Boron in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International Standards for Drinking-Water. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

GENERAL DESCRIPTION

Identity

Boron (CAS no. 7440-42-8) is never found in the elemental form in nature. It exists as a mixture of the ^{10}B (19.78%) and ^{11}B (80.22%) isotopes (Budavari et al., 1989). Boron's chemistry is complex and resembles that of silicon (Cotton & Wilkinson, 1988).

Physicochemical properties

Elemental boron exists as a solid at room temperature, either as black monoclinic crystals or as a yellow or brown amorphous powder when impure. The amorphous and crystalline forms of boron have specific gravities of 2.37 and 2.34, respectively. Boron is a relatively inert metalloid except when in contact with strong oxidizing agents.

Sodium perborates are persalts, which are hydrolytically unstable because they contain characteristic boron–oxygen–oxygen bonds that react with water to form hydrogen peroxide and stable sodium metaborate ($NaBO_2 \cdot nH_2O$)
.
Boric acid is a very weak acid, with a pK_a of 9.15, and therefore boric acid and the sodium borates exist predominantly as undissociated boric acid [$B(OH)_3$] in dilute aqueous solution at pH <7; at pH >10, the metaborate anion $B(OH)_4^-$ becomes the main species in solution. Between these two pH values, from about 6 to 11, and at high concentration (>0.025 mol/litre), highly water soluble polyborate ions such as $B_3O_3(OH)_4^-$, $B_4O_5(OH)_4^-$, and $B_5O_6(OH)_4^-$ are formed.

The chemical and toxicological properties of borax pentahydrate $Na_2B_4O_7 \cdot 5H_2O$, borax $Na_2B_4O_7 \cdot 10H_2O$, boric acid, and other borates are expected to be similar on a molar boron equivalent basis when dissolved in water or biological fluids at the same pH and low concentration.

Major uses

Boric acid and borates are used in glass manufacture (fibreglass, borosilicate glass, enamel, frit, and glaze), soaps and detergents, flame retardants, and neutron absorbers for nuclear installations. Boric acid, borates, and perborates have been used in mild antiseptics, cosmetics, pharmaceuticals (as pH buffers), boron neutron capture therapy (for cancer treatment), pesticides, and agricultural fertilizers.

Environmental fate

Waterborne boron may be adsorbed by soils and sediments. Adsorption–desorption reactions are expected to be the only significant mechanism influencing the fate of boron in water (Rai et al., 1986). The extent of boron adsorption depends on the pH of the water and the concentration of boron in solution. The greatest adsorption is generally observed at pH 7.5–9.0 (Waggott, 1969; Keren & Mezuman, 1981; Keren et al., 1981).

In natural waters, boron exists primarily as undissociated boric acid with some borate ions. As a group, the boron–oxygen compounds are sufficiently soluble in water to achieve the levels that have been observed (Sprague, 1972). Mance et al. (1988) described boron as a significant constituent of seawater, with an average boron concentration of 4.5 mg/kg.

ANALYTICAL METHODS

A spectrometric method using azomethine-H is available for the determination of borate in water. The method is applicable to the determination of borate at concentrations between 0.01 and 1 mg/litre. The working range may be extended by dilution (ISO, 1990).
A widely used method for the analysis of boron in bone, plasma, and food is inductively coupled plasma atomic emission spectroscopy (Hunt, 1989). This method is also used for water (ISO, 1996) and wastewater (Huber, 1982). Detection limits in water range from 6 to 10 µg of boron per litre.
Inductively coupled plasma mass spectroscopy (ICP-MS) is a widely used non-spectrophotometric method for the analysis of boron, as it uses small volumes of sample, is fast, and applies to a wide range of materials (fresh and saline water, sewage, wastewater, soils, plant samples, and biological materials). ICP-MS can detect boron down to 0.15 µg/litre (WHO, in press). Using direct nebulization, ICP-MS can give a detection limit of 1 ng/g in human blood, human serum, orchard leaves, and total diet (Smith et al., 1991).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Boron is not present in the atmosphere at significant levels (Sprague, 1972). Because borates exhibit low volatility, boron would not be expected to be present to a significant degree as a vapour in the atmosphere. Atmospheric emissions of borates and boric acid in a particulate (<1–45 µm in size) or vapour form occur as a result of volatilization of boric acid from the sea, volcanic activity, mining operations, glass and ceramic manufacturing, the application of agricultural chemicals, and coal-fired power plants.

Water

The natural borate content of groundwater and surface water is usually small. The borate content of surface water can be significantly increased as a result of wastewater discharges, because borate compounds are ingredients of domestic washing agents (ISO, 1990). Naturally occurring boron is present in groundwater primarily as a result of leaching from rocks and soils containing borates and borosilicates. Concentrations of boron in groundwater throughout the world range widely, from <0.3 to >100 mg/litre. In general, concentrations of boron in Europe were greatest in southern Europe (Italy, Spain) and least in northern Europe (Denmark, France, Germany, the Netherlands, and the United Kingdom). For Italy and Spain, mean boron concentrations ranged from 0.5 to 1.5 mg/litre. Values ranged up to approximately 0.6 mg/litre in the Netherlands and the United Kingdom, and approximately 90% of samples in Denmark, France, and Germany were found to contain boron at concentrations below 0.3, 0.3, and 0.1 mg/litre, respectively (WHO, in press). Monthly mean values of boron in the Ruhr River, Germany, ranged from 0.31 to 0.37 mg/litre in a survey conducted during 1992–1995 (Haberer, 1996).

