

# Boron Level in the Prostate of the Normal Human: A Systematic Review

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Review Article

Vladimir Zaichick

Radionuclide Diagnostics Department, Medical Radiological Research Centre, Obninsk, 249036, Russia.

## \*Correspondence author

**Prof. Dr. V. Zaichick**

Radionuclide Diagnostics Department  
Medical Radiological Research Centre  
Korolyev St. 4  
Obninsk 249036  
Russia  
ORCID: 0000-0002-4286-4267

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## Abstract

Knowledge of the etiology and pathogenesis of most prostate malfunctions and pathologies is very limited. Despite advances in medicine, the differential diagnosis of benign hypertrophic and carcinogenic prostate has steadily increased in complexity and controversy. It has been suggested that the prostate boron(B) level may help solve these problems related to prostate disorders, especially as an indicator of prostate cancer risk, as an elevated B level in the prostate may be a sign of prostate cancer in the future. These suggestions promoted more detailed studies of the B level in the prostate of healthy men. In present review, we analyze data published concerning B prostatic levels in healthy persons. In all 2302 items in the literature of the years dating back to 1921 were identified in the following databases: PubMed, Scopus, Web of Science, the Cochrane Library, and ELSEVIER-EMBASE. This data was subject to an analysis employing both the "range" and "median" of means. In this way, the disparate nature of published B content of normal prostates was evaluated. Of the articles examined, 24 were selected for objective analysis of data from 1075 healthy subjects. The contents of prostatic B (on a wet mass basis) spanned the interval from  $\leq 0.100$  mg/kg to 1.90 mg/kg with 0.177 mg/kg as median for their means. The data included a wide range of values and the samples were small, hence it is advisable that further studies with strong quality control of results be performed.

**Keywords:** Boron; Human prostate gland; Normal prostatic tissue; Biomarkers

## Introduction

Amongst the many pathological prostatic conditions, prostatic carcinoma (PCa), chronic prostatitis and benign prostatic hyperplasia (BPH) are very frequently encountered, especially in the elderly [1-3]. Their causes and pathogenesis are poorly understood. Moreover, despite biomedical advances, the differential diagnosis of prostate diseases has become progressively more complex and controversial. An improvement of this situation, especially recognition of relevant risk factors and the disorders' etiologies can allow great reduction in the incidence of these prostatic disorders.

In our previous studies the involvement of trace elements (TEs) in the function of the prostate gland was indicated. [4-15]. It was also found that content of TEs in prostatic tissue, including boron(B), can play a significant role in etiology of PCa [16-21]. Furthermore, it was demonstrated that the changes of some TE levels and Zn/B ratios in prostate tissue can be useful as biomarkers [22-28].

The first result of B content in human prostatic tissue was published in 1954 by Tipton et al. [29]. This team investigated one prostate sample and indicated that the content of B in the human prostate equals 0.20 mg/kg of wet tissue. This result sug-

gested that the prostate can accumulate B, because the level of metalloid in gland was almost one order of magnitude higher the blood level (0.02-0.05 mg/L) and more than two times than B content in liver ( $<0.10$  mg/kg of wet tissue) [30]. Moreover, recent epidemiological study identified that high exposure to B might have an implication within the prostatic cellular processes related to hyperplasia and carcinogenesis [31]. These findings promoted more extensive considerations of the B content of prostatic tissue of healthy persons, as well as of patients with different prostatic disorders, including BPH and PCa.

The effects of TEs, including B, are related to their level in tissues and fluids. Recorded observations range from a deficiency state, through normal function as biologically essential components, to an imbalance, when excess of one element interferes with the function of another, to pharmacologically active levels, and finally to toxic and even life-threatening concentrations [32-34]. In this context, growing evidence from a variety of studies shows that B is a bioactive chemical element and in low doses of this metalloid is beneficial for humans [35]. At the same time a lot of publications testify to adverse health effects in different organs or tissues of acute poisoning and chronic exposure to this metalloid and its compounds, in-

cluding suppression of male reproductive system function and PCa [31,36-38]. By now, a few publications have reported the level of B content in tissue of "normal" and affected glands. However, subsequent research works has been considered necessary to provide a practical reference data of B contents in prostate norm and disorders, because the findings of various investigations indicate some discrepancies.

