

Carcinogenicity

75. No studies have been carried out on the carcinogenicity of boron or boron compounds in humans. Based on evidence from two lifetime studies in mice (NTP, 1987) and rats (Weir and Fisher, 1972), boron compounds were classified by the US EPA (1994) in Group D, i.e. not classifiable as human carcinogens.

Vulnerable groups

76. Studies have shown that workers exposed to borax complain of symptoms due to respiratory irritation, including nosebleeds, eye and nasal irritation, sore throats, cough and shortness of breath. Dermatitis has also been reported (Birmingham and Key, 1963; NIOSH, 1978). People with hyperreactive respiratory tracts, for example asthmatics, may experience more severe irritant effects following inhalation exposure, but to date, there are insufficient data to support the existence of an especially sensitive high-risk human population for exposure to boron or boron compounds.

Toxicity in laboratory animals

77. Boric acid and borax have a low acute oral toxicity; LD₅₀ values for mice, rats and dogs range from 2000 to >6000 mg/kg body weight. Signs of acute toxicity for both borax and boric acid include depression, ataxia, convulsions and death; kidney degeneration and testicular atrophy are also observed. Of all boron hydrides, which are highly toxic, pentaborane is the most toxic, with 4-h LC₅₀ values for mice and rats of 6 and 12 mg/m³, respectively (American Conference of Governmental and Industrial Hygienists, 1981).

Short-term toxicity

78. The oral LD₅₀ values for boric acid and borax are given in Table 3 below (taken from IPCS Report, 1998).

Table 3

Route	Compound	Species	Compound LD ₅₀ (mg/kg body weight)	Boron ^a LD ₅₀ (mg/kg body weight)	Reference
Oral	Boric acid	Mice	3450	603	Pfeiffer <i>et al.</i> (1945)
	Borax	Rats	3493	396	Wang <i>et al.</i> (1984)
	Borax	Rats	4500	501 ^b	Weir and Fisher (1972)
	Borax	Rats	4980	560 ^b	Weir and Fisher (1972)
	Borax	Rats	5660	642	Smyth <i>et al.</i> (1969)
	Borax	Rats	6080	690 ^b	Weir and Fisher (1972)
	Boric acid	Rats	2660	465	Pfeiffer <i>et al.</i> (1945)
	Boric acid	Rats	3160	550 ^b	Weir and Fisher (1972)
	Boric acid	Rats	3450	600 ^b	Weir and Fisher (1972)
	Boric acid	Rats	4080	710 ^b	Weir and Fisher (1972)
	Boric acid	Rats	5140	899	Smyth <i>et al.</i> (1969)
Sub-cutaneous	Boric acid	Mice	1740 ^c	304	Pfeiffer <i>et al.</i> (1945)
	Boric acid	Mice	2070	362	Pfeiffer <i>et al.</i> (1945)
	Boric acid	Guinea-pigs	1200	210	Pfeiffer <i>et al.</i> (1945)
Intra-venous	Boric acid	Mice	1780	311	Pfeiffer <i>et al.</i> (1945)
	Boric acid	Rats	1330	232	Pfeiffer <i>et al.</i> (1945)

^aCalculated by multiplying the dose in mg boron compound/kg by the ratio of the molecular weights of boron/boron compound, except when noted otherwise.

^bReported by investigators.

^cSolution adjusted to pH 7.4 with sodium hydroxide.

79. General clinical effects of boric acid or borax in rats, mice, and guinea-pigs given single large doses orally are depression, ataxia, occasional convulsions, decreased

body temperature, and violet-red colour of skin and all mucous membranes (Pfeiffer *et al.*, 1945; Weir and Fisher, 1972). Toxic signs in dogs given boric acid (0.2-2.0 g/kg/bw) orally in combination with subcutaneous morphine to prevent vomiting were cyanosis of mucous membranes, red-violet skin colour, rigidity of legs, convulsion, and shock-like syndrome (Pfeiffer *et al.*, 1945). Rabbits given boric acid at 800 mg/kg body weight per day for 4 days showed anorexia, weight loss, and diarrhoea; 850 and 1000 mg/kg body weight per day for 4 days caused 100% mortality (Draize and Kelley, 1959). Cattle receiving 0.8, 150, or 300 mg boron/l in their drinking water for 30 days were lethargic at the highest dose and had swelling and irritation in the legs and around the dew claws, slight diarrhoea, and decreased food consumption at the middle and high doses (Green and Weeth, 1977).

