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Boron in drinking-water

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

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Preface

One of the primary goals of the World Health Organization (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 third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

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 and 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 of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, 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. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert 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.

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The first draft of Boron in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality* (GDWQ), was prepared by Mr J.K. Fawell, United Kingdom, to whom special thanks are due. This background document is an update of the background document published in the addendum to the second edition of the GDWQ.

The work of the following working group coordinators was crucial in the development of this document and others contributing to the fourth edition:

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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held on 19–23 June 2008. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

Acronyms and abbreviations used in the text

$BMDL_{05}$	95% lower bound on the benchmark dose corresponding to a 5% decrease in mean fetal weight
ICP-MS	inductively coupled plasma mass spectrometry
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NF	nanofiltration
NOAEL	no-observed-adverse-effect level
pK_a	acid dissociation constant
RO	reverse osmosis
TDI	tolerable daily intake
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

Boron (Chemical Abstracts Service Registry 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).

1.2 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 an acid dissociation constant (pK_a) of 9.15. Therefore, boric acid and the sodium borates exist predominantly as undissociated boric acid [$B(OH)_3$] in dilute aqueous solution below pH 7; above pH 10, the metaborate anion [$B(OH)_4^-$] becomes the main species in solution. From about pH 6 to pH 11 and at high concentrations (>0.025 mol/l), 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.

1.3 Major uses and sources in drinking-water

Boric acid and borates are used in glass manufacture (fibreglass, borosilicate glass, enamel, frit and glaze), soaps and detergents (to a decreasing extent), 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.

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, De Oude & Raymond, 1989). The borate content of surface water can be increased as a result of wastewater discharges, because borate compounds are ingredients of domestic washing agents (ISO, 1990). However, this use has decreased significantly, and levels of boron in wastewater discharges continue to fall. Naturally occurring boron is present in groundwater primarily as a result of leaching from rocks and soils containing borates and borosilicates.

1.4 Environmental fate

In natural waters, boron exists primarily as undissociated boric acid with some borate ions. 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 to soils and sediments 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, Gast & Bar-Yosef, 1981).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 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 as a vapour in the atmosphere to any significant degree. 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.

2.2 Water

The majority of Earth's boron occurs in the oceans, with an average concentration of 4.5 mg/l (Weast, Astle & Beyer, 1985).

Concentrations of boron in groundwater throughout the world range widely, from <0.3 to >100 mg/l. High concentrations of boron can be found in many parts of the world, particularly in highly mineralized, naturally carbonated groundwaters. Mean boron concentrations in Italy and Spain ranged from 0.5 to 1.5 mg/l, and values ranged up to approximately 0.6 mg/l in the Netherlands and the United Kingdom. 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/l, respectively (WHO, 1998). Concentrations in a region of Turkey with borax mining ranged from 2.0 to 29.0 mg/l (Cöl & Cöl, 2003). In eastern Europe, high concentrations of boron are found in some highly mineralized natural mineral waters; concentrations range up to 20 mg/l in Romania, up to 10 mg/l in Georgia, up to 9.48 mg/l in Slovakia and up to 5.5 mg/l in Slovenia (European Federation of Bottled Waters, personal communication, 2008).

Concentrations of boron in surface waters, except in areas of particularly high natural boron, are almost entirely less than about 0.5 mg/l (Coughlin, 1998; Neal et al., 1998; Wyness, Parkman & Neal, 2003). Boron concentrations in fresh surface water range from <0.001 to 2 mg/l in Europe, with mean values typically below 0.6 mg/l. For example, monthly mean values of boron in the Ruhr River, Germany, ranged from 0.31 to 0.37 mg/l in a survey conducted during 1992–1995 (Haberer, 1996). Similar concentration ranges, from 0.01 to 7 mg/l, have been reported for water bodies within Pakistan, the Russian Federation and Turkey, with most values below 0.5 mg/l.

Concentrations ranged up to 0.01 mg/l in Japan and up to 0.3 mg/l 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/l in areas rich in boron-containing soils. In other areas, the Rio Arenales contained boron at concentrations below 0.3 mg/l. Concentrations of boron in surface waters of North America (Canada, USA) ranged from 0.02 mg/l to as much as 360 mg/l, indicative of boron-rich deposits. However, typical boron concentrations were less than 0.1 mg/l, with a 90th-percentile boron concentration of approximately 0.4 mg/l.

Concentrations of boron found in drinking-water from Chile, Germany, the United Kingdom and the USA ranged from 0.01 to 15.0 mg/l, with most values below 0.5 mg/l. These values are consistent with ranges and means observed for groundwater and surface water. This consistency is supported by two factors: 1) boron concentrations in water are largely dependent on the leaching of boron from the surrounding geology and, to a decreasing extent, wastewater discharges; and 2) boron is not removed by conventional wastewater and drinking-water treatment methods (WHO, 1998).

