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Review Article

An Overview of Boron, Lithium, and Strontium in Human Health and Profiles of These Elements in Urine of Japanese*

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Abstract

The biological, medical and environmental roles of trace elements have attracted considerable attention over the years. In spite of their relevance in nutritional, occupational and toxicological aspects, there is still a lack of consistent and reliable measurement techniques and reliable information on reference values. In this review our understandings of the urinary profilings of boron, lithium and strontium are summarized and fundamental results obtained in our laboratory are discussed.

Over the past decade we have successfully used inductively coupled plasma emission spectrometry for the determination of reference values for urinary concentrations of boron, lithium and strontium. Taking into account the short biological half-life of these elements and the fact that their major excretion route is via the kidney, urine was considered to be a suitable material for monitoring of exposure to these elements. We confirmed that urinary concentrations of boron, lithium and strontium follow a lognormal distribution. The geometric mean reference values and 95% confidence intervals were 798 μg/l (398–1599 μg/l) for boron, 23.5 μg/l (11.0–50.5 μg/l) for lithium and 143.9 μg/l (40.9–505.8 μg/l) for strontium. There were no discrepancies between our values and those previously reported. Our reference values and confidential intervals can be used as guidelines for the health screening of Japanese individuals to evaluate environmental or occupational exposure to these elements.

Key words: boron, lithium, strontium, log-normal distribution, reference values

Introduction

Minerals along with protein, fatty acids, carbohydrates and vitamins are essential nutrients. In 1999, the Japanese Ministry of Health, Labor and Welfare declared copper, iodine, manganese, selenium, zinc, chromium and molybdenum as essential trace elements. In addition to these officially recognized trace elements, boron, lithium and strontium have been shown to have specific biological effects. For example, boron affects calcium absorption (1), lithium-rich drinking water is associated with low crime rates (2) and strontium has been shown to reduce the risk of vertebral fractures in postmenopausal women with osteoporosis (3). These elements are ubiquitous in the environment and are also widely used in various industrial applications. Thus, there is a risk of exposure through natural sources or in the working place (4–6).

Reference values (sometimes referred to as background-exposure levels) are useful for physicians and researchers because levels above the reference range usually indicate exposure to a particular source. To date, there are few reports on appropriate analytical techniques and the reference values for boron, lithium and strontium in human biological samples, which are indispensable for properly assessing nutritional intake and for the opportune diagnosis of occupational exposure. Inductively coupled plasma emission spectrometry (ICP-AES) is a powerful modern method used to determine concentration in various biological fluid specimens. This method has a low detection limit, simultaneous multielement analysis capabilities and a wide linear calibration dynamic range (7). Being part of one of the major excretion routes for trace elements, urine is frequently utilized for monitoring occupational and environmental exposures (8, 9).

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Consequently, we carefully optimized the conditions for using ICP-AES to analyze urine samples for boron, lithium and strontium concentrations in the Japanese population and determined the urinary reference values for these elements (10–12). In this review article, we summarize the role of boron, lithium and strontium in human health and the reference values of these elements in the urine of Japanese people.

Boron

In ancient Egypt, boron was used in the mummification process along with other common salts. Around the 8th and 10th centuries AD, regular imports of boron from the Far East began taking place in the trade routes established by Marco Polo. It was used in Chinese ceramic glazes and by Arabian gold- and silversmiths. The name boron originates from the combination of borax and carbon. The word boron also comes from the Arabic word meaning "white", as borax, the most common source for boron has a white appearance (13).

In 1892, the French chemist Henri Moissan (1852–1907) produced 98% pure boron. Recently, boron has extensively been used in a wide variety of industries, i.e., insecticides (14), food preservatives, fire retardants (15), glass products (16), detergents (17), semiconductors in electrical applications and reagents for chemical synthesis. Important boron sources are rasorite (kernite) and tincal (borax ore). The major deposits of these ores are found in the Mojave Desert (California, U.S.A.) and in Turkey.

Boron is an essential element for maintaining membrane integrity, cell wall formation in green algae, calcium uptake and the translocation of sugars (18). It is found primarily in plant foods and the human daily boron intake in different countries is in the range of 0.89–2.12 mg/day (19). Boron essentiality in humans is still unclear. In the past two decades, evidence suggesting that boron is essential for healthy bones and joint function has been mounting, possibly via effects on the balance and absorption of calcium, magnesium and phosphorus (20, 21).