80. Exposure to boric acid in mice, rats and dogs produced microscopic changes in the kidneys and nervous system (Pfeiffer *et al.*, 1945). In the kidneys, glomerular damage consisted of changes in permeability of the capillaries, and tubular damage consisted of cellular vacuolisation and shedding of cells into the tubular lumen. Nervous system damage consisted of an increase in small dark cells (probably microglia) in the spinal cord and in the grey matter of the brain cortex.

81. The LC₅₀ for sodium perborate tetrahydrate by inhalation in rats was >74 mg/m³ (Silaev, 1984). The 1-h inhalation LC₅₀ values for boron trichloride are reported as 12.2 g/m³ for male rats and 21.1 g/m³ for female rats; for boron trifluoride, the LC₅₀ values ranging from 0.89 to 1.2 g/m³ for rats (Vernot *et al.*, 1977).

82. Diets supplemented with up to 300 ppm boron from hatch to 21 days was not detrimental to the growth performance of broiler chicks (Rossi, *et al* (1993).

Chronic toxicity

83. Table 4 below (taken from the IPCS Report, 1998) summarises the effects of long-term oral exposure to boron in animals.

Table 4

Compound	Species	Dose ^a (mg boron/kg body weight per day)	Vehicle	Duration	Effects	Reference
Boric acid	Mice	0, 34, 70, 141, 281, 563 for males; 0, 47, 97, 194, 388, 776 for females ^b	Diet	13 weeks	Over 60% mortality in both sexes at 563 and 776 mg/kg/bw/day; 10% in males at 281 mg/kg body weight per day. At 141 mg/kg/bw/day, degeneration in seminiferous tubules and decreased tubules in males and decreased weight gain in males and females. Extramedullary haematopoiesis of the spleen in all dosed groups, hyperkeratosis and acanthosis of stomach at 563 and 776 mg/kg body weight per day.	NTP (1987)
Boric acid	Mice	0, 48, 96	Diet	103 weeks	Decrease in body weight (10—17%) in high-dose males after week 32 and in high-dose females after week 52. No clinical toxic signs observed. Testicular atrophy and interstitial cell hyperplasia were seen in males at both levels. Dose-related increase in incidence of splenic lymphoid depletion in males. No other significant increase in non-neoplastic lesions.	NTP (1987)
Boric acid	Rats	0, 22.7, 57 and higher	Drinking water	30 days	Growth was not inhibited at the low dose, but it was delayed at ≥ 57 mg/kg/bw/day. No haematological effects or histological alterations.	Pfeiffer <i>et al.</i> (1945)

Compound	Species	Dose ^a (mg boron/kg body weight per day)	Vehicle	Duration	Effects	Reference
Borax	Rats	0, 0.056 0.28 2.8, 28 ^d	Drinking water	198 days	Decrease in pancreas-to-body ratio at all doses in females at day 98. Increase in pancreas-to-body weight ratio in males at day 198. No details given; normal histology.	Wang <i>et al.</i> (1984)
Boric acid	Rats	0.95, 3.65, 5.2, 9.9	Diet	8 weeks	Decreased body weight at 5.2 and 9.9 mg/kg/bw/day. No other toxicity end-points evaluated.	Forbes and Mitchell (1957)
Borax or boric acid	Rats	0, 2.6, 8.8, 26.3, 87.5, 262.5 ^e	Diet	90 days	Mortality was 100% at the highest dose; testicular atrophy at 87.5 and 26.3 mg/kg/bw/day; decrease in body weight and in the weight of liver, kidney, spleen, and testes at 87.5 mg/kg body weight per day; weight changes were inconsistent at lower doses.	Weir and Fisher (1972)
Borax or boric acid	Rats	0, 5.9, 17.5, 58.5 ^a	Diet	2 years	Both compounds suppressed growth at 58.5 mg/kg body weight per day. Testes weight and testes-to-body weight ratios were decreased, and brain-to-body weight and thyroid-to-body weight ratios were increased at 58.5 mg/kg body weight per day; also, atrophy in seminiferous epithelium and decrease in tubular size; no effects observed at lower doses.	Weir and Fisher (1972)
Boric acid or borax	Rabbits	31	Oral gavage	5 days/week for 4 months	Elevated serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels, serum lactate dehydrogenase and aldolase were transiently increased, catalase and amylase were decreased.	Verbitskaya (1975)

