

BARIUM CONTENT OF THE NORMAL HUMAN PROSTATE: A REVIEW

ABSTRACT

The knowledge concerning etiology and pathogenesis of most prostatic malfunction and pathologies is very limited. In spite of advances in medicine, the differential diagnosis of benign hypertrophic and cancerous prostate has steadily increased in complexity and controversy. A proposal has been made that prostatic barium (Ba) level may aid in resolving these issues for prostate disorders and especially as an indicator of prostate cancer risk. As a result in many studies the normal prostatic Ba measurements have been made. In present review we analyze data published concerning Baprostatic levels in healthy persons. In all 2194 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 Ba content of normal prostates was evaluated. From the articles examined, 20 were selected for the objective analysis of data from their 1049 healthy subjects. Prostatic Be contents (on a wet mass basis) spanned the interval from 0.021 mg/kg to 222 mg/kg with 0.26 mg/kg as the median of their means. The data encompassed a wide range of values and the sample was small, hence it is advisable that further studies with strong quality control of results be performed.

Keywords: Barium; 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 barium(Ba), can play a significant role in etiology of PCa [16-21]. Furthermore, it was demonstrated that the changes of some TE levels and Zn/Ba ratios in prostate tissue can be useful as biomarkers [21-28].

For the first time low levels of Ba in human prostatic tissue (0.05 mg/kg of wet tissue) was indicated in studies published almost 63 years ago [29]. This finding allowed conclude that the prostate can accumulate Be, because the level of metal in glands was five times higher than in liver (0.01 mg/kg of wet tissue) and almost two orders of magnitude higher the blood level (0.0005 mg/L) of Reference Man [30]. Moreover, recent experimental and epidemiological results identified that Ba should be considered as genotoxic carcinogens [31-33]. These findings promoted more extensive considerations of the Ba 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 Ba, 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 [34-36]. In this context, until now there are no data on any biological function of Ba in organisms, but a lot of publications testify to adverse health effects in different organs or tissues of exposure to this metal and its compounds [37-40]. However, it still remains unclear what precise mechanism is responsible for Ba genotoxicity [31,32].

By now, a few publications have reported the level of Ba content in tissue of “normal” and affected glands. However, subsequent research works has been considered necessary to provide a practical reference data of Ba contents in prostate norm and disorders, because the findings of various investigations indicate some discrepancies.

The present study addresses the importance of Ba contents in prostatic tissue as a biomarker of the

gland's condition. Therefore, we systematically reviewed all the available relevant literature and performed a statistical analysis of Balevel in tissue of "normal" glands, which may provide valuable insight into the etiology and diagnosis of prostate diseases.

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, the Cochrane Library, Web of Science and ELSEVIER-EMBASE databases, as well as from the personal archive of the author collected between 1966 to 2020, using the key words: prostatic trace elements, prostatic Bacontent, prostatic tissue, and their combinations. For example, the search terms for Bacontent were: "Bamass fraction", "Bacontent", "Balevel", "prostatic tissue Ba" and "Baof prostatic tissue". The language of the paper 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 publications were examined as further search tools. Relevant studies noted for the each selected article were also evaluated for inclusion.

Eligibility criteria

Inclusion criteria

Only articles with quantitative results of Baprostatic content were accepted for further evaluation. Publications were included if the control groups were healthy men with no history or evidence of urological or other andrological disease and Bacontents were measured in samples of prostatic tissue.

Exclusion criteria

Articles were excluded if they were case reports. Studies involving persons that were Baoccupational exposed, as well as subjects from Bacontaminated area were also excluded.

Data extraction

A standard extraction of results was applied, and the following available variables were extracted from each article: method of Bameasurement, number and ages of healthy subjects, sample preparation, mean and median of Bacontent, standard deviations of mean, and range of Balevels. Abstracts and complete papers 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 Bacontents in prostatic tissue. The papers were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of Balevels. The objective analysis was performed on results from the 20 articles, with 1049 persons.

