Risk Assessment Boron

General information

Chemistry

Boron is a non-metallic element, which is found abundantly in nature, though only in compounds and in combination with sodium and oxygen. Examples of compounds containing boron are borax ($Na_2B_4O_7.10H_2O$) and boric acid (H_3BO_3). Within this risk assessment the word boron is used as a generic term for boron compounds. For comparative purposes doses of boron compounds are expressed as boron equivalents.

Natural occurrence

Boron is found (in the form of borates) in the oceans, rocks, coal, shale and some soils. Boron accumulates in plants.

Occurrence in foods, food supplements and medicines

Boron is present in foods, particularly nuts (14 mg/kg), fresh fruits (3 mg/kg) and green vegetables (2 mg/kg). Boron is present in a number of multi-vitamin and mineral food supplements at levels up to 10 mg, but not in licensed medicines in the UK.

Other sources of exposure

Intakes of boron from drinking water are estimated to be 0.2-0.6 mg/day. Exposure from cosmetics and consumer products (where boron is used as a preservative and pH adjuster) has been estimated to be up to 0.47 mg/day.

Recommended amounts

COMA was unable to make specific recommendations for boron intake. The World Health Organisation (WHO) acceptable range of intake is 1-13 mg boron/day for adults.

Analysis of tissue levels and boron status

The preferred methods for analysis of boron in bone and plasma are inductively coupled plasma atomic emission spectroscopy and more commonly inductively coupled plasma mass spectrometry. Blood and urine measurements of boron are suitable indicators of excessive boron intake.

Brief overview of non-nutritional beneficial effects

It has been claimed that boron alleviates some symptoms of osteoarthritis and rheumatoid arthritis.

Function

Boron is an essential element in plants and is presumed to be essential in animals, since boron deprivation in both experimental animals and humans causes changes in biological function which are reversible by restoration of boron. The function of boron is unknown, but it may be involved in metabolism and utilisation of various elements (including calcium, copper, magnesium), glucose, triglycerides, reactive oxygen and oestrogen.

Deficiency

Boron deficiency has not been observed definitively in human populations. However, it has been suggested that boron deficiency could be a contributing factor to Kashin-Beck disease (KBD), a musculoskeletal deficiency, which may cause severe joint deformity. Kashin-Beck disease affects children in China and the former Soviet Union, and has also been linked to selenium deficiency. A cross-sectional survey in China found significantly lower boron levels in the hair of children with KBD than in that of local children without KBD. Other authors have reported that short periods of restricted boron intake may affect brain function and cognitive performance in healthy humans.

In animals, boron deficiency is associated with symptoms which include reduced growth rate and decreased blood steroid hormone levels.

Interactions

Studies in animals and in humans have demonstrated that boron interacts with the metabolism of calcium, reducing its rate of excretion and increasing serum levels, but the mechanism is uncertain.

Absorption and bioavailability

Boron as borate is readily, and almost completely, absorbed from the human gut. The mechanism has not been defined.

Distribution and metabolism

Boron, as borate, is distributed evenly, via passive diffusion, throughout body fluids. The highest levels are found in bone, which possibly represents a second kinetic compartment, as elimination kinetics for bone differ from those of soft tissue and body fluids. It has been shown that boron compounds can cross the human placenta.

Boron compounds are not metabolised in biological systems.

Excretion

Boron is predominantly excreted in the urine as borate.

Toxicity

Human data

Data from accidental poisonings indicate that the acute, lethal dose of boric acid is 3000-6000 mg for infants and 15,000-20,000 mg for adults. Clinical effects include irritability, seizures and gastrointestinal disturbances. There have also been reports of inflammation, congestion, oedema, exfoliative dermatitis, exfoliation of the mucosa, and findings of cloudy swelling and granular degeneration of renal tubular cells. Clinical symptoms of boron toxicity have been reported within the dose range 100 to 55,500 mg depending on age/body weight. Inter-individual variability appears to be high.