Compound	Species	Dose ^a (mg boron/kg body weight per day)	Vehicle	Duration	Effects	Reference
Sodium tetraborate (not specified whether anhydrous or decahydrate)	Rats	0, 3 g/l sodium tetraborate (boron conversion not made due to uncertainty regarding compound)	Drinking water	14 weeks	Increase in RNA concentration and in succinate dehydrogenase and acid proteinase activation in the brain. Decrease in NADPH-cytochrome reductase and in the content of cytochrome b5 and P-450 in the liver. No effect on body or organ weight.	Settimi <i>et al.</i> (1982)
Sodium metaborate	Mice	0, 0.95 ^e	Drinking water	Lifetime	No effects on body weight or longevity.	Schroeder and Mitchener (1975)

^aCalculated by multiplying the dose in mg boron compound/kg body weight per day by the ratio of molecular weights of boron/boron compound.

^bEstimated based on feed consumption values of 161 g/kg body weight per day for male and 222 g/kg body weight per day for female controls at week 4 of treatment.

^cCalculated based on water consumption of 0.12-0.14 ml/g per day reported by authors.

^dCalculated by using assumed body weight of 0.35 kg and reported daily water consumption of 19.5 ml.

^eCalculated by assuming reference values of 0.35 kg body weight and daily water consumption of 0.049 l for rats, or food factor of 0.05 for rats and 0.025 for dogs, or 0.03 kg body weight and daily water consumption of 0.0057 l for mice.

84. In a 90-day drinking water study with male rats, the highest dose of 6 mg boron/l (as borax) (0.426 mg boron/kg body weight per day) caused no effects on fertility and reproduction or weight of the testes, prostate or seminal vesicles (Dixon *et al.*, 1979). In the study of Lee *et al.* (1978), which used much higher doses, male Sprague-Dawley rats were fed borax at concentrations of 0, 500, 1000, or 2000 mg boron/kg (equivalent to approximate doses of 0, 30, 60, or 125-131 mg boron/kg/bw/day) for 30 or 60 days. Body weights were not consistently affected by treatment. However, at 60 and 125-131 mg/kg body weight per day, absolute liver weights were significantly lower after 60 days, while epididymal weights were significantly lower (37.6% and 34.8%, respectively) after 60 days, but not after 30 days.

85. In addition to the studies tabulated above, several studies have been reported in larger mammals. Weir and Fisher (1972) fed boric acid or borax to beagle dogs for 90 days or 2 years. In the 90-day study (weight-normalised doses of 0, 0.44, 4.38, or 43.75 mg boron/kg), testicular effects were observed in males in the two highest dose groups. In the boric acid study, testis weight was reduced by 25% and 40%, respectively compared with controls in the middle- and upper-dose groups. Although testicular microscopic structure was not detectably abnormal in the controls and middle-dose group, four of five dogs in the high-dose group had complete atrophy, and the remaining high-dose dog had one-third of tubules showing some abnormality. In the borax study, testis weights in the low, middle-, and high-dose groups were 80%, 85%, and 50% of controls, respectively; only the last was significantly different from controls. No other signs of toxicity were reported in any animals. In the 2-year study, the dogs received boric acid or borax in the diet at weight-normalised doses of 1.5, 2.9, or 8.8 mg boron/kg/bw/day. An additional group received 29 mg boron/kg/bw/day for 38 weeks. No effects were observed on general appearance, body weight, food consumption, organ weights, haematology or serum chemistry. Changes in testicular morphology occurred in males in the highest (38-week) dose group.

86. Two studies have examined the effects of boron on bone growth. Seffner *et al.* (1990) exposed growing pigs to boron (4 or 8 mg/kg body weight per day). They reported dose-related thinning of the cortex of the humerus and a reduction (significant at 8 mg/kg/bw/day) in presumptively bone-derived serum alkaline phosphatase, suggesting reduced osteoblast activity. The source of the boron was not stated, and the authors were unable to replicate several previous biochemical findings.

87. A second report investigated the effects of boric acid (<0.2-68 mg boron/kg body weight per day) on several bone parameters in adult rats (Chapin *et al.*, 1997). This study found no change in physical bone measures (size, cortical thickness, etc.) but reported a 5-10% increase in resistance of vertebrae to a crush force.