The present study deals with the importance of B contents in prostate tissue as a biomarker of gland condition. Therefore, we systematically reviewed all relevant literature and performed a statistical analysis of the B level in "normal" gland tissue, which may provide insight into the etiology and diagnosis of prostate diseases as a higher B rate than these normal rates may be an indication of the possibility of pathological development in the prostate.

## Materials and Methods

### Data sources and search strategy

Aiming at finding the most relevant articles for this review, a thorough comprehensive web search was conducted by consulting the PubMed, Scopus, Web of Science, the Cochrane Library, and ELSEVIER-EMBASE databases, as well as from the personal archive of the author collected between 1966 to December 2020, using the key words: prostatic trace elements, prostatic B content, prostatic tissue, and their combinations. For example, the search terms for B content were: "B mass fraction", "B content", "B level", "prostatic tissue B" and "B of prostatic tissue". The language of the article was not restricted. The titles from the search results were evaluated closely and determined to be acceptable for potential inclusion criteria. Also, references from the selected articles were examined as further search tools. Relevant studies noted for each selected article were also evaluated for inclusion.

### Eligibility criteria

#### Inclusion criteria

Only papers with quantitative data of B prostatic content were accepted for further evaluation. Studies were included if the control groups were healthy human males with no history or evidence of urological or other andrological disease and B levels were measured in samples of prostatic tissue.

#### Exclusion criteria

Studies were excluded if they were case reports. Studies involving persons from B contaminated area and subjects that were B occupational exposed were also excluded.

#### Data extraction

A standard extraction of data was applied, and the following available variables were extracted from each paper: method of B determination, number and ages of healthy persons, sample preparation, mean and median of B levels, standard deviations of mean, and range of B levels. Abstracts and complete articles were reviewed independently, and if the results were different, the texts were checked once again until the differences were

resolved.

### Statistical analysis

Studies were combined based on means of B levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of B contents. The objective analysis was performed on data from the 24 studies, with 1075 subjects.

### Results

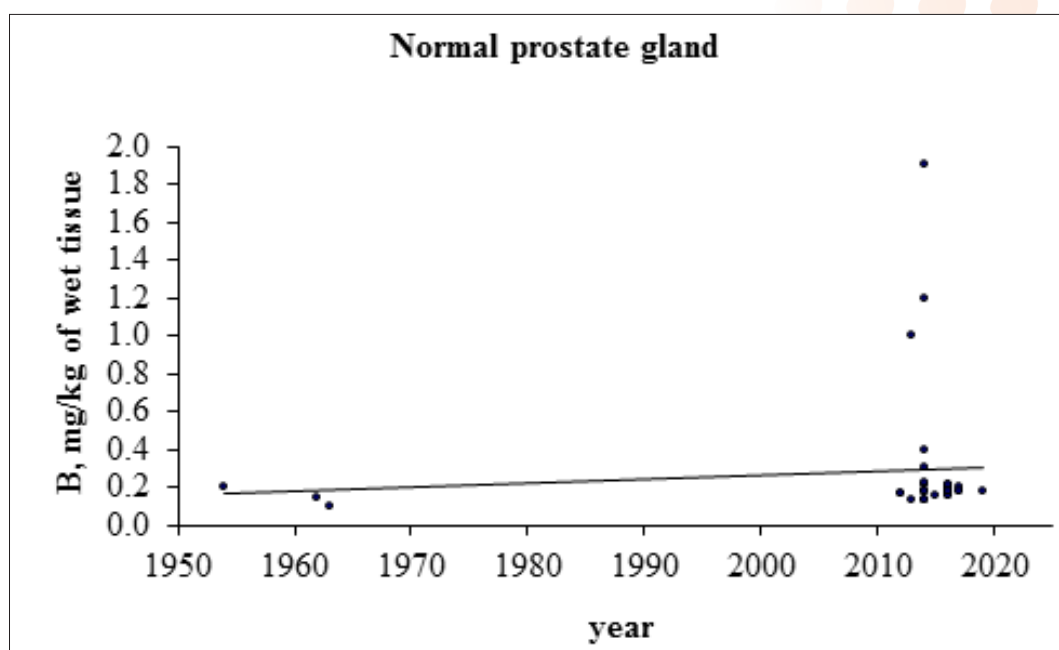
Information about B levels in prostatic tissue in different prostatic diseases is of obvious interest, not only to understand the etiology and pathogenesis of prostatic diseases more profoundly, but also for their diagnosis, particularly for PCa diagnosis and PCa risk prognosis [28,32]. Thus, it dictates a need for reliable values of the B levels in the prostatic tissue of apparently healthy subjects, ranging from young adult males to elderly persons.