Long-term exposure to boron in animal studies has been reported to affect male fertility. However, borax miners had a non-significant excess of births compared to the general population and a non-significant excess of female births compared to males in a study of 542 occupational workers in a borax mine (Whorton *et al*., 1994). No effects on fertility were apparent in a Turkish population exposed to boron in drinking water at levels up to 29 mg/L.

Supplementation studies

No adverse effects were identified in female volunteers supplemented with 3 mg boron/day for 1 year (Meacham *et al*., 1994). However, 10 mg boron/day for 4 weeks increased plasma oestradiol and testosterone levels in adult male volunteers (Naghii and Samman, 1997). Plasma oestradiol was also increased in peri-menopausal women supplemented with 2.5 mg boron/day for 60 days (Nielsen and Penland, 1999).

Animal data

Boron compounds have moderate acute toxicity, with lethal doses in the range 400-900 mg boron equivalents/kg body weight. Symptoms and signs include depression, ataxia, convulsions and weight loss. Damage to the kidneys and nerve cells were observed on histopathological examination.

Long-term exposure to boron has been associated with reduced body weights and decreased pancreas, spleen and kidney weights.

Boron has been shown to cause specific adverse effects in the male reproductive tract in all species, including shrunken scrota, inhibited spermiation and degeneration of seminiferous tubules with loss or absence of germ cells. However, mating behaviour in the animals was unaffected. Developmental toxicity has been reported following administration of boron to pregnant rats and rabbits.

Carcinogenicity and genotoxicity

There is no evidence of carcinogenicity from oral exposure to boron compounds in rats and mice. Boron compounds are not mutagenic in bacterial or *in vitro* mammalian cell mutation assays.

Mechanism of toxicity

Boric acid may affect DNA synthesis in germ cells and energy metabolism in Sertoli cells, possibly affecting the production of early germ cells. The mechanism by which boron inhibits spermiation is uncertain.

Dose-response characterisation

In humans, the lethal dose of boric acid is 3000-6000 mg for infants and 15000-20000 mg for adults. Clinical symptoms are apparent within the dose range 100 to 55500 mg depending on age/body weight.

Vulnerable groups

Pregnant women are a potential vulnerable group, as indicated by results of animal reproductive studies.

Genetic variations

No genetic variations have been identified.

Studies of particular importance in the risk assessment

(For full review see http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers or the enclosed CD).

Weir and Fisher, 1972

Ten Sprague Dawley rats of each sex per group were fed diets containing borax or boric acid for 90 days, at levels providing 2.6, 8.8, 26.3, 87.5 or 263 mg boron/kg bw/day. At the highest dose 100% mortality occurred. At 87.5 mg boron kg/bw/day, liver, kidney, spleen, testes, ovaries and body weights were decreased. Histological changes were observed in the adrenals at 87.5 mg boron/kg bw/day. Testicular atrophy occurred at 26.3 and 87.5 mg/kg bw/day. Detailed results were provided for the 87.5 mg/kg bw/day dose group only.

Thirty five Sprague Dawley rats/sex/group were fed diets containing borax or boric acid for 2 years at levels providing 5.9, 17.5 and 58.5 mg boron/kg bw/day. Growth rate was decreased, absolute and relative testes weights were decreased and relative brain and thyroid weights were increased at the top dose. Histological changes in the testes were observed in the top dose group. No other effects were apparent. Limited results were reported.

Five beagle dogs/group were fed diets containing borax or boric acid for 90 days, at levels providing 0.44, 4.4 or 44 mg boron/kg bw/day. In the group given the highest dose, one death occurred, histological changes in the adrenals and thyroid, and severe testicular atrophy were observed, and whereas relative weights of thyroid and testes were reduced, those of liver and brain were increased.

Four beagle dogs of each sex per group were fed diets containing borax or boric acid for 2 years, at levels providing 1.45, 2.93 and 8.75 mg boron/kg bw/day. No treatment related effects were found. Limited results were reported in the paper. In a second study, additional groups were given 29.25 mg boron/kg bw/day for 38 weeks. Histological changes in the testes were apparent, but (based on one animal) were reversible when treatment was stopped.