88. Mice exposed to amorphous elemental boron at 72 mg/m³ for 7h/day, 5 days/week, for 6 weeks showed no toxic effects (Stokinger and Spiegel, 1953). In longer-term experiments in rats and dogs exposed to boron oxide particles [median mass aerodynamic diameter (MMAD) 1.9-2.5 µm], exposures took place for 6 h/day and 5 days/week and included rats exposed at 77 mg boric oxide/m³ for 24 weeks, 175 mg boric oxide/m³ for 12 weeks, or 470 mg boric oxide/m³ for 10 weeks (Wilding *et*

al., 1959). Dogs were exposed to 57 mg boron oxide/m³ for 23 weeks. No clinical or microscopical toxic effects were observed.

89. Subchronic inhalation studies with boron trifluoride have reported pneumonitis and reduced body weight gains and organ weights (Torkelson *et al.*, 1961; Rusch *et al.*, 1986).

Reproductive toxicity

90. The male reproductive tract appears to be a consistent target for boric acid/borax exposure in laboratory animals. Testicular lesions have been observed in rats, mice and dogs administered boron compounds in food or drinking water (NTP, 1987; Ku *et al.*, 1993a). Signs include shrunken scrota, inhibited spermiation, degeneration of seminiferous tubules with variable loss of germ cells and complete absence of germ cells, but mating behaviour is unaffected.

91. Acute administration of boron compounds to Sprague-Dawley rats (Linder *et al.*, 1990) showed adverse effects on spermiation, sperm morphology and sperm reserves following doses of 350 mg boron/kg/bw. Animals were killed 2, 14, 28 or 57 days after exposure.

92. In the study of Weir and Fisher (1972), groups of four male or female beagle dogs were fed diets containing boric acid or borax in doses of 0, 1.45, 2.93 or 8.75 mg boron/mg kg/body weight per day. No signs of toxicity were observed. However, when the dose was increased to 29.3 mg boron/kg/bw/day for 38 weeks, testicular atrophy was observed in two dogs at 26 weeks, with spermatogenic arrest and atrophy of the seminiferous epithelium. However, the numbers of dogs used in this study were small and there were variable background lesions in controls.

93. Several studies on mice have been carried out by Fail's group. Swiss CD-11 mice were fed boric acid in their diet at 0, 1000, 4500 or 9000 mg/kg feed for 27 weeks, giving calculated doses of 0, 19.2, 104.7 and 222.1 mg boron/kg body weight per day for males and 0, 31.9, 148.1 and 290.5 mg boron/kg body weight per day for females (Fail *et al.*, 1990, 1991). Boric acid treatment reduced fertility in both males and females at the highest dose. At the middle dose, the number of litters per pair, number of live pups per litter, proportion of liveborn pups and pup weight adjusted for litter size were all decreased. Cross-mating of mid-dose males with control females resulted in significantly depressed mating and fertility indices, but when control males were mated with mid-dose females, these indices were not affected. Therefore, the male appears to be the affected sex.

94. Fail *et al.* (1989) tested the effects of boric acid on fertility, and their reversibility, in CD-1 mice and wild deer mice. Mice were exposed to boric acid for 27 weeks at levels of 0, 1000, 4500 or 9000 mg/kg in the diet. Males at the high and middle doses had testicular atrophy and decreased spermatogenesis. CD-1 mice had body weight loss at 5 weeks in the mid-dose group, but deer mice showed no weight loss even at the high dose. Deer mice recovered from the effects of boric acid exposure.

95. Ku *et al.* (1991) studied the tissue disposition of boron in reproductive, accessory sex organs, and other selected tissues in adult male Fischer rats fed diet containing 9000 mg/kg boric acid for up to 7 days. Animals were killed 1, 2, 3, 4, and 7 days after the start of exposure. There was a rapid increase in plasma and tissue boron 1 day after the start of exposure (range 2- to 20-fold), with the exception of adipose tissue. Bone showed the greatest concentration of boron (2- to 3-fold over plasma levels) while levels in adipose tissue were 20% of plasma levels during the 7-day exposure period. All other tissues appeared to show no significant accumulation of boron over plasma levels, suggesting that testicular toxicity previously observed with boron could be explained on the basis of selective accumulation of boron in the testis or brain/hypothalamus, respectively. Thus, testicular toxicity is likely the result of certain biological processes that are unique to the testis and which are targets of boron exposure.