Boron toxicity is relatively rare and boron compounds are believed to have a low acute toxicity. However, in a limited report, Moore warned about the risk of exporsure to boron in children when boric acid and borax are used in homes for cockroach control (22). In nature, boron-polluted volcanic areas can be found in various regions of the world, and reports on boron-exposed populations have been published by several researchers (23, 24). In an occupational study, Chang et al. reported a relationship between industrial boron exposure and reproductive health (4).

In the case of occupational and environmental quality guidelines, the American Conference of Governmental Hygienists (ACGIH) set the threshold limit value (TLV) for sodium tetraborate ($Na_2B_4O_7$) at 10 mg/m^3. The same level is listed as the permissible exposure limit (PEL) by the U.S. Occupational Safety and Health Administration (OSHA) for working environment air quality guidelines. The guidelines of the Health Advisory Committee of the U.S. Environmental Protection Agency (EPA) recommend concentrations below 0.6 mg/l for lifetime exposure to boron in drinking water, and the Food and Drug Administration (FDA) allows no more than 310 ppm boron as a food additive. Despite these governmental recommendations, suitable means of analysis and guidelines for biological index values for boron exposure have not been established.

Boron is entirely absorbed from the gastrointestinal (GI) tract and 99.6±7.9% of the ingested boron is excreted in the urine in 24 h (25). This makes urine the ideal sample for the screening of boron exposure.

Lithium

The Swedish chemist Johan August Arfwedson discovered lithium in 1817 during an analysis of the mineral petalite. The name comes from the Greek word *lithos*, "stone", because it was discovered from a mineral; however, the other alkali metals were first discovered from plant tissues. It is widely used in psychiatry as a mood stabilizer for treating manic depression and bipolar disorder. The prescription of lithium to that effect can be traced back to as early as the second century AD when the Greek physician Soranus suggested that mania should be treated with the alkaline spring waters of Ephesus, which contained very high levels of lithium salts (26, 27).

Lithium is ubiquitous element found in trace amounts in plants, animals and humans. The U.S. EPA estimated that the average daily lithium intake ranges from 650 to 3100 μg/day. Lithium had already been detected in human organs and fetal tissues in the late 19th century, leading to early suggestions of possible essentiality in humans; however, medical applications of lithium carbonate for the treatment of manic excitement preceded studies on lithium as an essential micronutrient. For this reason, Schrauzer indicated that it took another century until evidence of the essentiality of lithium became available (6).

Presently, the portable electronic industry is in continuous expansion and the need for suitable rechargable batteries has notably increased the demand for lithium (28). Lithium-based batteries contain extremely caustic lithium compounds and pose serious occupational risks to workers (29). In addition to its high-tech applications, lithium salts such as those of chloride and bromide are used as desiccants because they are extremely hygroscopic (30). Chile is currently the leading lithium metal producer in the world, followed by Argentina. In several studies, warnings about the risk of lithium exposure from naturally polluted environments in these countries have been given (31, 32).

To protect human health, the ACGIH set the PEL at 0.025 mg/m^3 and the immediately dangerous to life or health concentration value (IDLH) at 50 mg/m^3 for lithium hydride. The time-weighted average (TWA) was set at 0.025 mg/m^3 for the working environment air quality guidelines by OSHA and the EPA recommended that the lithium concentration in the drinking water supply should not exceed 700 μg/l. In a situation similar to that for boron, suitable means for the determination and of guidelines for biological index values for lithium exposure protection have not been established.

Over 90% of the lithium taken in is eliminated from the human body via the kidney (33). The human serum lithium half-life is reported to be less than 24 h (34). These properties make urine as a suitable material for a screening of lithium exposure.

Strontium

Strontium is named after the mineral strontianite, found in the Scottish village of Strontian. The British chemist Thomas Charles Hope is credited with the discovery of the element in 1787. It is an abundant and widely distributed element in the geosphere, natural water, and human tissues. Because strontium produces a brilliant red flame, its compounds are used in color television picture tubes and to produce a red color in fireworks (35).