Eight male and sixteen female Sprague Dawley rats/group were fed diets containing borax or boric acid for 14 weeks prior to mating and for 3 subsequent generations. The doses were provided 5.9, 17.5 and 58.5 mg boron/kg bw/day. No adverse effects were reported in the low and mid dose groups. The high dose animals were, however, sterile when mated with control animals. Decreased ovulation and lack of viable sperm were apparent. Limited results were provided in the paper.

Heindel et al., 1992

Feed containing boric acid at levels providing 13.6, 28.5, 57.7 mg boron/kg bw/day was given to pregnant Sprague Dawley rats throughout gestation (an additional group received 94.2 mg boron/kg bw/day on days 6-25 only). Decreased body weight gain was found in the dams in the 57.7 and 94.2 mg boron/kg bw/day dose groups and increased liver and kidney weights at 28.5 mg boron/kg bw/day and above. Average foetal body weight/litter was reduced in the offspring of the dams in all dose groups. Pre-natal mortality was increased in the 94.2 mg boron/kg bw/day group only. The incidence of malformed foetuses was increased at 28.5 mg boron/kg bw/day and above. The malformations and anatomical variations included enlarged lateral ventricles of the brain and shortening of rib XIII. The authors noted that developmental toxicity was occurring at lower doses than maternal toxicity.

Feed containing boric acid was given to groups of 10 pregnant Swiss mice throughout gestation. The average doses provided by the feed were 43.3, 79.0 or 175 mg boron/kg bw. Minor renal lesions were found in the dams at all doses, and decreased body weights and increased relative kidney weights at the highest dose. In the mice given the highest dose, the number of resorptions and malformed foetuses was increased, and foetal body weights were reduced in offspring. The malformations and anatomical variations included an increased incidence of short rib XIII and a decreased incidence of rudimentary or full ribs at lumbar 1, and were present at all dose levels. The authors argued that since the renal lesions were minor and occurred in 2/10 mice in the low dose group compared with 8/10 and 10/10 in the higher dose groups, that this dose level approached a NOAEL for maternal toxicity. Thus, as with the rat, developmental toxicity was occurring at lower doses than maternal toxicity.

Price et al., 1996

This study is a follow up to the Heindel *et al.* rat study and was designed to establish a NOAEL. Groups of 60 pregnant female Sprague Dawley rats were given feed containing boric acid throughout gestation. The average doses provided in the feed were 0, 3.3, 6.4, 9.6, 13.1 or 25.2 mg boron/kg bw/day. The only maternal effect observed was increased relative kidney weight at the 25.2 mg boron/kg bw/day level. There was no effect on pre-natal mortality. Foetal body weights were reduced in the offspring of the 13.1 and 25.2 mg boron/kg bw/day groups but had recovered by birth. The incidence of short rib XIII was increased in foetal rats at 13.1 and 25.2 mg boron/kg bw/day, but at 25.2 mg boron/kg bw/day only in pups of 21 days of age. The incidence of wavy rib was also increased in foetal rats at 13.1 and 25.2 mg boron/kg bw/day but was reversed in pups of 21 days of age. A slight decrease in the incidence of extra lumbar ribs was observed at 25.2 mg boron/kg bw/day in the day 20 foetuses. The authors concluded that the NOAEL was 9.6 mg boron/kg bw/day for foetal effects and 13.1mg boron/kg bw/day for

maternal toxicity. Developmental toxicity was noted to be occurring at lower doses than maternal toxicity. This is a well-reported study and is consistent with findings of Heindel *et al.*

Exposure assessment

Total exposure/intake:

Food	Mean: 1.5 mg/day (1994 TDS). 97.5th percentile: 2.6 mg/day
Water	0.2–0.6 mg/day (IPCS 1998)
Supplements	up to 10 mg/day (Annex 4)
Cosmetics and consumer products	up to 0.47 mg/day

Maximum estimated intake: 2.6 + 0.6 + 10 + 0.47 = 14 mg/day

Vegetarians have been identified as a potential high intake group.