96. In a later study, Ku *et al.* (1993a) investigated the reversibility of the testicular lesions, using F-344 rats dosed with 3000, 4500, 6000 or 9000 mg boric acid/kg diet (26, 38, 52 and 68 mg boron/kg/bw/day) in the diet for 9 weeks. Recovery was assessed for up to 32 weeks post-treatment. Inhibition of spermiation was exhibited at 3000/4500 mg boric acid/kg, with atrophy at 6000/9000 mg boric acid/kg. After treatment stopped, serum and testis boron levels in all dose groups fell to background levels. Inhibited spermiation at 4500 mg/kg was reversed by 16 weeks after treatment, but focal atrophy did not recover up to 32 weeks post-treatment.

Developmental toxicity

97. Developmental toxicity has been demonstrated experimentally. Heindel *et al.* (1992) demonstrated that treatment of Sprague-Dawley rats with boron 94 mg/kg per day on gestation days 6-15 reduced maternal liver and kidney weights and increased prenatal mortality. Average fetal body weight per litter was also reduced, and the percentage of malformed fetuses per litter and the percentage of litters with at least one malformed fetus was significantly increased. Malformations included anomalies of the eyes, CNS, cardiovascular system and axial skeleton. The LOAEL was 13.6 mg boron/kg/bw, and occurred in the absence of maternal toxicity.

98. A follow-up to this study was carried out by Price *et al.* (1996a), in Sprague-Dawley rats. Groups of 60 time-mated dams were fed 0, 250, 500, 750, 1000 or 2000 mg/kg boric acid in feed from day 0 to day 20 of gestation. Half of the dams were killed on gestational day 20, with the remaining half (phase II) being allowed to deliver their litters, with the offspring being monitored up to day 21. The doses given were equivalent to 0, 3.3 (3.2), 6.3 (6.5), 9.6 (9.7), 13.3 (12.9), 25 (25.3) mg B/kg bw/day (The figures in parentheses refer to the dams in phase II of the study). The study found NOAELs of 9.6 and 12.9 mg boron/kg body weight per day for foetal and maternal effects, based on decreased foetal body weights and increased relative kidney weights respectively. The corresponding LOAELs were 13.3 and 25.3 mg boron/kg body weight per day, confirming the results of the previous study. In addition to reduced foetal weights, boron administration was also associated with an increased incidences of short rib XIII and wavy rib occurring at doses of 12.9 mg B/kg bw/day and above. By post-natal day 21, the increased incidence of short rib XIII and wavy rib was apparent only in the 0.2% (25.3 mg B/kg bw) group giving a

NOAEL for developmental toxicity of 13.3 mgB/kg bw/day on post natal day 21. The NOAELs of 9.6 and 12.9mgB/kg bw determined on gestational day 20 were associated with maternal blood levels of $1.27 \pm 0.298 \mu\text{g/g}$ compared to levels of $0.229 \pm 0.143 \mu\text{g/g}$ in the controls (Price *et al.*, 1998). It was considered possible that the concentrations could underestimate the peak blood levels since they may have occurred prior to blood sampling.

99. A study by Heindel *et al.* (1992) in mice also revealed a dose-related decrease in average foetal body weight per litter at 79 and 175 mg boron/kg body weight per day. There was an increase in skeletal malformations in the offspring of mice treated with 79 and 175 mg boron/kg/bw/day. The LOAEL for developmental effects in mice was 79 mg boron/kg/bw/day, and the NOAEL was 43 mg boron/kg /bw/day.

100. Price *et al.* (1996) studied the developmental toxicity and teratogenicity of boric acid in rabbits at doses of 0, 10.9, 21.9 and 43.7 mg boron/kg body weight per day by gavage. Developmental effects were first evident at 43.7 mg boron/kg body weight per day, and included a high rate of perinatal mortality, increased number of pregnant females with no live foetuses and fewer live foetuses per live litter on day 30. The NOAEL was 21.9 mg boron/kg/bw/day and the LOAEL 43.7 mg boron/kg/bw/day.

Endocrine effects

101. In rats given 0, 2, 12.5 or 25 mg/day boron in drinking water for 6 weeks, testicular and plasma testosterone were significantly increased at the 2 mg/day dose level (Naghii, 1999). Plasma testosterone was positively correlated with testicular testosterone. Plasma follicle stimulating hormone (FSH) was increased at the top dose, confirming testicular atrophy. Plasma luteinizing hormone (LH) was increased at the 2 mg/day dose suggesting that low doses of boron may be of physiological significance

102. Samman *et al.* (1998) reported that in rats, increasing the intake of boron through the drinking water results in an increase in plasma testosterone and vitamin D, with a decrease in HDL cholesterol. Naghii (1999) suggested that the increase in the concentration of unrelated steroids suggests that boron may form unusual bridge bonds that augment the hydroxylation of related processes of cholesterol nucleus (hydroxylation of steroid rings).