Possible publications relevant to the keywords were retrieved and screened. A total of 2302 publications were primarily obtained, of which 2278 irrelevant papers were excluded. Thus, 24 studies were ultimately selected according to eligibility criteria that investigated B levels in tissue of normal prostates (Table 1) and these 24 papers [8,9,12,13,14,27,29,39-55] comprised the material on which the review was based.

A number of values for B mass fractions were not expressed on a wet mass basis by the authors of the cited references. However, we calculated these values using the medians of published data for water – 83% [56-59] and ash – 1% (on a wet mass basis) contents in normal prostates of adult men [29,58,60,61].

Table 1 summarizes general data from the 24 studies. The retrieved studies involved 1075 subjects. The ages of subjects were available for 21 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 23 studies. All studies determined B levels by destructive (require high temperature drying, ashing or acid digestion of tissue samples) analytical methods (Table 1): two using atomic emission spectrometry (AES), eight - inductively coupled plasma atomic emission spectrometry (ICPAES), eight - inductively coupled plasma mass spectrometry (ICPMS), and five – ICPAES combined with ICPMS (2 methods).

Figure 1 illustrates the data set of B measurements in 24 studies during the period from 1954 to 2020.



**Figure 1:** Data on B content in normal prostate tissue reported from 1954 to 2020 year.

Reference	Method	n	Age, years Range	Sample preparation	B	
					M±SD	Range
Tipton et al. 1954 [29]	AES	1	Adult	D, A	0.20	-
Zakutinsky et al. 1962 [39]	-	-	-	-	<0.15	-
Tipton et al. 1963 [40]	AES	50	Adult	D, A	≤0.1	Max 0.11
Zaichick et al. 2012 [41]	ICP-AES	64	13-60	AD	0.165±0.128	0.051-0.544
Zaichick et al. 2012 [42]	ICP-MS	64	13-60	AD	0.165±0.128	0.051-0.544
Zaichick et al. 2013 [8]	ICPAES	16	20-30	AD	0.138±0.054	-
Zaichick et al. 2013 [9]	ICPMS	16	20-30	AD	1.00±2.92	-
Zaichick et al. 2014 [43]	ICPAES	28	21-40	AD	0.131±0.046	0.068-0.221
		27	41-60	AD	0.175±0.150	0.051-0.510
		10	61-87	AD	0.182±0.145	0.051-0.476
Zaichick et al. 2014 [44]	ICPMS	28	21-40	AD	0.131±0.046	0.068-0.221
		27	41-60	AD	0.175±0.150	0.051-0.510
		10	61-87	AD	0.182±0.145	0.051-0.476
Zaichick et al. 2014 [12]	ICPAES	50	0-30	AD	0.31±0.31	-
		29	0-13	AD	0.40±0.39	-
		21	14-30	AD	0.21±0.19	-
Zaichick et al. 2014 [13]	ICPMS	50	0-30	AD	1.2±3.5	-
		29	0-13	AD	1.9±4.5	-
		21	14-30	AD	0.22±0.22	-
Zaichick et al. 2014 [14]	2 Methods	16	20-30	AD	0.138±0.054	-
Zaichick 2015 [45]	2 Methods	65	21-87	AD	0.160±0.119	-
Zaichick et al. 2016 [46]	ICPAES	28	21-40	AD	0.157±0.016	-
		27	41-60	AD	0.203±0.039	-
		10	61-87	AD	0.216±0.063	-
Zaichick et al. 2016 [47]	ICPMS	28	21-40	AD	0.157±0.016	-