The majority of the Earth′s boron occurs in the oceans, with an average concentration of 4.5 mg/litre (Weast et al., 1985). The amount of boron in fresh water depends on such factors as the geochemical nature of the drainage area, proximity to marine coastal regions, and inputs from industrial and municipal effluents (Butterwick et al., 1989).

Boron concentrations in fresh surface water range from <0.001 to 2 mg/litre in Europe, with mean values typically below 0.6 mg/litre. Similar concentration ranges have been reported for water bodies within Pakistan, Russia, and Turkey, from 0.01 to 7 mg/litre, with most values below 0.5 mg/litre. Concentrations ranged up to 0.01 mg/litre in Japan and up to 0.3 mg/litre in South African surface waters. Samples taken in surface waters from two South American rivers (Rio Arenales, Argentina, and Loa River, Chile) contained boron at concentrations

ranging between 4 and 26 mg/litre in areas rich in boron-containing soils. In other areas, the Rio Arenales contained less than 0.3 mg of boron per litre. Concentrations of boron in surface waters of North America (Canada, USA) ranged from 0.02 mg/litre to as much as 360 mg/litre, indicative of boron-rich deposits. However, typical boron concentrations were less than 0.1 mg/litre, with a 90th-percentile boron concentration of approximately 0.4 mg/litre.

Concentrations of boron found in drinking-water from Chile, Germany, the United Kingdom, and the USA ranged from 0.01 to 15.0 mg/litre, with most values clearly below 0.4 mg/litre. These values are consistent with ranges and means observed for groundwater and surface waters. This consistency is supported by two factors: (i) boron concentrations in water are largely dependent on the leaching of boron from the surrounding geology and wastewater discharges, and (ii) boron is not removed by conventional drinking-water treatment methods.

Food

The general population obtains the greatest amount of boron through food intake. Concentrations of boron reported in food after 1985 have more validity because of the use of more adequate analytical methods.

The richest sources of boron are fruits, vegetables, pulses, legumes, and nuts. Dairy products, fish, meats, and most grains are poor sources of boron. Based on the recent analyses of foods and food products, estimations of daily intakes of various age/sex groups have been made (WHO, in press). The estimated median, mean, and 95th-percentile daily intakes of boron were 0.75, 0.93, and 2.19 mg/day, respectively, for all groups, and 0.79, 0.98 and 2.33 mg/day, respectively, for adults aged 17 and older. Using food included in US Food and Drug Administration Total Diet Studies, Iyengar et al. (1988) determined the mean adult male daily intake of boron to be 1.52 mg/day, whereas Anderson et al. (1994) determined the intake to be 1.21 mg/day. Based on the United Kingdom National Food Survey (MAFF, 1991), the dietary intake of boron in the United Kingdom ranges from 0.8 to 1.9 mg/day. It should be noted that increased consumption of specific foods with high boron content will increase boron intake significantly; for example, one serving of wine or avocado provides 0.42 and 1.11 mg, respectively (Anderson et al., 1994).

Estimated total exposure and relative contribution of drinking-water

The mean daily intake of boron in the diet is judged to be near 1.2 mg/day (Anderson et al., 1994). Concentrations of boron in drinking-water have wide ranges, depending on the source of the drinking-water, but for most of the world the range is judged to be between 0.1 and 0.3 mg/litre. Based on usage data, consumer products have been estimated to contribute a geometric mean of 0.1 mg/day to the estimate of total boron exposure (WHO, in press). The contribution of boron intake from air is negligible. The total daily intake can therefore be estimated from mean concentrations and concentration ranges to be between 1.5 and 2 mg.

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Numerous studies have shown that boric acid and borax are absorbed from the gastrointestinal tract and from the respiratory tract, as indicated by increased levels of boron in the blood, tissues, or urine or by systemic toxic effects of exposed individuals or laboratory animals.

Clearance of boron compounds is similar in humans and animals. The ratio of mean clearance values as a function of dose in non-pregnant rats versus humans is approximately 3- to 4-fold — i.e. similar to the default value for the toxicokinetic component of the uncertainty factor for interspecies variation [Report of informal discussion to develop recommendations for the WHO *Guidelines for drinking-water quality* — Boron. Cincinnati, OH, 28–29 September 1997. Report available from WHO, Division of Operational Support in Environmental Health,

Geneva] (WHO, 1994). Elimination of borates from the blood is largely by excretion of >90% of the administered dose via the urine, regardless of the route of administration. Excretion is relatively rapid, occurring over a period of a few to several days, with a half-life of elimination of 24 hours or less. The kinetics of elimination of boron have been evaluated in human volunteers given boric acid via the intravenous and oral routes (Jansen et al., 1984; Schou et al., 1984). Absorption is poor through intact skin but is much greater through damaged skin.

EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

Acute exposure

The oral LD_{50} values for boric acid or borax in mice and rats are in the range of about 400–700 mg of boron per kg of body weight (Pfeiffer et al., 1945; Weir & Fisher, 1972). Oral LD_{50} values in the range of 250–350 mg of boron per kg of body weight for boric acid or borax exposure have been reported for guinea-pigs, dogs, rabbits, and cats (Pfeiffer et al., 1945; Verbitskaya, 1975). Signs of acute toxicity for both borax and boric acid in animals given single large doses orally include depression, ataxia, convulsions, and death; kidney degeneration and testicular atrophy are also observed (Larsen, 1988).

Short-term exposure

In a 13-week study, mice (10 per sex per dose) were fed diets containing boric acid at approximately 0, 34, 70, 141, 281, or 563 mg of boron per kg of body weight per day. At the two highest doses, increased mortality was seen. Degeneration or atrophy of the seminiferous tubules was observed at 141 mg of boron per kg of body weight per day. In all dose groups, extramedullary haematopoiesis of the spleen of minimal to mild severity was seen (NTP, 1987).

In a study in which borax was given in the diet to male Sprague-Dawley rats (18 per dose) at concentrations of 0, 500, 1000, or 2000 mg of boron per kg of feed (approximately equal to 0, 30, 60, or 125 mg of boron per kg of body weight per day) for 30 or 60 days, body weights were not consistently affected by treatment. Organ weights were not affected by 500 mg of boron per kg of feed; at 1000 and 2000 mg of boron per kg of feed, absolute liver weights were significantly lower after 60 days, and epididymal weights were significantly lower (37.6% and 34.8%, respectively) after 60 days, but not after 30 days. Weights of prostate, spleen, kidney, heart, and lung were not changed at any dose (Lee et al., 1978).

In a 90-day study in rats (10 per sex per dose) receiving 0, 2.6, 8.8, 26, 88, or 260 mg of boron per kg of body weight per day in the diet as boric acid or borax, all animals at the highest dose died within 3–6 weeks (Weir & Fisher, 1972). In animals receiving 88 mg of boron per kg of body weight per day, body weights in males and females were reduced; absolute organ weights, including the liver, spleen, kidneys, brain, adrenals, and ovaries, were also significantly decreased in this group. Organ-to-body-weight ratios for the adrenals and kidneys were significantly increased, but relative weights of the liver and ovaries were decreased. A pronounced reduction in testicular weights in males in the 88 mg of boron per kg of body weight per day group was also observed.

Boric acid or borax was also fed to beagle dogs for 90 days or for 2 years. In the 90-day boric acid study (weight-normalized doses of 0, 0.44, 4.4, or 44 mg of boron per kg of body weight per day; five animals per sex per dose), testis weight was significantly lower than controls in the middle and upper dose groups (reduced by 25% and 40%, respectively). 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 mention was made of the testicular microscopic structure of the controls or low-dose animals; middle-dose animals were not detectably altered (aside from the considerable fixation-induced artifact in the outer third of the tissue), whereas four of five high-dose dogs had complete testicular atrophy, and the remaining high-dose dog had "partial" atrophy. No other clinical or microscopic signs of toxicity were reported in any animals (Weir & Fisher, 1972).

In the 2-year study, the dogs (four per sex per dose) received the boric acid or borax in the diet at weight-normalized doses of 0, 1.5, 2.9, or 8.8 mg of boron per kg of body weight per day. An additional group received 29 mg of boron per kg of body weight per day for 38 weeks. Testicular atrophy was observed in two test dogs receiving borax at 26 weeks and in the two and one dogs, respectively, killed after 26 or 38 weeks of boric acid consumption. The authors stated that boric acid caused testicular degeneration in dogs, including spermatogenic arrest and atrophy of the seminiferous epithelium. The study was terminated at 38 weeks. In these studies, the number of dogs was small and variable (one or two dogs at each of three time points) and inadequate to allow statistical analysis. All three treated dogs had widespread and marked atrophy in 25–40% of the seminiferous tubules. A common control group was used for both the borax and boric acid studies. Testicular lesions occurred in the controls (one of four controls had slight to severe seminiferous tubular atrophy, another had moderate to severe atrophy, whereas a third had a detectable but insignificant reduction in spermatogenesis and 5% atrophic seminiferous tubules) (Weir & Fisher, 1972). These studies were conducted before the advent of Good Laboratory Practices (GLPs). Confidence in these studies is low, and they were considered not suitable for inclusion into the risk assessment because of 1) small and variable numbers of dogs, 2) variable background lesions in controls leading to uncertainty of the strength of the response to treatment, 3) lack of GLPs, and 4) other, more recent studies of greater scientific quality with findings at similar intake levels of boron (Ku et al., 1993; Price et al., 1996a).

Long-term exposure

A 2-year study in mice (50 per sex per dose) receiving approximately 0, 275, or 550 mg of boric acid per kg of body weight per day (0, 48, or 96 mg of boron per kg of body weight per day) in the diet (NTP, 1987; Dieter, 1994) demonstrated that body weights were 10–17% lower in high-dose males after 32 weeks and in high-dose females after 52 weeks. Increased mortality rates were statistically significant in males, with significant lesions in male mice appearing in the testes and no significant non-neoplastic lesions in female mice.