RESULTS

Information about Bacontents in prostatic tissue in different prostatic diseases is of obvious interest, not only to understand the etiology and pathogenesis of prostatic disorders more profoundly, but also for their diagnosis, particularly for PCa diagnosis and PCa risk prognosis [27,28,34]. Thus, it dictates a need for reliable values of the Bacontents in the prostatic tissue of apparently healthy subjects, ranging from young adult men to elderly persons.

Possible articles relevant to the keywords were retrieved and screened. A total of 2194 papers were primarily obtained, of which 2174 irrelevant publications were excluded. Thus, 20 articles were ultimately selected according to eligibility criteria that determined Balevels in tissue of normal prostates (Table 1) and these 20 studies [8,12,13,29,41-56] comprised the material on which the review was based. A number of values for Bacontents were not expressed on a wet mass basis by the authors of the cited references. However, we calculated these contents using the medians of published data for water – 83% [57-60] and ash – 1% (on a wet mass basis) in normal prostates of adult males [42,59,61,62].

Table 1 summarizes general results from the 20 publications. The retrieved studies involved 1049 persons. The ages of men were available for 19 papers and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 19 articles.

Most of studies determined Ba levels by destructive (require high temperature drying, ashing, or acid

digestion of tissue samples) analytical methods (Table 1): one using radiochemical neutron activation analysis (RNAA), one – X-ray fluorescence analysis (XRF), two– atomic emission spectrometry (AES), and fourteen – inductively coupled plasma atomic emission spectrometry (ICP-AES). One study tried to detect Ba level in intact prostatic tissue samples by nondestructive analytical method, such as instrumental neutron activation analysis (INAA).

Figure 1 illustrates the data set of Ba determinations in 20 studies during the period from 1958 to 2020.

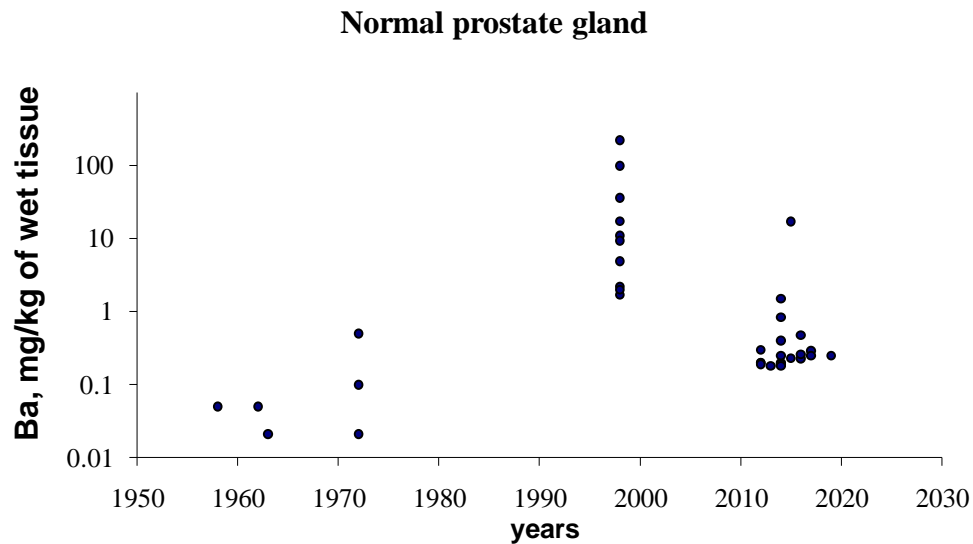


Figure 1: Data set of Ba content in 20 studies published during the period from 1958 to 2020.