Carcinogenicity and mutagenicity

103. Boron compounds were not mutagenic in *Salmonella typhimurium* with or without rat or hamster S9 fraction (Haworth *et al.*, 1983; Benson *et al.*, 1984; NTP, 1987) or in mouse lymphoma L5 178Y/TK+/- cells with or without rat liver S9 (NTP, 1987; McGregor *et al.*, 1988). Refined borax, crude borax ore, and kermite ore were not mutagenic in V79 Chinese hamster cells, C3HI10T1/2 mouse embryo fibroblasts, or diploid human foreskin fibroblasts (Landolph, 1985). Sodium perborate (NaBO_3) was shown to interact with DNA in the *Escherichia coli* Pol A assay, probably through its conversion to hydrogen peroxide (Rosenkranz, 1973). It therefore appears

that genotoxicity is not a likely sequela following exposure to boron compounds in humans.

104. A 2-year feeding study (NTP, 1987; Dieter, 1994) showed no evidence of carcinogenicity in B6C3F1 mice. Weir and Fisher (1972) showed no evidence of boric acid-related carcinogenicity in rats. Taking into account the lack of human data, and basing their classification on the data from these two animal tests, boron is classified by the US EPA as a Group D chemical (not classifiable as to human carcinogenicity) (US EPA, 1994).

105. In summary, current data suggest that boron compounds are neither mutagenic nor carcinogenic.

Mechanisms of toxicity

106. Ku *et al.* (1993b) examined the mechanism of testicular toxicity of boric acid in cell culture systems. Their data suggested an effect of boric acid on the DNA synthesis activity of mitotic and meiotic germ cells, and on energy metabolism in Sertoli cells. The effect on DNA synthesis occurred at boron concentrations associated with atrophy *in vivo*, suggesting that boric acid interferes with the production and/or maturation of early germ cells. However, these observations, although consistent with testicular atrophy, do not explain the inhibition of spermiation.

107. Ku and Chapin (1994) showed that testicular toxicity and CNS hormonal effects were not due to boron accumulation in testis or brain/hypothalamus. Changes in testicular phosphorus, calcium and zinc levels did not precede atrophy. Inhibited spermiation was apparently also not due to increased testicular cyclic adenosine monophosphate or reduced serine protease plasminogen activators. Further studies revealed that DNA synthesis was impaired by boric acid in cell culture, with energy metabolism in Sertoli cells being less affected. However the mechanisms of inhibited spermiation remain to be elucidated.

108. Fail *et al.* (1998) reported that testicular effects occurred at approximately 26 mg boron equivalents/kg/day. New data on endocrine toxicity includes altered follicle stimulating hormone and testosterone within 14 days of treatment, but because these hormonal changes may be secondary to testicular toxicity, borates are not thought to directly affect sex hormone levels. However, Naghii (1999) has argued that boron may be involved in steroid synthesis.

109. To investigate the skeletal effects of boron more closely, Narotsky and colleagues (1998) dosed animals with 500 mg/kg boric acid on gestational days 5-9, 6-9, 6-10 or on individual days between gestational days 6-11. Shortening/absence of the XIII rib was seen particularly on days 5-9 and 6-10. Most of the groups exposed on single days were unaffected by treatment. However, approximately 90% of the animals treated on day 9 had only six cervical vertebrae, whereas treatment on day 20 resulted in agenesis of thoracic/lumbar vertebrae in 60% of the treated animals. Post-natal assessment indicated increased mortality on day 10 treated pups. The authors concluded that boric acid was able to act on the fundamental control mechanisms that define the positional identity of the somites and, consequently the vertebrae. It was

noted that posteriorization of *Hoxa10* expression has been associated with lumbar ribs in mice exposed to teratogens. Other homeotic genes directly or indirectly involved could include *Hoxd-4*, *a-4*, *a-5*, *c-5*, *c-6* and *a-6*.

Regulatory considerations

110. There are no maximum levels of boron specified for food in the UK, with the exception of caviar. However, the maximum levels of boron specified for drinking water, spring water and bottled water is 2000Tg/l (The Natural Mineral Water, Spring Water and Bottled Drinking Water Regulations, 1999 and The Private Water Supplies Regulations 1991).