In a 2-year study, rats (35 per sex per dose) were administered weight-normalized boron doses of 0, 5.9, 18, or 59 mg/kg of body weight per day in the diet (Weir & Fisher, 1972). High-dose animals had coarse hair coats, scaly tails, hunched posture, swollen and desquamated pads of the paws, abnormally long toenails, shrunken scrotum, inflamed eyelids, and bloody eye discharge. The haematocrit and haemoglobin levels were significantly lower than controls, the absolute and relative weights of the testes were significantly lower, and relative weights of the brain and thyroid gland were higher than in controls. In animals in the mid- and low-dose groups, no significant effects on general appearance, behaviour, growth, food consumption, haematology, serum chemistry, or histopathology were observed.

Reproductive and developmental toxicity

Short- and long-term oral exposures to boric acid or borax in laboratory animals have demonstrated that the male reproductive tract is a consistent target of toxicity. Testicular lesions have been observed in rats, mice, and dogs administered boric acid or borax in food or drinking-water (Truhaut et al., 1964; Weir & Fisher, 1972; Green et al., 1973; Lee et al., 1978; NTP, 1987; Ku et al., 1993). The first clinical indication of testicular toxicity in dogs is

shrunken scrota observed during treatment; significant decreases in absolute and relative testicular weight are also reported. After subchronic exposure, the histopathological effects range from inhibited spermiation (sperm release) to degeneration of the seminiferous tubules with variable loss of germ cells to complete absence of germ cells, resulting in atrophy and transient or irreversible loss of fertility, but not of mating behaviour.

In time–response and dose–response reproductive studies (Linder et al., 1990), adult male Sprague-Dawley rats were administered two doses in one day, with a total dose of 0 or 350 mg of boron per kg of body weight in the time–response experiment (animals were sacrificed at 2, 14, 28, or 57 days post-treatment) and a total dose of 0, 44, 87, 175, or 350 mg of boron per kg of body weight in the dose–response experiment (animals were sacrificed after 14 days). Adverse effects on spermiation, epididymal sperm morphology, and caput sperm reserves were observed during histopathological examinations of the testes and epididymis. The NOAEL for male reproductive effects in the dose–response study was 87 mg of boron per kg of body weight per day.

In a multi-generation study, doses of 0, 117, 350, or 1170 mg of boron per kg of feed (as borax or boric acid) were administered to male and female rats (Weir & Fisher, 1972). At the highest dose, rats were found to be sterile, males showed atrophied testes in which spermatozoa were absent, and females showed decreased ovulation. The NOAEL in this study was 350 mg of boron per kg of feed, equivalent to 17.5 mg of boron per kg of body weight per day.

To investigate the development of testicular lesions, boric acid was fed at 61 mg of boron per kg of body weight per day to male F344 rats; sacrifice of six treated and four control rats was conducted at intervals from 4 to 28 days. At 28 days, there was significant loss of spermatocytes and spermatids from all tubules in exposed rats, and basal serum testosterone levels were significantly decreased from 4 days on (Treinen & Chapin, 1991). In another study, the activities of enzymes found primarily in spermatogenic cells were decreased, and enzyme activities associated with premeiotic spermatogenic cells were significantly increased in rats exposed to 60 or 125 mg of boron per kg of body weight per day for 60 days (Lee et al., 1978). Mean plasma follicle-stimulating hormone levels were significantly elevated in a dose-dependent manner in all treatment groups (30, 60, or 125 mg of boron per kg of body weight per day) in this study after 60-day exposures.

Reversibility of testicular lesions was evaluated by Ku et al. (1993) in an experiment in which F344 rats were dosed at 0, 3000, 4500, 6000, or 9000 mg of boric acid per kg of feed (equivalent to 0, 26, 39, 52, or 78 mg of boron per kg of body weight per day) for 9 weeks and assessed for recovery up to 32 weeks post-treatment. Inhibited spermiation was exhibited at 3000 and 4500 mg of boric acid per kg of feed (5.6 µg of boron per mg of tissue), whereas inhibited spermiation progressed to atrophy at 6000 and 9000 mg of boric acid per kg of feed (11.9 µg of boron per mg of testes); there was no boron accumulation in the testes to levels greater than those found in the blood during the 9-week period. After treatment, serum and testis boron levels in all dose groups fell to background levels. Inhibited spermiation at 4500 mg of boric acid per kg of feed was reversed by 16 weeks post-treatment, but focal atrophy, which did not recover up to 32 weeks post-treatment, was detected.

Developmental toxicity has been demonstrated experimentally in rats, mice, and rabbits (NTP, 1990; Heindel et al., 1992; Price et al., 1996b). Rats were fed a diet containing 0, 14, 29, or 58 mg of boron per kg of body weight per day as boric acid on gestation days 0–20 (Heindel et al., 1992). An additional group of rats received boric acid at 94 mg of boron per kg of body weight per day on gestation days 6–15 only. Average fetal body weight per litter was significantly reduced in a dose-related manner in all treated groups compared with controls. The percentage of malformed fetuses per litter and the percentage of litters with at least one malformed fetus were significantly increased at =29 mg of boron per kg of body

weight per day. Malformations consisted primarily of anomalies of the eyes, the central nervous system (CNS), the cardiovascular system, and the axial skeleton. The most common malformations were enlargement of lateral ventricles in the brain and agenesis or shortening of rib XIII. The LOAEL of 14 mg of boron per kg of body weight per day (the lowest dose tested) for rats occurred in the absence of maternal toxicity; a NOAEL was not found in this study.