2.3 Food

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 (United Kingdom Expert Group on Vitamins and Minerals, 2002). Estimations of daily intakes of boron by various age and sex groups have been made based on analyses of foods and food products (WHO, 1998). 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 foods included in the United States Food and Drug Administration's total diet studies, Iyengar et al. (1988) determined the mean adult male daily intake of boron to be 1.52 mg/day, whereas Anderson, Cunningham & Lindstrom (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. This was re-examined under the United Kingdom total diet study in 1994, which showed an average population intake of 1.5 mg/day and an upper 97.5th-percentile intake of 2.6 mg/day (United Kingdom Expert Group on Vitamins and Minerals, 2002). This is similar to the assessment by the United States Institute of Medicine (2001), which determined that the mean intake of boron in women of childbearing age and pregnant women was 1.0 mg/day (median 1.05 mg/day; 1.27 mg/day for lactating women). 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 mg and 1.11 mg, respectively (Anderson, Cunningham & Lindstrom, 1994).

2.4 Estimated total exposure and relative contribution of drinking-water

The mean daily intake of boron in the diet was judged to be near 1.2 mg by Anderson, Cunningham & Lindstrom (1994). Based on usage data, consumer products have been estimated to contribute a geometric mean daily intake of 0.1 mg to total boron exposure (WHO, 1998). The contribution of boron intake from air is negligible. Concentrations of boron in breast milk were reported to be about 4 µg/l (Hunt, Butte & Johnson, 2005). The contribution of drinking-water to total daily intake would normally be similar to that of the diet, except at high boron concentrations (>1 mg/l), when drinking-water would be the major contributor to total daily intake. Although some highly mineralized naturally carbonated groundwaters used for bottled water can contain high concentrations of boron, consumption is relatively low.

3. 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 in exposed individuals or laboratory animals. Absorption is poor through intact skin but is much greater through damaged skin (WHO, 1998).

Clearance of boron compounds is similar in humans and experimental 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 (WHO, 1994, 1997). 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 h or less. The kinetics of elimination of boron have been evaluated in human volunteers given boric acid via the intravenous and oral routes (Jansen, Andersen & Schou, 1984; Schou, Jansen & Aggerbeck, 1984).

Pahl et al. (2001) studied the clearance of boron in pregnant and non-pregnant women and concluded that clearance was slightly higher in pregnant subjects than in non-pregnant subjects. They also concluded that tubular reabsorption of boron occurred in both.

Dourson et al. (1998) re-evaluated the toxicokinetics of boron for data-derived uncertainty factors and concluded that a data-derived adjustment factor of 6 was appropriate for intrahuman variability, rather than the default factor of 10, but that additional studies were needed on rats to be able to modify the interspecies uncertainty factor with confidence. This factor was also used by the European Food Safety Authority's Scientific Panel on Dietetic Products, Nutrition and Allergies (EFSA, 2004). The International Programme on Chemical Safety expert group, however, recommended a combined uncertainty factor of 25 (WHO, 1998). USEPA (2004) also considered data-derived uncertainty factors and concluded that a combined uncertainty factor of 66 was appropriate.

4. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Acute exposure

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

4.2 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/kg body weight per day as boron. At the two highest doses, increased mortality was seen, and there was a dose-related decrease in body weight gain. Degeneration or atrophy of the seminiferous tubules was observed at a boron dose of 141 mg/kg 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 boron concentrations of 0, 500, 1000 or 2000 mg/kg feed (approximately equal to 0, 30, 60 or 125 mg/kg body weight per day as boron) for 30 or 60 days, body weights were not consistently affected by treatment. Organ weights were not affected by boron at 500 mg/kg feed; at boron concentrations of 1000 and 2000 mg/kg 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, Sherins & Dixon, 1978).

In a 90-day study in rats (10 per sex per dose) receiving boron (as boric acid or borax) at 0, 2.6, 8.8, 26, 88 or 260 mg/kg body weight per day in the diet, all animals at the highest dose died within 3–6 weeks (Weir & Fisher, 1972). In animals receiving boron at a dose of 88 mg/kg 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/kg 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/kg body weight per day as boron; five animals per sex per dose), testis weight was significantly lower than in controls in the middle- and high-dose groups (reduced by 25% and 40%, respectively). Testicular atrophy was observed in all of the dogs in the high-dose group but not in the other groups. In the borax study, testis weights were reduced compared with controls, but the reduction reached significance only in the

high-dose group. All of the dogs in the high-dose group showed testicular 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/kg body weight per day as boron. An additional group received boron at a dose of 29 mg/kg body weight per day for 38 weeks. Testicular atrophy was observed in two test dogs receiving borax at 26 weeks and in the two dogs and one dog, respectively, killed after 26 or 38 weeks of boric acid consumption. The study was terminated at 38 weeks. 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 treated dogs at termination had widespread and marked atrophy in the seminiferous tubules, but testicular lesions also occurred in the control group (Weir & Fisher, 1972). Confidence in these studies is low, and they were considered not suitable for inclusion in the risk assessment, as there are other, more recent studies of greater scientific quality with findings at similar levels of intake of boron (Ku et al., 1993; Price et al., 1996a).