		27	41-60	AD	0.203±0.039	-
		10	61-87	AD	0.216±0.063	-
Zaichick et al. 2016 [48]	ICPAES	37	41-87	AD	0.177±0.146	0.051-0.510
Zaichick et al. 2016 [49]	ICPAES	32	44-87	AD	0.177±0.146	0.051-0.510
Zaichick et al. 2016 [50]	ICPAES	37	41-87	AD	0.177±0.146	0.051-0.510
Zaichick et al. 2016 [51]	ICPMS	32	44-87	AD	0.177±0.173	-
Zaichick et al. 2016 [52]	ICPMS	37	41-87	AD	0.177±0.184	-
Zaichick et al., 2017 [27]	ICPMS	37	41-87	AD	0.177±0.184	-
Zaichick et al. 2017 [53]	2 Methods	37	41-87	AD	0.197±0.149	0.0531-0.574
Zaichick 2017 [54]	2 Methods	37	41-87	AD	0.177±0.145	0.051-0.510
Zaichick et al. 2019 [55]	2 Methods	37	41-87	AD	0.177±0.145	0.051-0.510
Median of means				0.177		
Range of means (Mmin - Mmax),				≤0.100 – 1.9		
Ratio Mmax/Mmin				(1.9/≤0.100) = ≥19		
All references				24		

M – arithmetic mean, SD – standard deviation of mean, AES – atomic emission spectrometry, ICPAES – inductively coupled plasma atomic emission spectrometry, ICPMS – inductively coupled plasma mass spectrometry, 2 Methods – ICPAES and ICPMS  
D – drying at high temperature, A – ashing, AD – acid digestion.

**Table 1:** Reference data of B mass fractions (mg/kg wet tissue) in “normal” human prostatic tissue M – arithmetic mean, SD – standard deviation of mean, AES – atomic emission spectrometry, ICPAES – inductively coupled plasma atomic emission spectrometry, ICPMS – inductively coupled plasma mass spectrometry, 2 Methods – ICPAES and ICPMS

D – drying at high temperature, A – ashing, AD – acid digestion.

## Discussion

The range of means of B mass fractions reported in the literature for “normal” prostatic tissue varies widely from ≤0.100 mg/kg [40] to 1.9 mg/kg [13] with median of means 0.177 mg/kg wet tissue (Table 1). Thus, the maximal value of mean B mass fraction reported [13] was more than 19 times higher the minimal value of mean [40]. This variability of reported mean values can be explained by a dependence of B content on many factors, including analytical method imperfections, differences in “normal” prostate definitions, possible non-homogeneous distribution of B levels throughout the prostate gland volume, age, ethnicity, diet, smoking, alcohol intake, consuming supplemental Zn and Se, and others. Not all these factors were strictly controlled in the cited studies. For example, in some studies the “normal” prostate means a gland of an apparently healthy man who had died suddenly, but without any morphological confirmation of “normality” of his prostatic tissue. In other studies, the “normal” prostate means a non-cancerous prostate (but hyperplastic and inflamed glands were included) and even a visually normal prostatic tissue adjacent to a prostatic malignant tumor. Some researchers used as the “normal” prostate the glands of patients who died from acute and chronic non-prostatic diseases including subjects who had suffered from prolonged wasting illnesses. In some studies, whole glands were used for the investigation while in others the B content was measured in pieces of the prostate. Therefore, published data allowed us to estimate the effect of only a few factors on B content in “normal” prostate tissue.