Price et al. (1996a) did a follow-up to the Heindel et al. (1992) study in Sprague-Dawley (CD) rats to determine a NOAEL for fetal body-weight reduction and to determine whether the offspring would recover from prenatally reduced body weight during postnatal development. Boric acid was administered in the diet to CD rats on gestation days 0–20. Dams were terminated and uterine contents examined on gestation day 20. The intake of boric acid was 0, 3.3, 6.3, 9.6, 13, or 25 mg of boron per kg of body weight per day. Fetal body weights were 99, 98, 97, 94, and 88% of controls for the low- to high-dose groups, respectively. Incidences of short rib XIII (a malformation) or wavy rib (a variation) were increased in the 13 and 25 mg of boron per kg of body weight per day dose groups relative to control litters. There was a decreased incidence of rudimentary extra rib on lumbar 1 (a variation) in the high-dose group that was deemed biologically but not statistically significant. The NOAEL in this study was 9.6 mg of boron per kg of body weight per day, based on a decrease in fetal body weight at the next higher dose.

Developmental toxicity and teratogenicity of boric acid in mice at 0, 43, 79, or 175 mg of boron per kg of body weight per day in the diet were investigated (Heindel et al., 1992). There was a significant dose-related decrease in average fetal body weight per litter at 79 and 175 mg of boron per kg of body weight per day. In offspring of mice exposed to 79 or 175 mg of boron per kg of body weight per day during gestation days 0–20, there was an increased incidence of skeletal (rib) malformations. These changes occurred at doses for which there were also signs of maternal toxicity (increased kidney weight and pathology); the LOAEL for developmental effects (decreased fetal body weight per litter) was 79 mg of boron per kg of body weight per day, and the NOAEL was 43 mg of boron per kg of body weight per day.

Developmental toxicity and teratogenicity of boric acid in rabbits were investigated by Price et al. (1996b) at doses of 0, 11, 22, or 44 mg of boron per kg of body weight per day, given by gavage. Frank developmental effects in rabbits exposed to 44 mg of boron per kg of body weight per day included a high rate of prenatal mortality, an increased number of pregnant females with no live fetuses, and fewer live fetuses per live litter on day 30. At the high dose, malformed live fetuses per litter increased significantly, primarily because of the incidence of fetuses with cardiovascular defects, the most prevalent of which was interventricular septal defect. Skeletal variations observed were extra rib on lumbar 1 and misaligned sternebra. The NOAEL for maternal and developmental effects was 22 mg of boron per kg of body weight per day.

Mutagenicity and related end-points

The mutagenic activity of boric acid was examined in the *Salmonella typhimurium* and mouse lymphoma assays, with negative results. No induction of sister chromatid exchange or chromosomal aberrations was observed in Chinese hamster ovary cells (NTP, 1987). Sodium borate did not cause gene mutations in the *S. typhimurium* preincubation assay (Benson et al., 1984). Borax was not mutagenic in cell transformation assays with Chinese hamster cells, mouse embryo cells, and human fibroblasts (Landolph, 1985).

Carcinogenicity

Tumour incidence was not enhanced in studies in which $B6C3F_1$ mice received 0, 2500, or 5000 mg of boric acid per kg of feed for 103 weeks (NTP, 1987) and Sprague-Dawley rats

received diets containing 0, 117, 350, or 1170 mg of boron per kg of feed (as borax or boric acid) for 2 years (Weir & Fisher, 1972).

EFFECTS ON HUMANS

Available human data on boron compounds for routes other than inhalation focus on boric acid and borax. According to Stokinger (1981), the lowest reported lethal doses of boric acid are 640 mg/kg of body weight (oral), 8600 mg/kg of body weight (dermal), and 29 mg/kg of body weight (intravenous injection). Stokinger (1981) stated that death has occurred at total doses of between 5 and 20 g of boric acid for adults and <5 g for infants. Litovitz et al. (1988) stated that potential lethal doses are usually cited as 3–6 g total for infants and 15–20 g total for adults. 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 concluded that exposures ranged from 12 to 90 g, with a very crudely estimated average daily ingestion of 18–56 mg of boron per kg of body weight (O Sullivan & Taylor, 1983). [Estimates given here are corrected values, as intakes reported in this publication were underestimated by a factor of 3 (M. Taylor, personal communication to M. Dourson, in a letter dated 28 August 1997).] Toxicity was manifested by generalized or alternating focal seizure disorders, irritability, and gastrointestinal disturbances. Although infants appear to be more sensitive than adults to boron compounds, lethal doses are not well documented in the literature.