Existing recommendations on maximum intake levels

111. NOAEL and LOAEL values reported in the literature for reproductive and developmental effects are tabulated below (Table 5).

Table 5

Reference	Adverse effect	Species	LOAEL	NOAEL
Leblond and Clermont (1952)	Male reproductive effects	Rat		87 mg/kg
Weir and Fisher (1972)	Decreased testes weights, testicular atrophy, increased brain/thyroid weights	Rat	58.5 mg/kg	17.5 mg/kg
Fail <i>et al.</i> (1990, 1991)	Decreased sperm motility	Mice	19.2 mg/kg	
Heindel <i>et al.</i> (1992)	Fetal malformations	Rat	13.6 mg/kg	
Heindel <i>et al.</i> (1992)	Developmental toxicity	Mouse		43 mg/kg
Heindel <i>et al.</i> (1992)	Decreased fetal body weight	Mouse	79 mg/kg	
Ku <i>et al.</i> (1993a)	Inhibition of sperm release	Rat	26 mg/kg	
Price <i>et al.</i> (1996a)	Fetal malformations	Rat	13.3 mg/kg	9.6 mg/kg
Price <i>et al.</i> (1996b)	Fetal malformations	Rabbit	43.8 mg/kg	21.9 mg/kg

112. Because a biochemical function has not been defined for boron, its nutritional requirement has not been firmly established. Nonetheless, Nielsen *et al.* (1998) has suggested that dietary guidance should be formulated for boron, because it has demonstrated beneficial, if not essential, effects in both animals and humans.

113. The tolerable intake (TI) is defined as an estimate of the intake of a substance that can occur over a lifetime without appreciable health risks. It is derived on the basis of the NOAEL of the critical effect, the adverse effect judged to be most appropriate. In the case of boron, this would be its reproductive toxicity. Price *et al.* (1996a) identified a NOAEL of 9.6mg/kg body weight per day based on this endpoint. Although data on the toxicity of boron in humans are sparse, its pharmacokinetics appear to be similar in humans and rats. Hence, an uncertainty factor of 25 has been proposed by Price *et al.* (1996a), giving a TI of 0.4 mg/kg body weight/day (24 mg/day for a 60 kg human), which is well above the calculated mean daily intake of boron in the diet (1.2 mg/day from IPCS report, 1.5 mg/day from 1994 UK TDS). This TI is similar to that suggested in the ECETOC Report of 1995 (19.2 mg/day).

114. Fail *et al.* (1998) came to a similar conclusion. They reported that prenatal growth and morphological development in the rat occurred at a dose of 12.9 mg boron equivalents/kg/day, with the NOEL for rat fetal development being 9.6 mg/kg boron equivalents. Considering the estimated human exposure levels and a safety factor of 30, they believe that humans are not at significant risk of reproductive failure due to borates from environmental sources. The margin of exposure is estimated at 72 for males and 129 for females. They conclude the likelihood of human toxicity caused by boric acid and inorganic borates from exposure during normal activities is remote.

115. IPCS derived a TI of 0.4 mg/kg bw/day, using a NOAEL of 9.6 mg B/kg bw/day and a total UF of 25 (Becking and Chen, 1998). The total interspecies UF was $10^{0.5}$ ($10^{0.4}$ for dynamics and $10^{0.1}$) and the total intra-individual UF was $10^{0.9}$ ($10^{0.5}$ for dynamics and $10^{0.4}$).

116. As noted previously, the WHO recommended a safe population mean intake of 1-13 mg B/day.

Existing recommendations on maximum supplementation levels

117. IPCS also recommended that dietary supplements that exceeded the TI should be avoided.

Summary

118. Boron is a naturally occurring element that is found in the form of borates in the oceans, sedimentary rocks, coal, shale and some soils. The most important commercial borate products and minerals are borax pentahydrate, borax, sodium perborate, boric acid, colemanite and ulexite.

119. Mounting evidence suggests that boron is essential to human beings. The greatest exposure to boron for most populations comes from food. An average intake of boron for humans is 0.44 µg/day from ambient air, 0.2–0.6 mg/day from drinking water, and 1.2 mg/day from the diet. The UK 1994 Total Diet Study estimate was 1.4 mg/day. The current regulatory maximum for boron in drinking water in England and Wales is 2 mg/l. Boron exposure from cosmetics is up to 0.46 mg/day.