The findings that boron can cause testicular atrophy in rodents at doses of a similar order of magnitude following short-term exposure have been confirmed by other workers (Fukuda et al., 2000; Kudo et al., 2000).

4.3 Long-term exposure

In a 2-year study in mice (50 per sex per dose) receiving boric acid at approximately 0, 275 or 550 mg/kg body weight per day (0, 48 or 96 mg/kg body weight per day as boron) in the diet, 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 appearing in the testes in male mice and with no significant non-neoplastic lesions in female mice (NTP, 1987; Dieter, 1994).

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 body weight per day in the diet. 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, 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 middle- and low-dose groups, no significant effects on general appearance, behaviour, growth, food consumption, haematology, serum chemistry or histopathology were observed (Weir & Fisher, 1972).

4.4 Reproductive and developmental toxicity

Short-term 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, Phu-Lich & Loisillier, 1964; Weir & Fisher, 1972; Green, Lott & Weeth, 1973; Lee, Sherins & Dixon, 1978; NTP, 1987;

Ku et al., 1993; Fukuda et al., 2000; Kudo et al., 2000). 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, Strader & Rehnberg, 1990), adult male Sprague-Dawley rats were administered two boron doses in 1 day, with a total boron dose of 0 or 350 mg/kg body weight in the time–response experiment (animals were sacrificed at 2, 14, 28 or 57 days post-treatment) and a total boron dose of 0, 44, 87, 175 or 350 mg/kg 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 no-observed-adverse-effect level (NOAEL) for boron for male reproductive effects in the dose–response study was 87 mg/kg body weight per day.

In a multigeneration study, boron (as borax or boric acid) at concentrations of 0, 117, 350 or 1170 mg/kg feed was 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 for boron in this study was 350 mg/kg feed, equivalent to 17.5 mg/kg body weight per day, compared with the top boron dose of 58.45 mg/kg body weight per day.

To investigate the development of testicular lesions, boric acid was fed at 61 mg/kg body weight per day as boron 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 boron at doses of 60 or 125 mg/kg body weight per day for 60 days. Mean plasma follicle-stimulating hormone levels were significantly elevated in a dose-dependent manner in all boron treatment groups (30, 60 or 125 mg/kg body weight per day) in this study after 60-day exposures (Lee, Sherins & Dixon, 1978).

Reversibility of testicular lesions was evaluated by Ku et al. (1993) in an experiment in which F344 rats were dosed with boric acid at 0, 3000, 4500, 6000 or 9000 mg/kg feed (equivalent to 0, 26, 39, 52 or 78 mg/kg body weight per day as boron) for 9 weeks and assessed for recovery up to 32 weeks post-treatment. Inhibited spermiation was exhibited at a boric acid concentration of 3000/4500 mg/kg feed (5.6 µg of boron per milligram tissue), whereas inhibited spermiation progressed to atrophy at a boric acid concentration of 6000/9000 mg/kg feed (11.9 µg of boron per milligram 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 a boric acid concentration of 4500 mg/kg feed was reversed by 16 weeks post-treatment, but focal atrophy, which did not recover up to 32 weeks post-treatment, was detected.

Yoshizaki et al. (1999) showed that male rats treated with boric acid doses of 150 mg/kg body weight per day for 3 weeks tended to have a lower fertility index, whereas those treated with 500 mg/kg body weight per day were sterile.

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 boric acid at boron doses of 0, 14, 29 or 58 mg/kg body weight per day on gestation days 0–20 (Heindel et al., 1992). An additional group of rats received boric acid at 94 mg/kg body weight per day as boron 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 boron doses of ≥29 mg/kg body weight per day. Malformations consisted primarily of anomalies of the eyes, the central nervous system, 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 lowest-observed-adverse-effect level (LOAEL) for boron of 14 mg/kg 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 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 Sprague-Dawley 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/kg body weight per day as boron. 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/kg body weight per day boron 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 for boron in this study was 9.6 mg/kg body weight per day, based on a decrease in fetal body weight at the next higher dose.

Developmental toxicity and teratogenicity of boric acid were investigated in mice exposed to boron during gestation days 0–17 at 0, 43, 79 or 175 mg/kg body weight per day in the diet (Heindel et al., 1992). There was a significant dose-related decrease in average fetal body weight per litter at boron doses of 79 and 175 mg/kg body weight per day. In offspring of mice exposed to boron at 79 or 175 mg/kg 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 boron for developmental effects (decreased fetal body weight per litter) was 79 mg/kg body weight per day, and the NOAEL for boron was 43 mg/kg body weight per day.