Goldbloom & 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. Toxicity was manifested by cutaneous lesions (erythema over the entire body, excoriation of the buttocks, and desquamation), gastrointestinal disturbances, and seizures. Approximately 35% of the 109 other case reports of boric acid poisoning involved children <1 year of age. The mortality rate was 70.2% for children, compared with 55.0% for all cases combined. Death occurred in 53% of patients exposed by ingestion, 75% of patients subjected to gastric lavage with boric acid, 68% of patients exposed by dermal application for treating burns, wounds, and skin eruptions, and 54% of patients exposed by other routes. Information on signs and symptoms for 80 patients showed that gastrointestinal disturbances were prevalent (73%), followed by CNS effects (67%). Cutaneous lesions were prevalent in 76% of the cases and in 88% of cases involving children <2 years of age. Gross and microscopic findings were reported for 45% of 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.

In addition to case reports, poison centres have published case-series reports. Unlike the case reports reviewed by Goldbloom & Goldbloom (1953), more recent reports suggest that the oral toxicity of boron in humans is milder 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; approximately 88.3% of the cases were asymptomatic. All but two of the cases had acute (single) ingestion, and 80.2% involved children <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 (primarily CNS and cutaneous) occurred in fewer cases: lethargy, rash, headache, light-headedness, fever, irritability, and muscle cramps. The average dose ingested was estimated at 1.4 g. According to Litovitz et al. (1988), 21 of the children <6 years of age, 15 of whom were <2 years of age, ingested the reported potential

lethal dose of 3 g; eight adults ingested the reported potential lethal dose of 15 g without clinical evidence of lethal effects.

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 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% noted mild gastrointestinal symptoms. One 2-year-old child died, presumably from repeated ingestion of an insecticide containing 99% boric acid.

Overall, owing to the wide variability of data collected from poisoning centres, the average dose of boric acid to produce clinical symptoms is still unclear, presumably in the range of 100 mg to 55.5 g, reported by Litovitz et al. (1988).

Findings from human experiments show that boron is a dynamic trace element that can affect the metabolism or utilization of numerous substances involved in life processes, including calcium, copper, magnesium, nitrogen, glucose, triglycerides, reactive oxygen, and estrogen. Although the first findings involving boron deprivation of humans appeared in 1987 (Nielsen et al., 1987), the most convincing findings have come mainly from two studies in which men over the age of 45, postmenopausal women, and postmenopausal women on estrogen 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 of boron per day for 49 days (Nielsen, 1989, 1994; Nielsen et al., 1990, 1991, 1992; Penland, 1994). These dietary intakes were near the low and high values in the range of usual dietary boron intakes. The major differences between the two studies were the intakes of copper and magnesium: in one experiment, they were marginal or inadequate; in the other, they were adequate. The marginal or inadequate copper and magnesium intakes caused apparent detrimental changes that were more marked during boron deprivation than during boron repletion. Although the function of boron remains undefined, boron is becoming recognized as an element of potential nutritional importance because of the findings from human and animal studies.

PROVISIONAL GUIDELINE VALUE

The TDI of boron is derived by dividing the NOAEL (9.6 mg/kg of body weight per day) for the critical effect, which is developmental toxicity (decreased fetal body weight in rats), by an appropriate uncertainty factor, which is judged to be 60. The value of 10 for interspecies variation (animals to humans) was adopted because of lack of toxicokinetic and toxicodynamic data to allow deviation from this default value. Available toxicokinetic data do support, however, reduction of the default uncertainty factor for intraspecies variation from 10 to 6 (WHO, 1994).
Interspecies (toxicokinetic) variations for boron relate primarily to clearance. The ratio of mean clearance values in non-pregnant rats versus non-pregnant humans for boron (based on all of the data considered suitable for inclusion) is 3–4. In view of the lack of adequate kinetic studies in rats and hence less than optimum confidence in much of the data that serve as the basis for the ratio, replacement of the default for the toxicokinetic component of the interspecies factor is considered premature at this time. The total uncertainty factor for interspecies variation is 10.

Intraspecies variation (toxicokinetics) for boron relates also primarily to variations in clearance. As the critical effect that serves as the basis for the TDI is developmental, pregnant women are the subgroup of interest in this regard. Based on pooled individual data from available studies, the mean glomerular filtration rate (GFR) in 36 healthy women was 145 ± 23 ml/minute in early pregnancy and 144 ± 32 ml/minute in late pregnancy. The standard deviation represented 22% of the mean value in late pregnancy. Based on division of the

mean GFR (144 ml/minute) by the GFR at two standard deviations below the mean (80 ml/minute) to address variability for approximately 95% of the population, the ratio for the toxicokinetic component of interspecies variation is 1.8 (compared with the default value for this component of 3.2). As there are no data to serve as a basis for replacement of the default value for the toxicodynamic component of the uncertainty factor for intraspecies variation, the total uncertainty factor for intraspecies variation is $1.8 \times 3.2 = 5.7$ (rounded to 6) [Report of informal discussions to develop recommendations for the WHO *Guidelines for drinking-water quality* — Boron. Cincinnati, OH, 28–29 September 1997. Report available from WHO, Division of Operational Support in Environmental Health, Geneva].

Using an uncertainty factor of 60, the TDI is therefore 0.16 mg/kg of body weight. With an allocation of 10% of the TDI to drinking-water and assuming a 60-kg adult consuming 2 litres of drinking-water per day, the guideline value is 0.5 mg/litre (rounded figure).