Table 1: Reference data of Ba mass fractions (mg/kg wet tissue) in “normal” human prostatic tissue

Reference	Method	n	Age range years	Sample preparation	Ba	
					M±SD	Range
Sowden 1958 [29]	RNAA	8	Adult	D, A	0.05	-
Zakutinsky et al. 1962 [41]	-	-	-	-	0.05	-
Tipton et al. 1963 [42]	AES	50	Adult	D, A	0.021	Max 0.042
Forssen 1972 [43]	XRF	12	Adult	A, AD	<0.1-0.5	<0.1-0.5
Schroeder et al. 1972 [44]	AES	198	Adult	D, A	0.021	-
Jaritz et al. 1998 [45]	ICP-AES	4	<1	D, A, AD	222±251	-
		9	1-3	D, A, AD	99±120	-
		5	4-10	D, A, AD	99±60	-
		8	11-20	D, A, AD	36±39	-
		10	21-30	D, A, AD	17.3±13.9	-
		5	31-40	D, A, AD	10.9±6.6	-
		7	41-50	D, A, AD	1.7±2.7	-
		6	51-60	D, A, AD	4.9±4.6	-
		10	61-70	D, A, AD	2.2±3.9	-
		5	71-80	D, A, AD	2.0±3.6	-
Zaichick et al. 2012 [46]	ICP-AES	64	13-60	AD	0.20±0.12	0.034-0.615
		9	13-20	AD	0.30±0.48	-
		28	21-40	AD	0.20±0.14	-
		27	41-60	AD	0.19±0.12	-
Zaichick et al. 2013 [8]	ICP-AES	16	20-30	AD	0.18±0.12	-
Zaichick et al. 2014 [47]	ICP-AES	28	21-40	AD	0.20±0.11	0.070-0.440
		27	41-60	AD	0.19±0.10	0.034-0.410
		10	61-87	AD	0.40±0.22	0.105-0.736

Zaichick et al. 2014 [12]	ICP-AES	50	0-30	AD	0.84±1.31	-
		29	0-13	AD	1.5±1.7	-
		21	14-30	AD	0.25±0.22	-
Zaichick et al. 2014 [13]	ICP-AES	16	20-30	AD	0.18±0.12	-
Zaichick et al. 2015 [48]	INAA	32	44-87	Intact	<17	-
Zaichick 2015 [49]	ICP-AES	65	21-87	AD	0.23±0.15	-
Zaichick et al. 2016 [50]	ICP-AES	28	21-40	AD	0.229±0.037	-
		27	41-60	AD	0.229±0.028	-
		10	61-87	AD	0.475±0.095	-
Zaichick et al. 2016 [51]	ICP-AES	37	41-87	AD	0.26±0.17	0.065-0.736
Zaichick et al. 2016 [52]	ICP-AES	32	44-87	AD	0.26±0.17	0.065-0.736
Zaichick et al. 2016 [53]	ICP-AES	37	41-87	AD	0.26±0.17	0.065-0.736
Zaichick et al. 2017 [54]	ICP-AES	37	41-87	AD	0.290±0.170	0.0510-0.862
Zaichick 2017 [55]	ICP-AES	37	41-87	AD	0.25±0.17	0.034-0.736
Zaichick et al. 2019 [56]	ICP-AES	37	41-87	AD	0.25±0.17	0.034-0.736
Median of means					0.26	
Range of means (M_{\min} - M_{\max}),					0.021 – 222	
Ratio M_{\max}/M_{\min}					(222/0.021) = 10571	
All references					20	

M – arithmetic mean, SD – standard deviation of mean,

RNAA – radiochemical neutron activation analysis, AES–atomic emission spectrometry, XRF – X-ray fluorescence analysis, ICP-AES – inductively coupled plasma atomic emission spectrometry, INAA – instrumental neutron activation analysis,

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

DISCUSSION

The range of means of Ba contents reported in the literature for “normal” prostate varies widely from 0.021 mg/kg [42] to 222mg/kg [45] with median of means 0.26 mg/kg of wet tissue (Table 1). This variability of reported means can be explained by a dependence of Ba mass fraction on many factors, including analytical method imperfections, differences in “normal” prostate definitions, possible non-homogeneous distribution of Ba 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 articles. 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. In some studies whole glands were used for the investigation while in others the Ba content was measured in pieces of the prostate. Thus, the very short list of published data not allowed us to estimate the effect of all these factors on Ba mass fraction in “normal” prostate.