Combined with iron, strontium forms a magnetic compound that is stronger than alnico and has much better resistance to corrosion than rare earth magnets, making it important in the production of ferrite ceramic magnets (36).

The biological effects of strontium are related to its chemical similarity to calcium and other elements in Group 2A of the periodic table (37). Because of its similarity to calcium and its bone-seeking behavior, strontium accumulates to a high degree in bone, can displace calcium in hard tissue metabolic processes and at high concentrations interferes with normal bone development (38). Because of this bone-seeking property, strontium drew attention as a drug for the management of osteoporosis in the 1950s. Strontium ranelate (Protelos, Servier) is expected to become a new drug for the prevention of postmenopausal osteoporosis (39). Although there are several pieces of evidence that support its role in anabolic activity in the skeletal system, strontium is not yet considered as essential for humans (40).

There is no evidence of strontium toxicity and its daily intake through food is not a cause of concern. However, Ozgur et al. reported a prevalence of rickets in a strontium-rich soil area in Turkey where the residents ingest excessive amounts of strontium (41). Other researchers have suggested that there is a potential risk of bone disease in cases of high dietary strontium intake (42), as well as risks of requiring hemodialysis and developing chronic renal failure (43, 44).

The average strontium intake in Finland was reported to be 1.9 mg/day/person (45). Strontium from foods or water enters the bloodstream after its absorption in the GI tract. Once strontium enters the bloodstream, it is distributed throughout the body, accumulating mainly in bone and is eliminated in the urine over long periods of time. The U.S. EPA recommends that the level of strontium in drinking water should not exceed 4 mg/l.

Warren et al. reported that 17.5% of dietary strontium is excreted via the urine (46). Being the major pathway for strontium elimination from the human body, urine was selected for the screening of strontium exposure.

Measurement of Boron, Lithium and Strontium Concentrations in Urine by ICP-AES

ICP-AES was developed in the early 1960s and quickly became the preferred technique for routine trace element analysis. It allows the determination of trace concentrations of elements in liquid samples at the μg/l level (7).

Other analytical methods, such as atomic absorption spectroscopy (AAS), inductively coupled plasma mass spectroscopy (ICP-MS), ion chromatography (IC) and ion selective electrode (ISE) analysis can also be used for trace element analysis. The advantages and limitations of these techniques are well documented (47).

Because there is a paucity of information on the normal ranges of boron, lithium and strontium in human urine, the use of ICP-AES for determining urinary trace amounts of these elements has been optimized in the authors' laboratory over the past 10 years. The quality assurances of these techniques have been amply described in several reports (10–12).

In brief, the spectra of urine samples were examined to confirm that there were no interfering lines near the selected wavelengths by a comparison with the spectra of standard solutions. Matrix spike samples were analyzed to determine the effect of a sample matrix on analytical accuracy. Accuracy was evaluated using % recovery, obtained by dividing spiked sample concentration by certificate value and then multiplying by 100. Reproducibility was evaluated using % coefficient of variation (% CV), obtained by dividing the standard deviation by the arithmetic mean concentration and then multiplying by 100.

Spot urine samples obtained from Japanese electronic workers not at risk of exposure were used for the analysis of boron (n=102, male), lithium (n=86, male) and strontium (n=146; 115 males and 31 females). The obtained concentrations of urinary boron, lithium and strontium were adjusted to normal urine density using Eq. 1

$$\{C\} = [C]\frac{24}{SG} \tag{1}$$

where SG corresponds to the last two digits of the specific gravity of the urine sample, {C} is the specific-gravity-corrected concentration of urinary boron, lithium or strontium and [C] is the observed concentration of urinary boron, lithium or strontium. This adjustment procedure normalizes all the results to a specific gravity of 1.024 by multiplying the analytical result by 24/SG. The specific gravity-adjusted concentrations of urinary boron, lithium and strontium were used in statistical analysis.

Lognormal Distributions of Boron, Lithium and Strontium in Urine

Figure 1 shows the distribution patterns of urinary boron, lithium and strontium. These patterns are characterized by their high degrees of positive skewness: 0.875 for boron, 0.816 for lithium and 1.46 for strontium. Skewness is a measure of the asymmetry of the probability distribution and indicates whether deviations from the mean will be positive or negative. The log-normality of these urinary trace element distributions was confirmed by the linearity of the log-probability plot.