120. Concentrations of boron in surface water range widely, from 0.001 to as much as 360 mg/litre. Boron concentrations in ambient air range from <0.5 to approximately 80 ng/m³, with an average over the continents of 20 ng/m³. However, in industrial situations, airborne concentrations can be many orders of magnitude higher.

121. The tolerable intake (TI) of boron has been set as 0.4 mg/kg body weight per day. No Reference Nutrient Intake has been set for boron. The World Health Organisation (WHO) have stated that a safe and acceptable intake range for adults is 1-13 mg/day.

122. The preferred method for analysis of boron in bone, plasma and food is inductively coupled plasma atomic emission spectroscopy. Detection limits range from 0.005 to 0.05 mg boron/litre in the solution analysed.

123. Boron appears to interact with other nutrients and plays a regulatory role in the metabolism of minerals, such as calcium, and subsequently bone metabolism. Although the mechanism of action has not been defined, it has been shown that boron supplementation after depletion enhances the elevation in serum 17 β -oestradiol and plasma copper caused by oestrogen therapy. The elevation of endogenous oestrogen as a result of boron supplementation suggests a protective role for boron in atherosclerosis.

124. Boron in foods, sodium borate and boric acid is apparently rapidly absorbed and excreted largely in the urine. Absorption appears to be virtually complete (95% in humans and rats), and boron appears rapidly in the blood and body tissues of several mammalian species following ingestion. Inhalation exposure to borax in the range of 3.3-18 mg/m³ produces increases in human blood and urine boron levels. Absorption across intact skin is negligible in all species evaluated, including human infants, human adults, rabbits and rats. However, when boric acid is applied to broken or damaged skin, dermal absorption of boric acid can be demonstrated. Distribution of boron appears to take place through passive diffusion through the body fluids. Boron is distributed throughout the tissues and organs of animals and humans at concentrations normally between 0.05 and 0.6 μ g/g fresh weight, and several times these concentrations in bones.

125. Borate compounds are not metabolised by biological systems, because of the considerable energy required to break the boron-oxygen bond. At low concentrations, inorganic borates can convert to boric acid at physiological pH in the aqueous layer overlying mucosal surfaces prior to absorption. Boron appears to be eliminated largely in the urine.

126. Boron appears to be an essential nutrient for humans, in that dietary deprivation of boron consistently results in changed biological functions that are detrimental and that can be corrected by increasing boron intake. Similar effects have been shown in animal models. However, as yet, no specific biochemical function for boron has been discovered. The signs of boron deficiency in animals are variable in nature and severity, being dependent on dietary intake of aluminium, calcium, cholecalciferol, magnesium, methionine and potassium. Variables affected by dietary

boron include plasma and organ calcium and magnesium concentrations, plasma alkaline phosphatase and bone calcification. Consistent signs of deficiency include depressed growth and a reduction in some blood indices, particularly steroid hormone concentrations.

127. The lowest lethal dose (LD) for humans exposed to boric acid has been reported as 640 mg/kg body weight by oral exposure, 8600 mg/kg body weight by dermal exposure, and 29 mg/kg body weight by intravenous injection. However, deaths have been reported at doses between 5 and 20 g of boric acid for adults and below 5 g for infants. Potential lethal doses are usually cited as 3-6 g total for infants and 15-20 g total for adults. Data regarding subchronic or chronic exposure to boron in the general population are limited. However, effects on the male reproductive system have been reported following long-term exposure.

128. In animals, boric acid and borax have a low acute oral toxicity; LD₅₀ values for mice, rats and dogs range from 2000 to >6000 mg/kg body weight. Signs of acute toxicity for both borax and boric acid include depression, ataxia, convulsions and death; kidney degeneration and testicular atrophy are also observed. Of all boron hydrides, which are highly toxic, pentaborane is the most toxic, with 4-h LC₅₀ values for mice and rats of 6 and 12 mg/m³, respectively. Current data suggest that boron compounds are neither mutagenic nor carcinogenic.

129. Data suggest an effect of boric acid on the deoxyribonucleic acid (DNA) synthesis activity of mitotic and meiotic germ cells, and on energy metabolism in Sertoli cells. The effect on DNA synthesis occurred at boron concentrations associated with atrophy *in vivo*, suggesting that boric acid interferes with the production and/or maturation of early germ cells.

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