Analytical method

The data set of Ba mass fractions in “normal” prostate (Figure 1) showed that an improvement of analytical techniques during last almost 60 years impacted significantly on reported results. In our opinion, the leading cause of inter-observer variability was an insufficient sensitivity of analytical methods and a lack of quality control of result in old study published in 50s-70s of the past century [34].

In most of reported studies destructive analytical technologies were applied. These technologies require high temperature drying, ashing, or acid digestion of tissue samples. There is evidence that use of such kind of processing causes some quantities of TEs to be lost [34,63,64]. On the other hand, the Ba content of chemicals used for tissue decomposition can contaminate the prostate samples. Thus, when using decomposition 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 acid digestion of the sample, which require addition of some chemicals. It is possible to avoid these problems by utilizing non-destructive methods, but up to now there are no analytical techniques which allow quantify Ba level in “normal” prostate without sample decomposition. It is, therefore, logically to conclude that the quality control of results is very significant factor for using the Ba level in prostatic tissue as biomarkers.

Age

In a few studies a significant changes in Ba content with increasing of age was shown by the comparison of different age groups or the Pearson's coefficient of correlation between age and Ba content in prostate tissue [12,45-47,50]. The most detailed investigations of age-dependence of prostatic Ba were done by Jaritz et al. [45]. For example, a strongly pronounced tendency for an age-related decrease of Ba mass fraction was observed in the prostate for the first to fourth decades [45]. In fifth and sixth decades Ba level does not changes and to old age begins to increase. In prostates of seniors, the mean Ba mass fraction can be 2-3 times greater than that in the prostates of 40-60 year old males [45,50]. Thus, the accumulated information, studied by us from reported data, allowed a conclusion that there is a significant increase in Ba mass fraction in “normal” prostate from age 61 years to the nine decades.

Androgen-independence of prostatic Ba levels

There was not found a meaningful increase of the mean of prostatic Ba content in the group of post-pubertal teenagers together with young adults in comparison with the group of teenagers before puberty [12,45]. These findings allowed us to suppose that the Ba mass fraction in “normal” prostates does not depend on the level of androgens, and vice versa. However, studies on the association between the Ba level in “normal” prostates and the concentration of androgens in blood were not found.

Ba intake

The general population can be exposed to low levels of Ba primarily through consumption of food (70-80%), ingestion of drinking water (approximately 20%), and inhalation of ambient air [37,38,65,66]. In geographic areas with elevated Ba levels in water, the percent contribution of drinking water exposure may be higher than 20% [65,66]. One may also be exposed to Ba through skin contact, with some plastics and rubber products, some sealants and adhesives, and other Ba-contained things. Ba exposures were also reported as a result of smoking (active and passive), because Ba is a chemical component, occurs naturally in tobacco and may be inhaled from cigarette smoke [67]. Another source of exposure to Ba may be using rat poison [68].

Ba is considered as elements with a high toxic potency for human and animal organisms. Moreover, Ba is regarded as a latent health hazard with potential risk of toxicity in humans within areas of "natural" contamination by this element [37-39]. In order to prevent Ba poisoning, its content must not exceed the safe limits for food, drinking water, and air.