Figure 2 shows the log-transformed normal distributions of urinary boron, lithium and strontium. The skewness values (0.089 for boron, −0.239 for lithium and −0.39 for strontium)

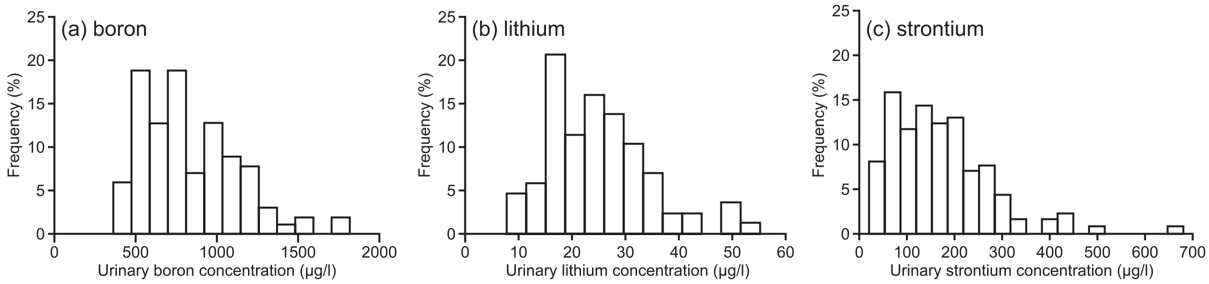

Fig. 1 Positively right-skewed lognormal distribution of (a) urinary boron (n=102), (b) urinary lithium (n=86) and (c) urinary strontium (n=146) concentrations. Concentrations were adjusted according to a specific gravity of 1.024.

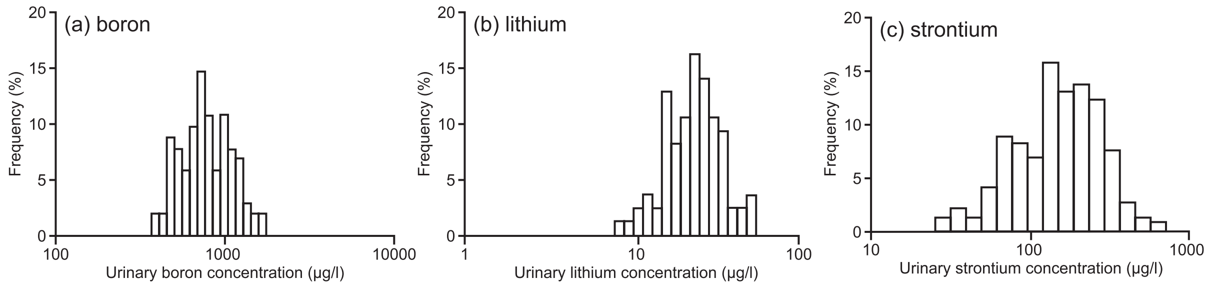

Fig. 2 Log-transformed normal distributions of (a) urinary boron (n=102), (b) urinary lithium (n=86) and (c) urinary strontium (n=146) concentrations. Concentrations were adjusted according to a specific gravity of 1.024.

showed no skewing. Kurtosis values (−1.004 for boron, −0.007 for lithium and −0.10 for strontium) showed a platykurtic distribution of relatively flat-topped peaks with a thin tail, with lithium and strontium showing mesokurtic distributions of taller and narrower peaks with fat tails. Kurtosis is a measure of the "peakedness" of the probability distribution and higher kurtosis values indicate that more of the variance is due to infrequent extreme deviations, as opposed to frequent moderately sized deviations. The obtained kurtosis values indicate that the urinary boron concentration fluctuates more frequently and shows higher volatility than the urinary concentrations of lithium and strontium (12, 48).