## Analytical method

The trend line of B content data in “normal” prostate (Figure 1) showed that an improvement of analytical technologies during last almost 60 years did not impact significantly on the means and variability of reported values. Thus, in our opinion, the leading cause of inter-observer variability was insufficient detection limit of AES methods and poor quality control of results in studies published in the 50-60s [29,39,40]. In all reported papers, destructive analytical methods (AES, ICP-AES, and ICP=MS) were used. These methods require drying, ashing or acid digestion of the samples at a high temperature. There is evidence that use of this treatment causes some quantities of TEs to be lost [32,62,63]. On the other hand, the B content of chemicals used for acid digestion can contaminate the prostate samples. Thus, when using destructive analytical methods, it is necessary to allow for the losses of TEs, for example when there is complete acid digestion of the sample. Then there are contaminations by TEs during sample decomposition, which require addition of some chemicals. It is possible to avoid these problems by using non-destructive methods, but up to now there are no analytical methods which allow quantify B content in “normal” prostate without ashing or acid digestion of the samples at a high temperature. It is, therefore, reasonable to conclude that the strong quality control of results is very important factor for using the B content in prostatic tissue as biomarkers.



### Age

In a few studies a significant increase in B content with increasing of age was shown by the comparison of different age groups or the Pearson's coefficient of correlation between age and B content in prostate tissue [43,44,46,47]. The most detailed investigations of age-dependence of prostatic Bi were done by Zaichick and Zaichick [46,47]. For example, a strongly pronounced tendency for an age-related increase of B mass fraction was observed in the prostate for the third to ninth decades [46,47]. In prostates of 61-87-year-old men, the mean B mass fraction was 40% higher than that in the prostates of 20-39-year-old males. Thus, the accumulated information, studied by us from reported data, allowed a conclusion that there is a significant increase in B mass fraction in "normal" prostate from age 21 years to the ninth decades.

### Androgen-independence of prostatic B levels

There was not found any difference between B levels in prostates of teenagers before puberty and of postpubertal teenagers and young adults [8,9,12-14]. These findings allowed us to conclude that the B content in "normal" prostates does not depend on the level of androgens, and vice versa. However, it is necessary to remark that numerous studies indicate that B intake affects the presence or function of vitamin D and such hormones as estrogen, insulin, progesterone and thyroid hormone [35]. Furthermore, in elevated amounts inorganic B compounds can work as reproductive toxins [64,65]. Consequently, because the prostate gland is one of the organs of reproductive system, B has directly or indirectly to impact on the prostate function.

### Dietary B intake

B exposure occurs through various ways like food and water consumption, inhalation, and skin contact. Food and drinking water are the main sources of B exposure [35,66]. Most people receive the largest portion of their daily B intake via food and B is contained in all kinds of food. Moreover, people take B supplements as medicine [35].

World health Organization (WHO) suggested that an acceptable safe range of population mean B intake for adults could be 1–13 mg/d [67]. Maximum tolerable B intake equals approximately 20 mg/day [67]. The general intake of B via its presence in food and water depends on geographical region and dietary habits, but as usual it is inside the range indicated by WHO. For example, in the UK the dietary intake was estimated to be around 1-7 mg/d [68].

The highest contents of B were found in fruits and also in leafy green vegetables like kale and spinach [69,70]. For example, mass fractions of B in quinces, apples and pears were estimated to be 160, 110, and 70 mg/kg on wet mass basis, respectively. Foods especially high in B content include also grains, nuts, chocolate, avocado, dried fruits such as prunes and raisins, as well as juice and wine [70]. In the USA for all age groups up to 21% of B intake was contributed by vegetables, fruits, and fruit drinks [70].