Conventional water treatment (coagulation, sedimentation, filtration) does not significantly remove boron, and special methods would have to be installed in order to remove boron from waters with high boron concentrations. Ion exchange and reverse osmosis processes may enable substantial reduction but are likely to be prohibitively expensive. Blending with low-boron supplies might be the only economical method to reduce boron concentrations in waters where these concentrations are high (WRc, 1997).

The guideline value of 0.5 mg/litre is designated as provisional, because it will be difficult to achieve in areas with high natural boron levels with the treatment technology available.

REFERENCES

1. Anderson DL, Cunningham WC, Lindstrom TR (1994) Concentrations and intakes of H, B, S, K, Na, Cl and NaCl in foods. *Journal of food composition and analysis*, 7:59-82.
2. Benson WH, Birge WJ, Dorough HW (1984) Absence of mutagenic activity of sodium borate (borax) and boric acid in the *Salmonella* preincubation test. *Environmental toxicology and chemistry*, 3:209-214.
3. Budavari S et al., eds. (1989) *The Merck index*, 11th ed. Rahway, NJ, Merck and Co., Inc. Butterwick L, de Oude N, Raymond K (1989) Safety assessment of boron in aquatic and terrestrial environments. *Ecotoxicology and environmental safety*, 17:339-371.
4. Cotton PA, Wilkinson L (1988) *Advanced inorganic chemistry*, 5th ed. New York, NY, John Wiley & Sons, pp. 162-165.
5. Dieter MP (1994) Toxicity and carcinogenicity studies of boric acid in male and female B6C3F$_1$ mice. *Environmental health perspectives*, 102 (Suppl. 7):93-97.
6. Goldbloom RB, Goldbloom A (1953) Boric acid poisoning: Report of four cases and a review of 190 cases from the world literature. *Journal of pediatrics*, 43:631-643.
7. Green GH, Lott MD, Weeth HJ (1973) Effects of boron water on rats. *Proceedings, Western Section, American Society of Animal Science*, 24:254-258.
8. Haberer K (1996) [Boron in drinking water in Germany.] *Wasser-Abwasser*, 137:364-371 (in German).
9. Heindel JJ et al. (1992) Developmental toxicity of boric acid in mice and rats. *Fundamental and applied toxicology*, 18:266-277.
10. Huber L (1982) ICP-AES, ein neues verfahren zur multielement - bestimmung in wassern, abwassern und schlammen. *Wasser*, 58:173-185B.
11. Hunt CD (1989) Dietary boron modified the effects of magnesium and molybdenum on mineral metabolism in the cholecalciferol-deficient chick. *Biological trace element research*, 22:201-220.
12. ISO (1990) *Water quality — Determination of borate — Spectrometric method using azomethine-H*. Geneva, International Organization for Standardization (ISO 9390:1990).

13. ISO (1996) *Water quality — Determination of 33 elements by inductively coupled plasma atomic emission spectroscopy.* Geneva, International Organization for Standardization (ISO 11885:1996 (E)).

14. Iyengar GV et al. (1988) Lithium in biological and dietary materials. In: *Proceedings of the 5th international workshop on trace element analytical chemistry in medicine and biology,* pp. 267-269.

15. Jansen JA, Andersen J, Schou JS (1984) Boric acid single dose pharmacokinetics after intravenous administration to man. *Archives of toxicology*, 55:64-67.

16. Keren R, Mezuman U (1981) Boron adsorption by clay minerals using a phenomenological equation. *Clays and clay minerals*, 29:198-204.

17. Keren R, Gast RG, Bar-Yosef B (1981) pH-dependent boron adsorption by Na-montmorillonite. *Soil Science Society of America journal*, 45:45-48.

18. Ku WW et al. (1993) Testicular toxicity of boric acid (BA): relationship of dose to lesion development and recovery in the F344 rat. *Reproductive toxicology*, 7:305-319.

19. Landolph JR (1985) Cytotoxicity and negligible genotoxicity of borax and borax ores to cultured mammalian cells. *American journal of industrial medicine*, 7:31-43.

20. Larsen LA (1988) Boron. In: Seiler HG, Sigel H, eds. *Handbook on toxicity of inorganic compounds*. New York, NY, Marcel Dekker, pp. 129-141.

21. Lee IP, Sherins RJ, Dixon RL (1978) Evidence for induction of germinal aplasia in male rats by environmental exposure to boron. *Toxicology and applied pharmacology*, 45:577-590.

22. Linden CH et al. (1986) Acute ingestion of boric acid. *Journal of toxicology. Clinical toxicology*, 24:269-279.

23. Linder RE, Strader LF, Rehnberg GL (1990) Effect of acute exposure to boric acid on the male reproductive system of the rat. *Journal of toxicology and environmental health*, 31:133-146.

24. Litovitz TL et al. (1988) Clinical manifestation of toxicity in a series of 784 boric acid ingestions. *American journal of emergency medicine*, 31:209-213.

25. MAFF (1991) *Household food consumption and expenditure 1991. Annual report of the National Food Survey Committee.* London, Ministry of Agriculture, Fisheries and Food.