In a number of dietary studies, published in the second part of 20th century, the average intake of Ba ranged from 0.18 to 1.77 mg/day [65]. This is equivalent to 0.0025-0.025 mg/kg bw/day, assuming a 70 kg reference adult body weight (bw). In 1998 the U.S. Environmental Protection Agency (US EPA) developed an intake reference dose (RfD) of 0.07 mg/kg bw per day or 0.62–1.12 mg/day [69,70]. In 2001 the World Health Organization (WHO) estimated a tolerable intake of 0.02 mg/kg bw per day, using an uncertainty factor of 10 to account for some data base deficiencies and potential differences between adults and children [65]. Some later the oral US EPA RfD for Ba 0.07 mg/kg bw/day was revised to 0.66 mg/kg bw/day or in total, assuming a 70 kg reference adult body weight, 46 mg/day [38,71]. These reassessment values are nearly an order of magnitude higher than previous ones. However, the most recent and updated US EPA's estimate places the RfD for Ba at 0.2 mg/kg bw/day for the general adult population [38]. In studies performed in the different countries during the last ten years the means of dietary Ba exposure ranged from 0.006 to 0.045 mg/kg bw/day, but RfD US EPA 0.07 mg/kg bw/day or RfD WHO 0.02 mg/kg bw/day were used for the hazard characterisation of obtained results [70,72-76].

Ba content in food varies very widely. The reported mass fractions ranged from 0.0001 mg/kg in bottled water [76] to 4000 mg/kg in Brazil nuts [38,77], however, on average, most foods contain Ba in level less than 1-2 mg/kg [38,70,72-76]. The major dietary sources of Ba are bread, cereals, legumes, potatoes, vegetables, fruits, milk, mushrooms, seafood, oilseeds, freshwater fish, salt, chocolate, nuts,

different condiments and flavourings [38,70,72-78]. Ba contents in food products depend on this metal level in soil [65,79]. The background level of Ba in soils is considered to range from 100 to 3000 mg/kg, with an average of 500 mg/kg [65]. There are natural geochemical provinces with anomalous high levels of Ba in soils [80] and areas with mainly anthropogenic sources of Ba contamination [65]. Concentration of Ba in waters of different types variate very widely from 0.0001 mg/L in bottled water to 20 mg/L in water derived from wells that access deep rock formations containing Ba bearing minerals [38,76]. Ba concentrations of 6 mg/L and 7–15 mg/L have been measured in seawater and fresh water, respectively [65]. Ba concentrations in drinking-water in Canada, Netherlands, USA, Sweden, Norway, Italy (Tuscany region), Estonia, New Zealand (bottled water) and Iran (Zahedan city) were reported to be 0.018 mg/L (median), <0.05 mg/L (83% samples), <0.10 mg/L (94% samples), 0.001-0.020 mg/L (range), 0.009 mg/L (median), 0.70-1.16 mg/L (range), 0.07-6.37 mg/L (range), <0.0001 mg/L (detection limit) and 0.001-0.026 mg/L, respectively [38,66,81]. In accord with WHO data the total range of average daily Ba consumption through drinking water varies from 0.002 to 1.20 mg/day [65,66].

US EPA drinking water standard is 2.0 mg/L [38]. WHO health-based guideline of 0.7 mg/L was derived for Ba in drinking-water in 2004 [66] and confirmed in the 4th edition of the guidelines revised in 2011. However, by now, there are studies showed toxicity of Ba at low concentrations than 0.7 mg/L [32,82].

The data of Ba in air are not well documented and the reported results are contradictory. Due to the paucity of data on the Ba concentration in ambient air, it is difficult to estimate the intake from this source. In the USA, Ba concentrations in ambient air ranged from <0.005 to 1.5 mg/m³ and rarely exceed 0.05 mg/m³ [65]. In recent study in UK the average Ba concentration in ambient air was 0.00000633 mg/m³ and ranged from levels below the detection limit of 0.00000018 to 0.0000399 mg/m³ [83]. In the handbook published in 2017 reported that the air most people breathe contains less than 0.0015 parts of Ba per billion parts (ppb) of air [84]. This mass fraction value equals Ba concentration 0.0012 mg/m³ because the air relative density is 1,225 kg/m³.

Ba concentration in air can be traced from atmospheric deposition. In 1975 was reported that Ba content was estimated in dust fall and household dust samples obtained in three communities in New York City, USA. Ba mean mass fractions in dust fall and household dust were found to be 137 g/kg and 20 g/kg, respectively [65]. Till now, there are no legislative limits for Ba concentration in ambient air [83].

