Chemical Disposition of Boron in Animals and Humans

Robert F. Moseman

Radian Corporation, Research Triangle Park, North Carolina

Elemental boron was isolated in 1808. It typically occurs in nature as borates hydrated with varying amounts of water. Important compounds are boric acid and borax. Boron compounds are also used in the production of metals, enamels, and glasses. In trace amounts, boron is essential for the growth of many plants, and is found in animal and human tissues at low concentrations. Poisoning in humans has been reported as the result of accidental ingestion or use of large amounts in the treatment of burns. Boron as boric acid is fairly rapidly absorbed and excreted from the body via urine. The half-life of boric acid in humans is on the order of 1 day. Boron does not appear to accumulate in soft tissues of animals, but does accumulate in bone. Normal levels of boron in soft tissues, urine, and blood generally range from less than 0.05 ppm to no more than 10 ppm. In poisoning incidents, the amount of boric acid in brain and liver tissue has been reported to be as high as 2000 ppm. Recent studies at the National Institute of Environmental Health Sciences have indicated that boron may contribute to reduced fertility in male rodents fed 9000 ppm of boric acid in feed. Within a few days, boron levels in blood and most soft tissues quickly reached a plateau of about 15 ppm. Boron in bone did not appear to plateau, reaching 47 ppm after 7 days on the diet. Cessation of exposure to dietary boron resulted in a rapid drop in bone boron. The analytical methodology developed and validated for these tissues consisted of microwave digestion of samples in concentrated nitric acid, followed by inductively coupled argon plasma emission spectroscopy analyses. The recovery of added boron from tissue samples was quantitative. The precision and accuracy were typically better than 6% and 12%, respectively. The method detection limit is typically 0.02 to 0.04 ppm of boron, depending on the sample matrix. — Environ Health Perspect 102 (Suppl 7):113–117 (1994)

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Introduction

Compounds of boron have been used for a variety of applications for thousands of years. The ancient Greeks and Romans used borates as a cleaning agent. The first recorded internal use of boron compounds as a medication was by Arabian physicians in 875 AD (*1*). Boric acid was made from borax in 1702, and the chemical nature of borax was described in 1732 (*2*). Elemental boron was isolated and identified independently by Gay-Lussac and Sir Humphry Davey in 1808 by heating boron oxide with potassium metal. The pure crystalline material is black and lustrous. Pure boron is very hard and brittle and is a semiconductor. The elemental abundance in the earth's crust is about 0.001% or 10 ppm, occurring as borax, kernite, tincalconite, colemanite, tourmaline, and sassolite. China and Persia were the European suppliers of Tincal and Tankar prior to 1776. Later, a purer supply of Tuscany acid was imported from Italy and was the main source of borax until the mid-19th century, when borax was discovered in southern California.

Elemental boron is used to increase the hardenability of steel. It is used in nonferrous metals as a deoxidizer and a degasifier to refine the grain of poured metal. Small amounts of boron are added to silicon and germanium to enhance the control of conductance in semiconductors. For a number of years, boron was used as a food preservative in Europe and Asia. Borax and boric acid are used in making special glass and ceramics, disinfectants, washing powders, fireproofing for wood and fabrics, and in the manufacture of abrasives and rocket fuels.

Plants were first found to contain boron in 1857 by Wittstein and Apoiger (*3*). Since then it has been well recognized that boron, at about 0.5 ppm, is an essential element for normal plant growth. No other trace element can take the place of boron as a required plant nutrient. Large quantities of boron, however, can be toxic to plants. In fact, boron compounds have been developed and marketed as herbicides and fungicides.