26. Mance G, O Donnell AR, Smith PR (1988) *Proposed environmental quality standards for List II substances in water: Boron.* Medmenham, Water Research Centre (Report TR 256, March 1988; ISBN 0-902-15663-2).

27. Nielsen FH (1989) Dietary boron affects variables associated with copper metabolism in humans. In: Aulse M et al., eds. *Proceedings of the 10th international trace element symposium. Vol. 4.* Jena, Friedrich-Schiller-Universität, pp. 1106-1111.

28. Nielsen FH (1994) Biochemical and physiological consequences of boron deprivation in humans. *Environmental health perspectives*, 102 (Suppl. 7):59-63.

29. Nielsen FH et al. (1987) Effect of dietary boron on mineral, oestrogen, and testosterone metabolism in postmenopausal women. *The FASEB journal*, 1:394-397.

30. Nielsen FH, Mullen LM, Gallagher SK (1990) Effect of boron depletion and repletion on blood indicators of calcium status in humans fed a magnesium-low diet. *Journal of trace elements in experimental medicine*, 3:45-54.

31.Nielsen FH, Mullen LM, Nielsen EJ (1991) Dietary boron affects blood cell counts and hemoglobin concentrations in humans. *Journal of trace elements in experimental medicine*, 4:211-223.

32. Nielsen FH et al. (1992) Boron enhances and mimics some effects of oestrogen therapy in postmenopausal women. *Journal of trace elements in experimental medicine*, 5:237-246.

33. NTP (1987) *Toxicology and carcinogenesis studies of boric acid (CAS no. 10043-35-3) in B6C3F$_1$ mice (food studies).* Research Triangle Park, NC, US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program (NTP Technical Report Series No. 324).NTP (1990).

34. NTP *Final report on the developmental toxicity of boric acid (CAS no. 10043-35-3) in Sprague-Dawley rats.* Research Triangle Park, NC, US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program (NTP Report No. 90-105).

35. O'Sullivan K, Taylor M (1983) Chronic boric acid poisoning in infants. *Archives of diseases in childhood*, 58:737-739.

36. Penland JG (1994) Dietary boron, brain function and cognitive performance. *Environmental health perspectives*, 102 (Suppl. 7):65-72.

37. Pfeiffer CC, Hallman LF, Gersh I (1945) Boric acid ointment: A study of possible intoxication in the treatment of burns. *Journal of the American Medical Association*, 128:266-274.

38. Price CJ et al. (1996a) Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. *Fundamental and applied toxicology*, 32:179-193.

39. Price CJ et al. (1996b) The developmental toxicity of boric acid in rabbits. *Fundamental and applied toxicology*, 34:176-187.

40. Rai D et al. (1986) *Chemical attenuation rates, coefficients, and constants in leachate migration. Vol. 1: A critical review.* Report to Electric Power Research Institute, Palo Alto, CA, by Battelle Pacific Northwest Laboratories, Richland, WA (Research Project 2198-1).

41. Schou JS, Jansen JA, Aggerbeck B (1984) Human pharmacokinetics and safety of boric acid. *Archives of toxicology*, Suppl. 7:232-235.

42. Smith FG et al. (1991) Measurement of boron concentration and isotope ratios in biological samples by inductively coupled plasma mass spectrometry with direct injection nebulization. *Analytica Chimica Acta*, 248:229-234.

43. Sprague RW (1972) *The ecological significance of boron.* Anaheim, CA, US Borax Research Corporation, 58 pp.

44. Stokinger HE (1981) Boron. In: Clayton GD, Clayton FE, eds. *Patty's industrial hygiene and toxicology. Vol. 2B. Toxicology*, 3rd ed. New York, NY, John Wiley & Sons, pp. 2978-3005.

45. Treinen KA, Chapin RE (1991) Development of testicular lesions in F344 rats after treatment with boric acid. *Toxicology and applied pharmacology*, 107:325-335.

46. Truhaut R, Phu-Lich N, Loisillier F (1964) [Effects of the repeated ingestion of small doses of boron derivatives on the reproductive functions of the rat.] *Comptes Rendus de l'Académie des Sciences*, 258:5099-5102 (in French with English abstract).

47. Verbitskaya GV (1975) [Experimental and field investigations concerning the hygienic evaluation of boron-containing drinking water.] *Gigiena i Sanitariya*, 7:49-53 (in Russian with English abstract).

48. Waggott A (1969) An investigation of the potential problem of increasing boron concentrations in rivers and water courses. *Water research*, 3:749-765.

49. Weast RC, Astle MJ, Beyer WH, eds. (1985) *CRC handbook of chemistry and physics*, 69th ed. Boca Raton, FL, CRC Press, Inc., pp. B-77, B-129.

50. Weir RJ, Fisher RS (1972) Toxicologic studies on borax and boric acid. *Toxicology and applied pharmacology*, 23:351-364.

51. WHO (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 170).

52. WHO (in press) *Boron*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria monograph).

53. WRc (1997) *Treatment technology for aluminium, boron and uranium.* Document prepared for WHO by the Water Research Centre, Medmenham, and reviewed by S. Clark, US EPA; A. van Dijk-Looijaard, KIWA, Netherlands; and D. Green, Health Canada.