The European Food Safety Authority (EFSA) suggested 1.0 mg/L to be a safe drinking water standard for B [71]. WHO guidelines for drinking-water quality proposed a 0.5mg/l as the standard for B in drinking water [72]. However, it was reported that many drinking water sources had B concentrations exceeding 1.0 mg/L in the European Union and in other countries [73-77].

It was shown that a strong link exists between B intake and this metalloid level in blood and key organs [78,79]. From this it was hypothesized that dietary B intake affects the metalloid's levels in the prostate.

### Prostatic B content in comparison with other body organs, tissues, and fluids

The total content of B in the body of adults is about 20 mg [79]. About 40% of this amount is located in muscles and about 37% in the skeleton [79]. The skeleton is the major storage pool for long-term B accumulation [78,79]. Information on B content in human organs and tissues is very limited and inconsistent. For example, Moskalev [79] reported that the mass fractions of B in human bones range between 16-138 mg/kg on wet mass basis and increase with age, while in accord to Moseman's result mass fraction of this metalloid measured in bone of one individual was estimated to be 0.90 mg/kg on wet mass basis [69]. Along with bone, nails, and hair have higher B levels than other body tissues [69]. Among soft tissues of human body principle organs of B accumulation are kidney (0.25 mg/kg on wet mass basis) and liver (0.11 mg/kg on wet mass basis) [69].

Reported mean B level in whole blood of healthy persons  $0.019 \pm 0.004$  mg/L [80] agreed well with data for Reference Man (0.020mg/L) [30]. Because the median of prostatic B content means obtained in the present review (0.177 mg/kg of wet tissue) approximately equals the metalloid level in kidney and almost one order of magnitude higher than two times higher the whole blood level, we can conclude that the prostate gland is also a target organ for B.

B occurs naturally as minerals, such as ulexite, borax (tincal), natural boric acid (sassolite), colemanite, and kernite [81]. Although present in small amounts, B is widely distributed in the hydrosphere and lithosphere [81]. All natural chemical elements of the Periodic System, including B, also present in all subjects of biosphere [32,82,83]. The most common natural sources of B entrance in biosphere are borosilicate mineral tourmaline, volatile volcano emanations, geothermal streams, groundwater, and seawater. During the long evolutionary period intakes of B in organisms were more or less stable and organisms were adopted for such environmental conditions [84]. Moreover, organisms, including human body, involved low doses of this metal in their functions [35,66]. B-containing mineral borax (tincal) have been known and used in relative small amounts since times of ancient Babylonians and Egyptians [85]. The Babylonians used borax as a flux for gold production, while the ancient Egyptians used borax not only in metallurgic applications, but also in medicine and mummification. The first verified use of borax flux by European gold-

smith's dates to about the 12th century [85].

The situation with anthropogenic B contamination of environment began to change after the industrial revolution, particularly, over the last 100-150 years. In the 1870s, it was discovered that some B compounds could be used to preserve foods such as meat and dairy products [35,85]. For about the next 70 years up to the end of World Wars II B addition was used as a food preservative. However, by the 1950s, B as a food preservative was essentially forbidden throughout the world, because it was found that there is the limit (699 mg boron per day) beyond which a harm to humans would occur [35].

Besides the food preservation B has many other important properties like high thermal neutron capture and the ability to form trigonal as well as tetrahedral bonding patterns and to create complexes with organic functional groups, many of biologic importance [85,86]. B compounds now have many applications in a number of fields, including atomic industry, metallurgy, glass and ceramics production, cosmetic and medicinal chemistry. The primary use of B is in glass and ceramics industry for manufacturing the insulation fiberglass, textile fiberglass, thermo-stable borosilicate glass (Pyrex), porcelain, enamels and glazes [85]. This metalloid and its compounds are also widely used in the manufacture electronics, detergents and bleaches, alloys and metals, fire retardants, agricultural synthetic herbicides and fertilizers, adhesives, as well as in wood products as a wood preservative, in metallurgy for nuclear shields and for the production of aviation and rocket propellants [81,85].