Developmental toxicity and teratogenicity of boric acid in rabbits were investigated by Price et al. (1996b) at boron doses of 0, 11, 22 or 44 mg/kg body weight per day

given by gavage on days 6–19 of gestation. Frank developmental effects in rabbits exposed to boron at 44 mg/kg 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 sternebrae. The NOAEL for maternal (reduced body weight gain, reduced gravid uterine weight and number of corpora lutea) and developmental effects was 22 mg/kg body weight per day as boron.

4.5 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, Birge & Dorough, 1984). Borax was not mutagenic in cell transformation assays with Chinese hamster cells, mouse embryo cells or human fibroblasts (Landolph, 1985).

4.6 Carcinogenicity

Tumour incidence was not enhanced in studies in which B6C3F1 mice received diets containing boric acid at 0, 2500 or 5000 mg/kg feed for 103 weeks (NTP, 1987) and Sprague-Dawley rats received diets containing boron (as borax or boric acid) at 0, 117, 350 or 1170 mg/kg feed for 2 years (Weir & Fisher, 1972).

5. 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 body weight (oral), 8600 mg/kg body weight (dermal) and 29 mg/kg 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 boron of 18–56 mg/kg body weight (O'Sullivan & Taylor, 1983).[1] 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 4 cases of boric acid poisoning and reviewed an additional 109 cases in the literature. The 4 cases were infants exposed to

[1] 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).

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 below 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 central nervous system effects (67%). Cutaneous lesions were prevalent in 76% of the cases and in 88% of cases involving children less than 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 central nervous system 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 less than 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 (primarily central nervous system and cutaneous) symptoms 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 less than 6 years of age, 15 of whom were less than 2 years of age, ingested the reported potentially lethal dose of 3 g; eight adults ingested the reported potentially lethal dose of 15 g without clinical evidence of lethal effects.

Sayli (1998, 2001) compared reproductive success in highly exposed populations (0.7–29 mg/l as boron) in Turkey—which has some of the highest deposits of boron and hence high boron concentrations in drinking-water—with that in populations in low boron exposure areas (0.05–0.45 mg/l as boron) and found no significant differences.

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 in 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/8.4 MJ) for 63 days and then fed the same diet supplemented with 3 mg of boron per day for 49 days (Nielsen, 1989, 1994; Nielsen, Mullen & Gallagher, 1990; Nielsen, Mullen & Nielsen, 1991; Nielsen et al., 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.

The United Kingdom Expert Group on Vitamins and Minerals (2002) concluded that:

> 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.

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

A spectrometric method using azomethine-H is available for the determination of borate in water at concentrations between 0.01 and 1 mg/l. 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 for boron in water range from 6 to 10 µg/l.

Inductively coupled plasma mass spectrometry (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/l (WHO, 1998). 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).

6.2 Treatment and control methods and technical achievability

Conventional water treatment (coagulation, sedimentation and filtration) does not remove boron to any appreciable extent, and special methods have to be employed to remove boron from water with excessively high boron concentrations. Ion exchange and reverse osmosis may enable substantial reduction, but are likely to be very expensive.

Pilot-scale trials of iron and aluminium coagulation in the pH range 5–8 showed that coagulation was ineffective at removing boron from a 3 mg/l solution. However, use of sodium aluminate and lime gave 90% removal from a 1.7 mg/l solution. Lime softening gave removals of 25% and 15% from concentrations of 10 mg/l and 1.8 mg/l, respectively (Nicolai et al., 1996). Enhanced removal can be obtained using electrocoagulation (e.g., Yilmaz et al., 2005), but this process is rarely, if ever, used for drinking-water treatment.

Alternative techniques include adsorption using clays or metallic oxides. Treatment with magnesium oxide achieved 90% removal. A 50% removal from an initial 0.5–1.2 mg/l solution was achieved by dosing magnesium chloride and lime to precipitate magnesium hydroxide (Nicolai et al., 1996). Adsorption capacities of 14.0 and 3.6 mg/g adsorbent were obtained using synthetic hydrotalcites containing aluminium and iron, respectively (Ferreira et al., 2006).

Activated carbon has a capacity of about 1 g/g. About 60% removal can be obtained from an influent concentration of 5 mg/l at pH 8–9. However, the capacity of granular activated carbon is greatly reduced in the presence of other ions, and the retention of boron falls off rapidly, making granular activated carbon treatment impractical (Nicolai et al., 1996).