A lognormal distribution is characterized by a positively right-shifted data distribution that will fit a normal (Gaussian) distribution on a probability distribution or histogram when its logarithms are plotted instead. This type of distribution is quite common in both biological and nonbiological applications, such as trace elements in human samples (10, 49–57), organic substances in human samples (58–68) and other substances in natural ecosystems (69–76). Since boron, lithium and strontium might not be under strict homeostatic control, they are largely excreted into the urine and the excretion rate of these trace elements directly depends on their concentrations. This elimination phase can be described by a negative exponential function of time. The lognormal distribution shown by these trace elements reflects this nonlinear process of elimination from the body over time.

Urinary Concentrations of Boron, Lithium and Strontium

The geometric mean (GM) is preferable to the arithmetic mean (AM) for representing log normally distributed data. For that reason, we calculated the urinary reference values for

Table 1 Literature reported values of urinary boron, lithium and strontium concentrations

Element	Mean (μg/l)	Range (μg/l)	Subjects	Method	Reference
(a) Boron	798^{GM}	398–1599^{CI}	Japan (n=102)	ICP-AES	Usuda et al. (10)
	713^{median}, 919^{AM}	40–6600$^{min-max}$	USA (n=148)	Spectrographic	Imbus et al. (77)
	753^{median}	155–2888$^{min-max}$, 347–866^{quartile}	UK (n=50)	ICP-MS	Abou-Shakra et al. (78)
	1890^{AM}	470–7800$^{min-max}$, 490–3290^{CI}	Italy (n=119)	ICP-AES	Minoia et al. (79)
(b) Lithium	23.5^{GM}	11.0–50.5^{CI}	Japan (n=86)	ICP-AES	Iguchi et al (11)
	29.3^{AM}		Uruguay (n=10)	Flame AAS	Dol et al. (80)
	9.6^{median}	0.8–40.5$^{min-max}$, 5.4–19.6^{quartile}	UK (n=50)	ICP-MS	Abou-Shakara et al. (78)
(c) Strontium	143.9^{GM}	40.9–505.8 μg/l^{CI}	Japan (n=146)	ICP-AES	Usuda et al. (12)
	139.4^{AM}	19.0–256.1 μg/l^{CI}	USA (n=1439)	ICP-MS	Komaromy-Hiller et al. (81)
	158^{AM}		Netherlands (n=6)	Flameless AAS	Leeuwenkamp et al. (82)
		110–390 μg/l^{CI}			Iyengar et al. (83)

AM: arithmetic mean, GM: geometric mean, CI: 95% confidential interval.

boron, lithium and strontium using GM and CI and compared these to reported values.

The reported urinary boron (10, 77–79), lithium (11, 78, 80) and strontium (12, 81–83) concentrations are summarized in Table 1. These results suggest that urinary boron concentration is on the order of several hundred μg/l with a mean value of approximately 1000 μg/l, that urinary lithium concentration is on the order of μg/l with a mean value of approximately 20 μg/l, and that urinary strontium concentration is on the order of 10–100 μg/l with a mean value of approximately 150 μg/l.

Although the data summarized in Table 1 were obtained from a limited number of subjects using different methods in various countries, the urinary concentrations of boron, lithium and strontium are in the above-described ranges and values. These ranges and values, when compared with the reported daily intake and excretion rates, support the notion that our obtained results can be regarded as reliable reference values.

The use of spot urine is advantageous for the biological monitoring of occupational and environmental exposures to chemical substances. Urine sampling is simple, non-invasive and can be performed in a routine manner (12). We recommended that our obtained GM with CI reference values could be used as practical biological benchmarks for the prevention and early diagnosis of exposure to these three elements.

Conclusions

Recently, continuing advancements in industry and chemical technology have provided the opportunities to utilize boron, lithium and strontium. Thus, the most of the related articles reviewed have paid considerable attention to the health effect of these trace elements (84–89) including beneficial, adverse and potential aspects. However, it is noteworthy that the reference values of boron, lithium and strontium that can be compared with those of other populations for exposure assessment. For this purpose, in this review article, we summarized the reported reference values of boron, lithium and strontium along with our current understanding of these elements. The reference values of boron, lithium and strontium described in this review can be used as references for screening subjects at risk, making an early diagnosis of exposure possible. Performing up-to-date studies using a larger study group from various countries is recommended and the analysis of other trace elements will be also necessary as their future demand grows.

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