For a long time, B compounds are also widely used in medicine for prevention and treating osteoarthritis, for bone growth and maintenance, for building muscles and increasing testosterone levels, and for improving thinking skills and muscle coordination [35]. Women use capsules containing B compound (boric acid) to treat intravaginal yeast infections. People also apply boric acid to prevent skin infection or use it as an eye and ear wash. Nowadays B-based drugs represent a new class of molecules that possess several biomedical applications including use as imaging agents for both optical and nuclear imaging as well as therapeutic agents with anticancer, antiviral, antibacterial, antifungal and other disease-specific activities [86-88].

Low molecular weight B-containing drugs were used for neutron capture therapy (BNCT) for decades [86,89]. Because of their limitations, great effort has been expended over the past 40 years to develop new B delivery agents, including B-containing nanoparticles, that have more favorable bio distribution and uptake for clinical use [90-92].

Thus, B is ubiquitously distributed in environment and food, water, and air everywhere contain this element. In addition to the abundant natural sources of B, there are a large number of industrial and agricultural sources of B to the soil, water, and air. In this regard, anthropogenic influences on B releases into the environment are predominately via irrigation water, although the element often enters the ecosystem as wastewater,

fertilizer, herbicide, combustion product, and waste from mining or processing industry [93]. In contrast to organic pollutants the non-biodegradable nature of B, as all other chemical elements, is the prime reason for its prolonged persistence in the environment. Due to its non-biodegradable nature and continuous use, B concentration accumulates in the environment with increasing hazards [93]. From the polluted environment B is subsequently introduced into the food chain [81].

B is an important product in the world industry. For example, the world production of B in 2013 was estimated to be about 3.5 million metric tons [94]. The world's largest producer is Turkey. Other countries as Chile, Argentina, Russia, Peru, China, Bolivia, and Kazakhstan continue to increase this metal production [83]. Since the use of B is linked to the rapidly developing modern technologies, we can conclude that the need of industry in this metal increased for decades and would for continue to increase in the future. Age-dependent increase of B mass fractions in the 'normal' prostate tissue, which was indicated in the present review, indirectly confirm this conclusion. Elevated B level is a poisonous factor affecting every organ in the body and the prostate gland is not the exclusion.

Thus, according our study for not polluted areas no one influencing factor could explain the variability of published means for prostatic B levels from  $\leq 0.100$  mg/kg to 1.9 mg/kg of wet tissue. Moreover, prostate tissue B contents showed large variations among individuals (values  $\pm$ SD for means in Table 1), but sources of the variation remain unknown. It is, therefore, reasonable to assume from data of our study that inaccuracy of analytical technologies employed caused so great variability of published means for prostatic B levels. This conclusion was supported the fact that the Certified Reference Materials for quality control of results were not used in old studies.

There are some limitations in our study, which need to be taken into consideration when interpreting the results of this review. The sample size of each study was sometimes relatively small (from 1 to 65), and a total of 1075 normal controls were investigated from all 24 studies. As such, it is hard to draw definite conclusions about the reference value of the B content in "normal" prostate as well as about the clinical value of the B levels in "normal" prostates as a biomarker.

## Conclusion

The present study is a comprehensive study regarding the determination of B content in "normal" human prostates. With this knowledge B levels, may then be considered as a biomarker for the recognition of prostate disorders. The study has demonstrated that level of B in "normal" prostates depends on many factors such as age, dietary B intake, and others. Because of the uncertainties we have outlined, we recommend other studies on B content in "normal" human prostate with the strong quality control of results be performed.

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