Borate removal by conventional anion exchange resins is poor (Meyers, 1998). A boron-specific macroporous ion exchange resin had a capacity of ~2 mg/ml and produced a treated water concentration of <1 µg/l from a 50 mg/l influent concentration in the pH range 5.5–8. Regeneration required the sequential use of acid, base and rinsing water (Nicolai et al., 1996). In laboratory column tests, the following loadings were obtained (Simonnot et al., 2000):

Influent boron concentration (mg/l)	Loading (g/l)
1	1.66
3	1.87
5	1.85
10	1.94
20	1.83

Provided the water to be treated is sufficiently mineralized, the resin removes only boron; in poorly mineralized waters, however, some removal of other anions occurs (Simonnot et al., 2000). The regenerant requirements are rather high. For example, a 10 m^3 bed of resin could treat about 3800 m^3 of water containing boron at 5 mg/l, but regeneration would require 40 m^3 of hydrochloric acid (0.25 mol/l) and 40 m^3 of sodium hydroxide (0.25 mol/l). A boron-specific resin gave effectively complete removal from an influent concentration of up to 60 µg/l (Wilcox et al., 2000). The feed rate was 0.68 m/s, and boron broke through after treatment of about 30 000 bed volumes. The capacity was ~3500 g/m^3 of resin.

Laboratory batch and column tests were used to compare cellulose, magnesium oxide and a boron-specific ion exchange resin for boron removal from solutions containing up to 600 mg/l. Cellulose was ineffective (capacity ~0.5 mg/g cellulose); magnesium oxide was effective but required 20 mol of magnesium oxide per mole of boron for 85% removal. The ion exchange resin had a capacity of 2.25 mg/ml resin, but it was

considered that the required two-stage regeneration made this process uneconomical (Okay et al., 1985). Activated alumina (8 g/l) removed only 40% of boron from an initial concentration of 5 mg/l at pH 8 (Bouguerra et al., 2008).

Conventional reverse osmosis can achieve 25–50% removal. Nanofiltration with a commercial membrane was ineffective (Nicolai et al., 1996). Boron rejection by reverse osmosis membranes is relatively poor because near neutral pH, the uncharged species boric acid [$B(OH)_3$] predominates, and this can pass through the membrane. At pH values above 9.24 (the pK_a of boric acid), borate ion [$B(OH)_4^-$] is formed, which is more readily removed.

Pilot plant studies using a reverse osmosis membrane showed that by increasing the pH to 9.5, practically 100% removal could be obtained from groundwater containing boron at 4 mg/l; at lower pH values, only about 40% removal was achieved (Rodríguez Pastor et al., 2001). A removal of 69% from a concentration of 5 mg/l at pH 9 was achieved using a commercial reverse osmosis system (Öztürk, Kavak & Köse, 2008). A boron concentration of 2.3 mg/l in groundwater was 50%, 75% and 95% removed at pH values of 6.5, 9 and 11 using another commercial reverse osmosis system (Georghiou & Pashalidis, 2007).

Removal of boron using electrodialysis is also pH dependent. With a 100 mg/l solution treated in an electrodialysis cell containing cation exchange and anion exchange membranes, 20% removal was obtained at pH 9, rising to 80% at pH 10.5. However, with a lower boron concentration of 25 mg/l, only 40% removal was obtained at pH 10.5 (Kabay et al., 2008). In water of low dissolved solids concentration containing boron at 3 mg/l, removals of 60–80% were obtained at near-neutral pH, depending on the arrangement of the spacers between the cationic and anionic membranes (Oren et al., 2006).

Removal of boron during the desalination of seawater presents a particular challenge. Boron removal in seawater reverse osmosis desalination systems is usually achieved by a second desalination pass operating at or above pH 10 (Glueckstern & Priel, 2007). Depending on the composition of the feed water, operation at such high pH can require the use of anti-scalants to prevent fouling of the membrane with calcium and magnesium salts (Redondo, Busch & De Witte, 2003). In a study of several reverse osmosis plants treating water for public water supplies, boron removal ranged from 43% to 78% (Magara et al., 1996). Effective boron removal can be achieved using multistage reverse osmosis using ultra-low pressure reverse osmosis membranes (Magara et al., 1998). Two commercial high-rejection seawater reverse osmosis membranes gave removals of 88–89% from a boron concentration of 5.1 mg/l in seawater at pH 8.2; increasing the pH to 10.5 increased removal to >98% (Koseoglu et al., 2008). A reverse osmosis membrane developed specially for boron removal was able to achieve 94–96% removal from seawater containing boron at 5 mg/l (Taniguchi et al., 2004). In a full-scale reverse osmosis plant, boron removals from seawater of 78–92% were obtained as pH was increased from 7.5 to 8.5 (initial boron concentration not stated) (Faigon & Hefer, 2008). The following removals were obtained from seawater containing boron at 4 mg/l treated with a range of nanofiltration (NF) and reverse osmosis (RO) membranes: loose NF 1%, tight NF 6%, brackish RO 22%, seawater RO 96% (Sarp et al., 2008). A full-scale two-pass reverse osmosis system, operating without pH increase for the second pass but using

membranes with high boron rejection, consistently achieved a boron concentration less than 1 mg/l in the final water (Bartels et al., 2008).