Plants tend to take up boron from soil in proportion to the amount of boron in soil. The boron content of some common foods is presented in Table 1 (*4–7*). Very recent data (*8*) on the boron content in a variety of National Institute of Standards and Technology (NIST) biologic reference materials (including many foods) showed that the U.S. Total Diet Samples contained 2.61 ppm of boron. A mixed diet (RM8431) contained 3.65 ppm and a human diet (IAEA-H9) contained 3.44 ppm of boron. Iyengar et al. (*9*) found a range of 2.41 to 4.58 ppm of boron in six different mixed human diets. They also reported 0.65 and 0.58 ppm of boron in rice flour and wheat flour, respectively. Nonfat milk powder was found to contain 2.13 ppm boron.

On average, humans consume several milligrams of boron each day in the foods they eat. Thus, it is not surprising that

Table 1. Boron content of some foods.

Food	Boron, ppm
Apple (*4*)	110
Quince	160
Pear	70
Grapes (*4*)	40
Human milk (*5*)	0.80
Cows milk	0.20
Egg yoke	0.0008
Egg white (*5*)	0.14
Barley (*6*)	2.3 (dry wt)
Sugar beet	76 (dry wt)
Dandelion	80 (dry wt)
White flour (*7*)	0.45
Brown flour	1.6

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Address correspondence to Dr. Robert F. Moseman, Webb Technical Group, Inc., 4325 Pleasant Valley Road, Raleigh, NC 27612. Telephone (919)787-9171. Fax (919)571-8637.

Table 2. Boron levels in human tissues of one individual.

Tissue	Boron, ppm
Skin	0.12
Bone	0.90
Muscle	0.07
Nervous system	0.11
Liver	0.11
Heart	0.04
Lung	0.07
Kidney	0.25
Intestine	0.08
Fat	0.07
Blood	0.14
Feces	0.18

boron can be found in the tissues and body fluids of humans as a normal dietary consequence. Alexander, et al. (*10*) analyzed 116 human bone samples and found an average of 61 ppm of boron, based on the ashed weight. The boron levels in these samples ranged from 16 to 138 ppm for individuals aged 5 months to 75 years. The age of the individual did not appear to have a bearing on the boron content of the bone.

Forbes et al. (*11*) determined boron levels in several tissues of one individual, as shown in Table 2. Most soft tissues appear to contain about the same amount of boron as blood. Bone tends to have a higher level of boron, while fat, muscle, heart, lung, and intestine show lower amounts of the element.

Fisher and Freimuth (*12*) analyzed blood samples from 34 normal human infants for boron. They found an average of 0.25 ppm boron. The levels of boron ranged from nondetectable to 1.25 ppm.

Imbus and co-workers (*13*) determined boron in blood and urine of 148 normal adult males. The average level in blood was 0.11 ppm and ranged from 0.04 to 0.36 ppm. In urine, the average boron content was 0.92 ppm; ranging from 0.04 to 6.6 ppm. More recently, Clarke et al. (*14*) analyzed whole blood in 13 normal humans and found an average boron concentration of 0.03 ppm. In a separate study, Clark et al. (*15*) found an average of 0.097 ppm of boron in the blood of seven normal human donors. Minola et al. (*16*) determined boron levels in the urine of 119 normal human subjects. They found a mean concentration of 1.89 ppm with a range of 0.47 to 7.8 ppm.

Abou-Shakra et al. (*17*) analyzed blood, urine, hair, and nails of 50 normal humans for boron content. The median and range of boron levels found in these tissues are shown in Table 3. Woittiez and Iyengar (*18*) reported that the mean level of boron

Table 3. Normal boron levels in 50 humans.

Sample type	Median boron, ppm	Range, ppm
Whole blood	0.057	0.008–0.17
Blood serum	0.022	0.008–0.048
Urine	0.75	0.16–2.9
Scalp hair	4.3	0.83–10.2
Finger nails	15.2	7.4–82.7
Toe nails	17.9	7.6–57.4

in whole blood was 0.031 ppm ± 0.006, and in serum was 0.022 ppm ± 0.005 (in normal humans). These data were based on recent literature values compiled by the authors in an effort to establish reference values.