Other potential sources of Ba exposure include active and passive tobacco smoking. Ba presents in cigarette smoke and poses health threats to the life of smokers due to direct inhalation and at the same time increases health risks to non-smokers present in the vicinity of smokers. Range of this metal mass fraction reported in cigarette tobacco produced in USA was estimated to be 40.7–75.1 mg/kg tobacco [67].

Ba compounds were historically used in the treatment of many diseases [37]. Nowadays, only a gastrointestinal X-ray examination with Ba sulfate swallow is a widely used investigative technique all over the world. Generally regarded as a safe examination procedure in clinical practice, rare cases of aspiration of Ba sulfate during gastrointestinal X-ray examination or contamination of Ba contrast solution have been observed that has led to complication and even death [85,86].

All Ba compounds, with only Ba sulfate exclusion, are very toxic. Among them, Ba carbonate (BaCO₃) and Ba chloride (BaCl₂), the commonly used pesticides (rodenticides), are the highly toxic substances [68]. For example, for humans the lowest lethal acute oral dose of BaCl₂ is 11.4 mg/kg bw [87]. In spite of Ba toxicity had been recognized 230 years ago, it is known that Ba compounds have caused many accidental, occupational and therapeutic poisonings in the entire world [37,38], but suicide by ingestion of Ba compounds is exceptionally rare [87-89].

Aside from the naturally occurring sources, exposure of people to Ba is limited to inhalation and dermal contact during occupational processes. Most of the exposures occur in steel, semiconductor, and medical industries, as well as in the manufacturing operations during production of drilling muds, paints, bricks, plastics, steel, aluminum, textile, leather, sugar, pigments, glass, rubber, ceramics, paper, rodenticides, pharmaceuticals and cosmetics [38,65,90].

Ba content in body fluids, tissues and organs

The total body burden of Ba for adults is about 22 mg [91]. Almost 90% of this amount (about 20 mg) is located in the skeletal system, which is the major storage pool for long-term Ba accumulation

[91]. Information on Ba content in human organs and tissues is very limited. Ba mass fraction in bone and teeth ranged from 0.5 to 10 mg/kg [91,92] and from 0.1 to 3 mg/kg, respectively [38]. Among soft tissues of human body principle organs of Ba retention are heart, lung, kidney, and liver with the content range 0.01–1 mg/kg of wet tissue for each organ [38]. Reference values of Ba mass fraction in bone, lung, ocular tissue and skin are 2.0 mg/kg, 0.33 mg/kg, 0.16 mg/kg and 0.05 mg/kg, respectively [89]. Reported Ba level in whole blood of healthy persons under normal exposure conditions are 0.030–0.200 mg/L [93] are almost two orders of magnitude higher than data for Reference Man (0.0005–0.0025 mg/L) [30]. Reference values of Ba in serum have been reported from 0.001 to 0.060 mg/L [89]. The reference mean of Ba urinary level is 0.0035 mg/L (ranges 0.001–0.007 mg/L) [89] and in the USA investigation, the 95th percentile of urinary Ba levels 0.0068 mg/L reported for children, adolescent, or adults (males and females) was inside of this range [38].

Because the median of prostatic Ba content means obtained in the present review (0.26 mg/kg of wet tissue) almost equals the metal level in principle organs of Ba retention among soft tissue (heart, lung, kidney, and liver) and two order of magnitude higher the reference blood Ba level, we can conclude that the prostate gland is also a target organ for Ba.

Ba, as all other natural chemical elements of the Periodic System, presents in all components and objects of biosphere [34,94,95]. During the long evolutionary period intakes of Ba in organisms were more or less stable and organisms were adopted for such environmental conditions. As was mentioned above, until now there are no data on any biological function of Ba in organisms. However, inordinately high content of Ba was found in an iris (about 10% of ash) [91]. Such high Ba accumulation means that eyes need in this element.