No information was found on boron removal using point of entry or point of use devices.

7. GUIDELINE VALUE

The critical effect is considered to be decreased fetal body weight in rats, for which the NOAEL was 9.6 mg/kg body weight per day. Allen et al. (1996) developed a benchmark dose based on the studies of Heindel et al. (1992), Price, Marr & Myers (1994) and Price et al. (1996a). The benchmark dose was defined as the 95% lower bound on the dose corresponding to a 5% decrease in the mean fetal weight ($BMDL_{05}$) and was used by the United States Environmental Protection Agency in its re-evaluation (USEPA, 2004). The $BMDL_{05}$ of 10.3 mg/kg body weight per day as boron is close to the Price et al. (1996a) NOAEL of 9.6 mg/kg body weight per day. The uncertainty factor was derived following the methodology of Doursen et al. (1998).

Intraspecies variation (toxicokinetics) for boron relates primarily to variations in clearance. As the critical effect that serves as the basis for the tolerable daily intake (TDI) is developmental toxicity, pregnant women are the subgroup of interest in this regard. Based on pooled individual data from available studies, the mean glomerular filtration rate in 36 healthy women was 145 ± 23 ml/min in early pregnancy and 144 ± 32 ml/min in late pregnancy. The standard deviation represented 22% of the mean value in late pregnancy. Based on division of the mean glomerular filtration rate (144 ml/min) by the glomerular filtration rate at two standard deviations below the mean (80 ml/min) to address variability for approximately 95% of the population, the toxicokinetic component of interspecies variation is 1.8 (compared with the default value for this component of 3.2). As there are insufficient 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 $1.8 \times 3.2 = 5.76$ (rounded to 6). Data are inadequate to determine a different uncertainty factor for interspecies variation; therefore, the default value of 10 is used (Doursen et al., 1998), giving a total uncertainty factor of 60.

Applying an uncertainty factor of 60 to the $BMDL_{05}$ of 10.3 mg/kg body weight gives a TDI of 0.17 mg/kg body weight, rounded to 0.2 mg/kg body weight. Extensive data from the United Kingdom and the USA on dietary intakes of the group of primary concern indicate that intake from sources other than water is low compared with the TDI, and so the allocation to drinking-water can be significantly increased without approaching the TDI. A source allocation of 40% gives rise to a guideline value of 2.4 mg/l, assuming a body weight of 60 kg and 2 litre/day drinking-water consumption.

Conventional water treatment (coagulation, sedimentation and 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).

It should be noted that because it will be difficult to achieve the guideline value of 2.4 mg/l in some desalinated supplies and in areas with high natural boron levels, local regulatory and health authorities should consider a value in excess of 2.4 mg/l by making a rough assessment of exposure from other sources. In general, exposure from food and sources other than drinking-water is considerably less than the TDI, and a higher allocation can be made to drinking-water when meeting the guideline value would compromise the use of a supply and exposure from other sources is low. The allocation of 40% made in developing the guideline value is likely to be conservative in many regions, and the need for microbiologically safe water is a primary requirement. Although high levels of boron that are present naturally can be removed from saline water, there is a significant cost in terms of both the membranes and the energy required for operating the plants.

8. REFERENCES

Allen BC et al. (1996) Benchmark dose analysis of developmental toxicity in rats exposed to boric acid. *Fundamental and Applied Toxicology*, 32:194–204.

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.

Bartels C et al. (2008) Long term experience with membrane performance at the Larnaca desalination plant. *Desalination*, 221(1/3):92–100.

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.

Bouguerra W et al. (2008) Boron removal onto activated alumina and by reverse osmosis. *Desalination*, 223(1/3):31–37.

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.

Cöl M, Cöl C (2003) Environmental boron contamination in waters of Hisarcik area in the Kutahya province of Turkey. *Food and Chemical Toxicology*, 41(10):1417–1420.

Cotton PA, Wilkinson L (1988) *Advanced inorganic chemistry*, 5th ed. New York, NY, John Wiley & Sons, pp. 162–165.

Coughlin JR (1998) Sources of human exposure: overview of water supplies as sources of boron. *Biological Trace Element Research*, 66(1–3):87–100.

Dieter MP (1994) Toxicity and carcinogenicity studies of boric acid in male and female B6C3F1 mice. *Environmental Health Perspectives*, 102(Suppl. 7):93–97.

Dourson M et al. (1998) Boron tolerable intake: re-evaluation of toxicokinetics for data-derived uncertainty factors. *Biological Trace Element Research*, 66(1–3):453–463.