Vigier (*19*), in 1883 noted that boric acid could be detected in the urine within 2 hr and as long as 24 hr after ingestion of a single dose of 2.5 g of boric acid. In addition, he reported traces of boron in the saliva.

In the early years of this century, Wiley (*20*) performed a series of experiments with human volunteers, to study the excretion of borax and boric acid from the body. Several young men were given 100 to 150 g of boric acid or borax by mouth. Wiley was able to account for 77 to about 83% of the administered boron compounds in the urine. In subsequent similar experiments, perspiration was found to contain about 1.5% of a 1- to 3-g dose of boric acid. About 1% of a 3-g dose could be accounted for in the feces, and 10 to 285 ppm was detected in human breast milk after administration of 1 to 13 g of boric acid.

Today it is generally accepted that boric acid is absorbed very little through healthy, intact skin. However, significant quantities of boric acid can be absorbed through burned or abraded skin. In 1928, Kahlenberg and Barwasser (*21*) reported that boric acid was rapidly absorbed through healthy skin and appeared at ppm concentrations in the urine within a few minutes of exposure. This work was widely disputed in the subsequent literature and has gained little credibility.

There have been a few incidents of fatal poisoning as a result of ingestion of large quantities of boron compounds. One such tragedy was reported by McNally and Rust (*22*) in 1928. Six infants died as a result of ingestion of 60 to 160 ml of a saturated solution of boric acid (about 3 to 6 g of boric acid) thought to be distilled water. Subsequent analyses of brain and liver tissue showed these samples to contain about 2000 ppm of boric acid (350 ppm as boron).

Kent and McCance (*7*) studied the fate and disposition of boron in two normal women. A total of 352 mg of boron (as boric acid) was given in addition to the 80 to 140 mg of boron per day in food, in the course of a metabolism study. They determined that greater than 90% of the ingested boron was eliminated from the body via urine in the first week after dosing. They also demonstrated that the lesser amounts of boron in a brown bread diet (75–96 mg/day) were quickly excreted in the urine.

Pfeiffer and co-workers (*23*) studied the accumulation and distribution of boron in dogs. Fifteen dogs were dosed with 2 g of boric acid per kilogram of body weight. At sacrifice, the average level of boric acid found in the brain, liver, and fat were 1110, 910, and 260 ppm, respectively. They reported that the gray matter of the brain contained more boric acid than the white matter. This observation was later confirmed by Bauer (*24*) who also studied

Table 4. Boron determined in blood of mice dosed intravenously with boron.

Time after dose, min	0.5 mg dose, ppm residue	2.1 mg dose, ppm residue
1	40	158
20	25	100
30	22	85
40	20	75
60	18	60
90	18	40
120	18	40

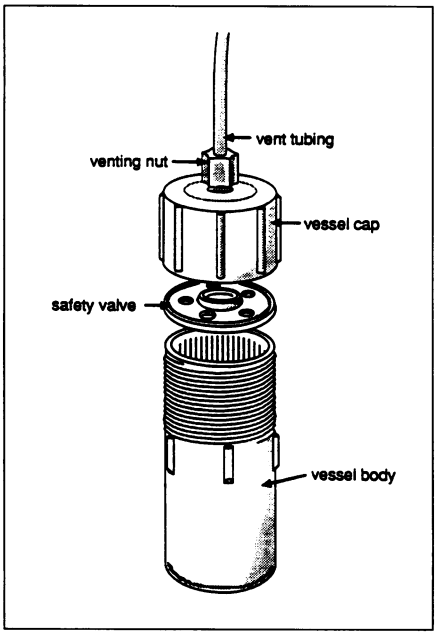

Figure 1. Digestion vessel assembly.

the disposition of boron in dogs. Additionally, Pfeiffer (*23*) found little boric acid in striated muscle. Analyses of the urine of dogs given 0.2 to 2 g of boric acid, indicated that about half was excreted in the urine 1 day after exposure.