The situation with Ba presence in biosphere began to change after the industrial revolution, particularly, over the last 100 years. Ba compounds and Ba-contained minerals and products are used in petroleum, steel, semiconductors, plastic, ceramic, glass, rubber, bricks, paper, textile, sugar and other industries, as well as in manufacturing rodenticides, pharmaceuticals, cosmetics, primers, signal flares, welding fluxes, and a variety of other products [38,65]. Thus, inorganic Ba is ubiquitously distributed in environment and food, water, and air everywhere contain this element. In addition to the abundant natural sources of Ba, there are a large number of industrial producers of Ba to the soil (through atmospheric emissions originating from residues from coal, oil, and gas combustion, power plants, oil industry, phosphate minerals in agricultural fertilizers and insecticides, waste of aluminum, leather, textile, paper, sugar, pigments, and other productions which need in refining, urban refuse, mine tailings, smelter slag, hospital waste from using X-ray contrast medium, etc.), water (through using drilling mud for oil and gas drilling, through irrigation and industrial liquid waste, and wastewater sludge application), and air (Ba may be released from coal, oil, gas and waste combustion, diesel engine exhaust, power plants activity, emissions may also result from mining, refining, or processing of Ba minerals and manufacture of Ba-contained products, etc.) contamination [38,65]. From the polluted environment this metal is subsequently introduced into the food chain and drinking water. As was mentioned above, for the general population, the food and drinking water are the main sources of exposure to Ba [38,65,66].

Ba is an important product in the world industry. For example, the world production of barite (Ba sulfate, BaSO_4) in 2008 was estimated to be about 9 million tons [96]. The world's largest producers are China and India. Other countries as Kazakhstan, Mexico, Morocco, and Vietnam continue to increase this mineral production [96]. Within US, barite is produced mainly from mines in Nevada [96]. During the last 40 years industrial and medicinal use of Ba increased in two times [38]. Since the use of Ba is linked to the rapidly developing modern technologies, we can suppose that the need of industry in this metal would continue to increase in the future.

As was mentioned above, a chronic ingestion or inhalation of Ba low dose by humans can cause a variety of disorders. Acutely Ba poisoning causes such disorders as cardiac and/or renal failure, pulmonary edema, respiratory paralysis, gastric and intestinal hemorrhages, pneumonitis, sepsis, and even death [38,97]. Chronically, it results in vomiting, diarrhea, cardiac arrhythmia, liver and kidney failure, disorders of nervous system (i.e., tremors, hearing loss, anxiety), dyspnea, and a shorter life span [38,39,65,66]. Furthermore, as was shown in the experimental and epidemiological studies, Ba and its compounds are cytotoxic and genotoxic [31–33]. Moreover, an association between potential risk of duct carcinoma and Ba level in drinking water was observed using the Brisbane Australia

breast cancer cluster [33] However, precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined [21,31-33].

Thus, for unpolluted areas, according our systematic review, there are no information could explain the variability of published means for “normal” prostatic Ba content from 0.021 mg/kg to 222 mg/kg of wet tissue. Moreover, prostate tissue Ba contents showed large variations among individuals, but reasons of the variation remain unknown. It is, therefore, reasonable to assume from data of our study that inaccuracy of analytical techniques employed caused so great variability of published means for prostatic Ba contents. This conclusion was supported the fact that the Certified Reference Materials for quality control of results were not used in old studies [29,41-44].

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 4 to 198), and a total of 1049 “normal” prostate glands were analyzed from all 20 studies. As such, it is hard to draw definite conclusions about the reference value of the Ba level in “normal” prostate as well as about the clinical value of the Ba content in “normal” prostates as a biomarker.

CONCLUSION

The present systematic review is a comprehensive study regarding the determination of Ba content in “normal” human prostates. With this knowledge Ba levels may then be considered as a biomarker for the recognition of prostate disorders and primary such as PCa. The review has demonstrated that content of Ba in “normal” prostates depends on many unknown factors. Because of the uncertainties we have outlined, we recommend other primary studies with the strong quality control of results be performed.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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