EFSA (2004) Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the tolerable upper intake level of boron (sodium borate and boric

acid) (Request N° EFSA-Q-2003-018) (adopted on 8 July 2004). *The EFSA [European Food Safety Authority] Journal*, 80:1–22.

Faigon M, Hefer D (2008) Boron rejection in SWRO at high pH conditions versus cascade design. *Desalination*, 223(1/3):10–16.

Ferreira OP et al. (2006) Evaluation of boron removal from water by hydrotalcite-type compounds. *Chemosphere*, 62(1):80–88.

Fukuda R et al. (2000) Collaborative work to evaluate toxicity on male reproductive organs by repeated dose studies in rats. Testicular toxicity of boric acid after 2- and 4-week administration periods. *Journal of Toxicological Science*, 25:233–239.

Georghiou G, Pashalidis I (2007) Boron in groundwaters of Nicosia (Cyprus) and its treatment by reverse osmosis. *Desalination*, 215(1/3):104–110.

Glueckstern P, Priel M (2007) Boron removal in brackish water desalination systems. *Desalination*, 205(1/3):178–184.

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.

Green GH, Lott MD, Weeth HJ (1973) Effects of boron-water on rats. *Proceedings, Western Section, American Society of Animal Science*, 24:254–258.

Haberer K (1996) [Boron in drinking water in Germany.] *Wasser-Abwasser*, 137:364–371 (in German).

Heindel JJ et al. (1992) Developmental toxicity of boric acid in mice and rats. *Fundamental and Applied Toxicology*, 18:266–277.

Huber L (1982) ICP-AES, ein neues verfahren zur multielement - bestimmung in wassern, abwassern und schlammen. *Wasser*, 58:173–185.

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.

Hunt CD, Butte NF, Johnson LK (2005) Boron concentrations in milk from mothers of exclusively breast-fed healthy full-term infants are stable during the first four months of lactation. *Journal of Nutrition*, 135(10):2383–2386.

ISO (1990) *Water quality—Determination of borate—Spectrometric method using azomethine-H*. Geneva, International Organization for Standardization (ISO 9390:1990).

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

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, 15–18 April 1988, Neuherberg*. Berlin, Walter de Gruyter, pp. 267–269.

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

Kabay N et al. (2008) Removal of boron by electrodialysis: effect of feed characteristics and interfering ions. *Desalination*, 223(1/3):63–72.

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

Keren R, Gast RG, Bar-Yosef B (1981) pH-dependent boron adsorption by Namontmorillonite. *Soil Science Society of America Journal*, 45:45–48.

Koseoglu H et al. (2008) The removal of boron from model solutions and seawater using reverse osmosis membranes. *Desalination*, 223(1/3):126–133.

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.

Kudo S et al. (2000) Collaborative work to evaluate toxicity on male reproductive organs by repeated dose studies in rats. A comparative 2- and 4-week repeated oral dose testicular toxicity study of boric acid in rats. *Journal of Toxicological Science*, 25:223–232.

Landolph JR (1985) Cytotoxicity and negligible genotoxicity of borax and borax ores to cultured mammalian cells. *American Journal of Industrial Medicine*, 7:31–43.

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

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.

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.

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.

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

Magara Y et al. (1996) The behaviour of inorganic constituents and disinfection by-products in reverse osmosis water desalination process. *Water Science and Technology*, 34(9):141–148.

Magara Y et al. (1998) Development of boron reduction system for seawater desalination. *Desalination*, 118(1/3):25–34.

Meyers P (1998) Removal of more (or less) unconventional impurities from water. *Ultrapure Water*, 15(6):31–37.

Neal C et al. (1998) Boron in the major UK rivers entering the North Sea. *Science of the Total Environment*, 210–211:41–52.

Nicolai M et al. (1996) [State of knowledge about the main ways of removing boron from water.] *Techniques, Sciences et Méthodes*, 10:686–689 (in French).

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.

Nielsen FH (1994) Biochemical and physiological consequences of boron deprivation in humans. *Environmental Health Perspectives*, 102(Suppl. 7):59–63.

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.

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.

Nielsen FH et al. (1987) Effect of dietary boron on mineral, oestrogen, and testosterone metabolism in postmenopausal women. *The FASEB [Federation of American Societies for Experimental Biology] Journal*, 1:394–397.

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.

NTP (1987) *Toxicology and carcinogenesis studies of boric acid (CAS no. 10043-35-3) in B6C3F1 mice (food studies).* Research Triangle Park, NC, United States Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program (NTP Technical Report Series No. 324).

NTP (1990) *Final report on the developmental toxicity of boric acid (CAS no. 10043-35-3) in Sprague-Dawley rats.* Research Triangle Park, NC, United States Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program (NTP Report No. 90-105).