Schou et al. (*25*) administered 750 mg to 1.5 g of boric acid to six human volunteers in an ointment or dissolved in water. They determined that 92 to 94% of the administered dose was excreted in the urine within 4 days. They also infused 600 mg of boric acid into seven human subjects and calculated a mean half-life of 21 hr.

Farr and Konikowski (*26*) dosed groups of mice intravenously with about 0.5 mg and 2.1 mg of boron as sodium pentaborate, in a study to determine the blood boron concentration relative to time. For the animals injected with 0.5 mg of boron, the blood boron level was 40 ppm 1 min after dosing, and dropped to about 18 ppm 2 hr later. For the animals that received 2.1 mg of boron, the blood boron level was initially 158 ppm and 40 ppm after 2 hr (Table 4). Boron was rapidly eliminated in the urine of these mice. About half of the administered boron was excreted within about an hour, for both dosage levels.

Astier et al. (*27*) reported blood plasma levels and cumulative urinary excretion of boron in an individual following an accidental oral ingestion of an unspecified amount of boron. The plasma level was 64 ppm of boron, and 200 mg had been excreted in urine 4 hr after ingestion. Five days later, the plasma concentration had fallen to 4 ppm, and the patient had excreted about 1.5 g of boron. The half-life of boron in this poisoning case was calculated to be about 29 hr, very near the half-life of boron in dogs as reported by Pfeiffer et al. (*23*) and in humans as reported by Schou et al. (*25*).

Analytical Method Validation

Boric acid has been shown to adversely affect the reproductive organs of male rats causing testicular atrophy and cellular dystrophy. As part of an investigation to study this effect in male rats, an analytical method for the determination of parts per million levels of boron in various tissues was developed and validated. For this effort, we were challenged to provide accurate and precise analyses on samples as small as a few milligrams.

All glass and plastic ware used in the preparation of samples was washed with soapy water, rinsed, and soaked for 8 hr in 10% nitric acid. All containers were thoroughly rinsed with deionized water before use.

Table 5. Method validation summary.

Tissue	Number of measurement	Correlation coefficient	Precision, % RSD	Average recovery, %	Quantitation range, µg/g
Kidney	10	0.999	4.4, 1.2	99.8	6–60
Testis	10	0.999	3.9, 0.9	99.4	3–30
Liver	10	0.999	3.1, 2.5	101.2	3–30
Plasma	10	0.997	4.4, 5.9	98.8	6–60
Blood	10	0.999	1.0, 1.2	100.8	6–60
Epididymis	9	0.997	25, 4.0	100.6	6–60

Tissue samples (<0.1 to about 1 g) were weighed into a tared microwaveable pressure relief vessel (Figure 1). Five ml of concentrated nitric acid was added to the container; the cap was tightened, and the container was loaded into a 12-position carousel and placed into the microwave oven. The samples were heated with 600 W of power for about half of a 12.5-min program. The samples were allowed to cool to room temperature, the digestion containers opened, and 0.75 ml of 30% hydrogen peroxide was added. The containers were recapped and heated again as before. The samples were removed from the oven, allowed to cool and filtered through Whatman 541 filter paper, and diluted to 15 ml with deionized water. Each sample, blank, method blank, and quality control sample was treated in the same manner.

A 6-point calibration curve was developed from a certified boron reference stock solution. The calibration standards were prepared at 0, 2, 4, 6, 8, and 10 µg/ml. The analytical instrument used for analysis of standards and samples was a Thermo Jarrell Ash Model 61 Inductively Coupled Argon Plasma (ICAP) spectrometer. The wavelength used for the analyses was 249.68 nm.

Table 6. Method performance evaluation results for boron-spiked testis standards.