Risk assessment

In animals, the main toxic effect associated with boron involves the reproductive system. Boron caused specific adverse effects in the male reproductive tract in rats, mice and dogs, including shrunken scrota, inhibited spermiation and degeneration of seminiferous tubules with loss or absence of germ cells. Boron also caused a reduction in ovulation in female rats and renal lesions in female mice. Boron also causes developmental toxicity, with foetal malformations occurring in mice and rats at levels lower than those associated with maternal toxicity.

The human data are scarce, although a study in two Turkish populations (Sayli *et al.,* 1998a) demonstrated that higher levels of boron in well water appeared not to affect reproduction. Similarly, Whorton *et al.* (1994) examined the standardised birth ratio (SBR) in US borate workers. No effects on fertility were apparent (the SBR was increased compared to the general population), a small but insignificant excess of female births was found in both studies. Neither study investigated more sensitive markers of reproductive toxicity or the effects of boron on neonatal body weight, this being the limiting toxicity in the animal studies.

The human epidemiology data are negative but could be compatible with the available animal data since they involved lower exposure levels than used in the animal studies. However, limited conclusions can be drawn from these studies due to the relative insensitivity of the end-points measured. There was no effect on fertility, but more subtle effects on sperm quality (which could be significant in sub-fertile men) or on other aspects of reproductive health could not be ruled out. The supplementation trial by Naghii and Samman, found that 10 mg boron/day for 4 weeks significantly increased plasma oestradiol

levels in male volunteers. The clinical significance of the increase is uncertain. The study is of interest, but limited due to the small numbers involved and the lack of follow up. Other studies have not demonstrated this effect but lower doses of boron were used. Boron has also been reported to enhance the effects of oestrogen in post-menopausal women taking oestrogen therapy. Further work on the effects of boron on the endocrine system is therefore desirable.

ESTABLISHMENT OF SAFE UPPER LEVEL

Key Study:	Price *et al.* (1996).
NOAEL:	9.6 mg boron/kg bw/day.
Uncertainty Factor:	10 for inter-species variation x 6 for inter-individual variation in humans = 60
Safe Upper Level for daily consumption over a lifetime:	9.6/60 = 0.16 mg boron/kg bw/day (equivalent to 9.6 mg boron/day for a 60 kg adult).

The key adverse effect associated with boron is reproductive toxicity. However, the human data are limited regarding reproductive toxicity and so the SUL is based on animal studies. Reproductive toxicity is apparent in laboratory animals, with characteristic effects being produced in the testes. A clear dose-response relationship has been demonstrated. The NOAELs for reproductive effects are 4.4 mg boron/kg bw/day in dogs and 9.6 mg boron/kg bw/day in rodents. Similar effects are observed in different animal species.

A Safe Upper Level can be derived from animal data with the appropriate use of uncertainty factors. Although the Weir and Fisher study resulted in the lower NOAEL of 4.4 mg/kg bw/day, the number of animals in this study was low and the differences between the dose levels tested were large, so that the lowest dose at which adverse effects were observed was ten times this level. Considering the totality of the data, the highest intake without significant adverse effects (the NOAEL) is 9.6 mg/kg bw/day, based on the study of Price *et al*. (1996) and so this has been used to establish an SUL. The usual uncertainty factor of 10 for differences between animals and humans was used to allow for the known differences in renal clearance of boron between animals and humans, and to allow for the possibility that human tissues may be inherently more sensitive than rat tissues. The factor of 10 for inter-individual variability in humans was revised to a chemical-specific adjustment factor of 6 as proposed by Dourson *et al.* (1998). This comprises a factor of 1.8 to allow for glomerular filtration in some women being 2 standard deviations below the average, and a factor of 3.1 to allow for possible, but undefined, inter-subject variability in tissue sensitivity. Pregnant women are a potential vulnerable group given the effects of boron on foetal weights. However, the critical animal studies cover this endpoint and there appears to be no need for an additional uncertainty factor. This results in a safe upper level for total intake of 9.6 mg boron/day for a 60 kg adult. This is higher than the present maximum UK intake from food, water and consumer products (estimated to be up to 3.7 mg boron/day), suggesting a margin of 6 mg/day for supplemental intake.

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