Okay O et al. (1985) Boron pollution in the Simav River, Turkey and various methods of boron removal. *Water Research*, 19(7):857–862.

Oren Y et al. (2006) Boron removal from desalinated seawater and brackish water by improved electrodialysis. *Desalination*, 199(1/3):52–54.

O'Sullivan K, Taylor M (1983) Chronic boric acid poisoning in infants. *Archives of Diseases in Childhood*, 58:737–739.

Öztürk N, Kavak D, Köse TE (2008) Boron removal from aqueous solution by reverse osmosis. *Desalination*, 223(1/3):1–9.

Pahl MV et al. (2001) The effect of pregnancy on renal clearance of boron in humans: a study based on normal dietary intake of boron. *Toxicological Sciences*, 60(2):252–256.

Penland JG (1994) Dietary boron, brain function and cognitive performance. *Environmental Health Perspectives*, 102(Suppl. 7):65–72.

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.

Price CJ, Marr MC, Myers CB (1994) *Determination of the no-observable adverse-effect-level (NOAEL) for developmental toxicity in Sprague-Dawley (CD) rats exposed to boric acid in feed on gestational days 0 to 20 and evaluation of postnatal recovery through postnatal day 21.* Research Triangle Park, NC, Research Triangle Institute (RTI Identification No. 65C-5657-20O).

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.

Price CJ et al. (1996b) The developmental toxicity of boric acid in rabbits. *Fundamental and Applied Toxicology*, 34:176–187.

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).

Redondo J, Busch M, De Witte JP (2003) Boron removal from seawater using FILMTEC™ high rejection SWRO membranes. *Desalination*, 156(1/3):229–238.

Rodríguez Pastor M et al. (2001) Influence of pH in the elimination of boron by means of reverse osmosis. *Desalination*, 140(2):145–152.

Sarp S et al. (2008) Boron removal from seawater using NF and RO membranes, and effects of boron on HEK 293 human embryonic kidney cell with respect to toxicities. *Desalination*, 223(1/3):23–30.

Sayli BS (1998) An assessment of fertility in boron-exposed Turkish subpopulations 2. Evidence that boron has no effect on human populations. *Biological Trace Element Research*, 66(1–3):409–422.

Sayli BS (2001) Assessment of fertility and infertility in boron-exposed Turkish subpopulations. 3. Evaluation of fertility among sibs and in "borate families". *Biological Trace Element Research*, 81(3):255–267.

Schou JS, Jansen JA, Aggerbeck B (1984) Human pharmacokinetics and safety of boric acid. *Archives of Toxicology, Supplement*, 7:232–235.

Simonnot M-O et al. (2000) Boron removal from drinking water with a boron selective resin: is the treatment really selective? *Water Research*, 34(1):109–116.

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.

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

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.

Taniguchi M et al. (2004) Boron removal in RO seawater desalination. *Desalination*, 167:419–426.

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

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).

United Kingdom Expert Group on Vitamins and Minerals (2002) *Revised review of boron*. London, Food Standards Agency (EVM/99/23/P.RevisedAug2002; http://www.food.gov.uk/multimedia/pdfs/boron.pdf).

United States Institute of Medicine (2001) *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc*. Washington, DC, National Academy Press.

USEPA (2004) *Toxicological review of boron and compounds (CAS No. 7440-42-8) in support of summary information on the Integrated Risk Information System.* Washington, DC, United States Environmental Protection Agency, June (EPA 635/04/052; http://www.epa.gov/iris).

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

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

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.

Weir RJ, Fisher RS (1972) Toxicologic studies on borax and boric acid. *Toxicology and Applied Pharmacology*, 23:351–364.

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; http://www.inchem.org/documents/ehc/ehc/ehc170.htm).

WHO (1997) *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 Division of Operational Support in Environmental Health, WHO, Geneva.

WHO (1998) *Boron*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 204; http://www.inchem.org/documents/ehc/ehc/ehc204.htm).

Wilcox D et al. (2000) Boron removal from high-purity water by selective ion exchange. *Ultrapure Water*, 17(6):40–51.

WRc (1997) *Treatment technology for aluminium, boron and uranium*. Document prepared for WHO by the Water Research Centre, Medmenham, and reviewed by S. Clark, United States Environmental Protection Agency; A. van Dijk-Looijaard, Kiwa, Netherlands; and D. Green, Health Canada.

Wyness AJ, Parkman RH, Neal C (2003) A summary of boron surface water quality data throughout the European Union. *Science of the Total Environment*, 314–316:255–269.

Yilmaz AE et al. (2005) The investigation of parameters affecting boron removal by electrocoagulation method. *Journal of Hazardous Materials*, 125(1/3):160–165.

Yoshizaki H et al. (1999) Availability of sperm examination for male reproductive toxicities in rats treated with boric acid. *Journal of Toxicological Science*, 24(3):199–208.