Theoretical concentration, µg/g	Found concentration, µg/g	Relative error Accuracy %	Recovery, %
3.13	2.82	−9.9	90.1
3.13	2.94	−6.1	93.9
3.13	3.05	−2.6	97.4
	$\bar{x}$ = 2.94 RSD: 3.91%		$\bar{x}$ = 93.8
6.91	6.76	−2.2	97.8
13.2	14.5	9.8	109.8
16.3	17.6	8.0	108.0
22.6	22.8	0.9	100.9
25.8	25.6	−0.8	99.2
25.8	25.6	−0.8	99.2
25.8	25.2	−2.3	97.7
	$\bar{x}$ = 25.5 RSD: 0.91%		$\bar{x}$ = 98.7

The analytical method was validated by adding known amounts of boron to control rat tissue samples, and analyzing replicate samples over a range of six concentra-

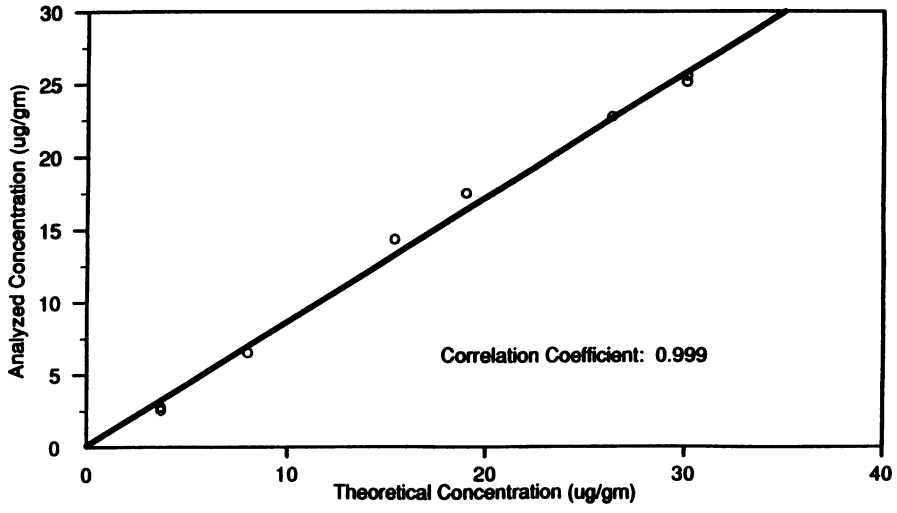

Figure 2. Boron-spiked testis standards.

Table 7. Boron distribution in tissues of rats fed 9000 ppm of boric acid in feed for 7 days.

Days on diet	Brain	Kidney	Liver	Muscle	Adrenal	Fat	Plasma	Bone	Testes	Seminal vesicle	Epididymis	Prostate
Control	0.76	1.6	0.66	3.7	8.0	1.7	1.9	1.2	0.96	1.6	0.81	1.2
1	11	20	10	14	17	2.1	11	24	10	14	9	14
3	13	22	13	11	20	2.6	14	31	14	15	19	12
7	14	20	13	14	22	3.8	16	47	16	17	17	15

Table 8. Boron distribution in tissues of rats fed 9000 ppm of boric acid in feed for 28 days.

Days on diet	Kidney	Liver	Epididymis	Testis	Blood	Plasma
Control	0.77	0.27	0.55	0.29	0.64	0.98
4	15	14	11	14	10	
7	14	14	11	14	13	
28	18	12	10	14	12	11

tions. For kidney, blood plasma, whole blood, and epididymis, the validation range was 6 to 60 μg per g of sample. For testis and liver, the quantitation range was 3 to 30 μg per g of sample. For each tissue type, the lowest and the highest concentrations were prepared in triplicate. The four concentrations in the middle of the validation range were prepared as single samples. Thus a total of 10 spiked samples was prepared and analyzed for each tissue type.

Following ICAP analyses the precision was calculated for the triplicates at the low and high end of the range. For all but epididymis, the relative standard deviation was less than 5% (Table 5). The recovery of boron from spiked samples was between 98 and 101%. The correlation coefficient of boron added, compared to boron recovered was 0.997 or better for all six tissue types. A plot of added versus recovered boron for testis is shown in Figure 2. All of the data for the validation of the method for testis are presented in Table 6. For this tissue, the recovery of boron ranged from about 94 to 110%. As would be expected, the recovery of boron and the precision of the analyses are poorest at the low spiking level and better at the highest concentrations.

In a separate study, seven method spikes were prepared by adding 0.2 μg of boron to the reagents used for sample preparation of 5-g urine samples. These method spikes were carried through the microwave digestion process, filtered, and diluted to a final volume of 15 ml. At this dilution, the concentration of boron was 0.013 ppm in the final digestate. For a sample size of 5 g this would correspond to a sample concentration of 0.04 ppm. The average measured boron concentration for the seven method spikes was 0.0409 ppm with a standard deviation of 0.0004 ppm (1% relative standard deviation).

Results and Discussion

Using the analytical method as described above, several hundred rat tissue samples from two studies (*28,29*), were analyzed for boron. A summary of the results of the analyses are presented in Tables 7 and 8. For both the 7- and 28- day studies, the soft tissues did not appear to accumulate boron at levels substantially above that found in blood. Fat tissue contained significantly less boron that other tissues. This is not surprising since boron is probably in the very polar form of boric acid in the body and thus not likely to accumulate in the nonpolar fat tissue.

The adverse reproductive effects in male rats, and the visible testicular lesions, do not appear to be the result of accumulation of very high concentrations of boron in the testis or other reproductive organs. The levels of boron in these tissues are no higher than the boron found in blood and the other soft tissues of the exposed animals.

Bone contained the highest level of boron of any tissue. After only 1 day on the diet, the boron content of bone increased 20-fold. After 1 week, the boron level in bone had increased to nearly 50 ppm. The boron concentration in bone decreased rapidly when the rats were removed from the 9000-ppm boric acid diet, and placed on a "clean" diet. After 9 weeks on the "clean" diet, the bone boron was substantially reduced and continued to drop slowly over the next 5 months. At this point, the boron in bone of exposed animals was reduced to within about three times the level in control animals, but never returned to preexposure concentrations.

Limited information concerning the distribution of boron in blood was determined during the course of the 28 day feeding study. It appears that most of the blood boron is associated with the plasma fraction of rat blood (Table 8). At 28 days on the diet, essentially all of the boron appears to be associated with plasma.

Extrapolation of toxicity data from animals to humans is best accomplished with knowledge about dosimetry at sites of toxicologic importance. Even though this information is available for rats (*30*), similar data are not available in humans. Blood-level data are often used as a surrogate for target-site tissue concentrations, but the relative importance of mean concentration in blood versus peak blood concentrations, and the impact of mode of exposure, vehicle, duration of exposure, and chemical form(s) of boron, make it difficult to extrapolate between species based on literature data. Exposure (via inhalation, ingestion, or skin) is also an uncertain basis for predicting relative toxicity because of possible differences in absorption, distribution, metabolism, and elimination. Thus, additional studies need to be conducted to define, with greater certainty, the proper scaling factors to predict human risk on the basis of animal data. As a default until more data are available, predictions of human risk from measured or estimated levels of exposure must recognize these uncertainties.

Conclusions

Boron is normally found at ppm levels in the foods we eat. Boron is found in human and animal tissues and fluids at ppm concentrations. Ingested boron is rapidly absorbed and excreted in the urine. The urine is the major route of excretion of boron.

The element does not appear to accumulate significantly in soft tissues. The adverse testicular effects and the reduced reproductive capability in male rats does not seem to be due to the preferential accumulation of boron in the testis or other reproductive organs. These organs appear to contain about the same concentration of boron as the other soft tissues.

Boron tends to accumulate in bone at levels far above those in blood and soft tissues of rats fed a diet containing boric acid. After cessation of exposure to boron in the diet, bone boron concentrations drop rapidly over a period of several months, returning to a concentration about three times that of control animals.

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