**Review Article**

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**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 tissuecan 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, recentexperimental and epidemiological results identified that Ba should be considered as genotoxic carcinogens [31-33]. These findings promoted more extensive considerations of the Bacontent of prostatic tissue of healthypersons, 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 Bain organisms, but a lot of publications testify to adverse health effects in different organs or tissuesof exposure to this metal and its compounds [37-40]. However, it still remains unclear what precise mechanism is responsible for Bagenotoxicity [31,32].

By now, a few publications have reported the level of Bacontent 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”, “Ba level”, “prostatic tissue Ba” and “Ba of 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 detectBa 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****prepara-****tion** | **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 | - |
|  |  | 8 | >80 | D, A, AD | 9.3±4.3 | - |
| 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 (Mmin - Mmax),  | 0.021 – 222 |
| Ratio Mmax/Mmin | (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 Bacontents 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 Bamass fraction on many factors, including analytical method imperfections, differences in “normal” prostate definitions, possible non-homogeneous distribution of Balevels 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 Bamass 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 technologieswere applied. Thesetechnologies requirehigh temperature drying, ashing, or acid digestion of tissue samples. There is evidence that use of such lind of processing causes some quantities of TEs to be lost [34,63,64]. On the other hand, the Bacontent 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 Balevel 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 Balevel in prostatic tissue as biomarkers.

**Age**

In a few studies a significant changes in Bacontent with increasing of age was shown by the comparison of different age groups or the Pearson’s coefficient of correlation between age and Bacontent in prostate tissue [12,45-47,50]. The most detailed investigations of age-dependence of prostatic Bawere done by Jaritz et al. [45]. For example, a strongly pronounced tendency for an age-related decrease of Bamass 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 Bamass fraction can be2-3 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 significantincrease in Bamass fraction in “normal” prostate from age 61 years to the nine decades.

**Androgen-independence of prostatic Balevels**

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 Bathrough skin contact, with some plastics and rubber products, some sealants and adhesives, and other Ba-contained things. Baexposures were also reported as a result of smoking (active and passive), because Baas 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].

Bais considered as elements with a high toxic potency for human and animal organisms. Moreover, Bais 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 Bapoisoning, 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 of20th 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/kgbw/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 EPARfD for Ba 0.07 mg/kgbw/day was revised to 0.66 mg/kgbw/day or in total, assuming a 70 kg reference adult body weight, 46mg/day [38,71]. These reassessment valuesare 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/kgbw/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/kgbw/day,butRfD US EPA 0.07 mg/kgbw/day or RfD WHO 0.02 mg/kgbw/day were used for the hazard characterisationof obtained results [70,72-76].

Ba content in foot varies very widely.The reported mass fractions ranged from 0.0001mg/kg in bottled water [76] to 4000 mg/kg in Brazil nuts [38,77], however, on average, most foods contain Ba in level less than1-2 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]. Bacontents 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 0.0001mg/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 be0.018 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 0.000000018 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 sulfateexclusion, are very toxic. Among them, Ba carbonate (BaCO3) and Ba chloride (BaCl2), the commonly used pesticides (rodenticides),arethe 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 compoundshave 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 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 Bafor 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 conditionsare 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 insideof 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 evolutional 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 contentof 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 otherindustries, as well as in manufacturingrodenticides, pharmaceutics, cosmetics, primers, signal flares, welding fluxes, and a variety of other products[38,65].Thus, inorganic Bais 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 Bato 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 productionswhich 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, BaSO4) 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 Vietnamcontinue to increase this mineralproduction [96]. Within US, barite is produced mainly from mines in Nevada [96]. During the last 40 yearsindustrial and medicinal use of Ba increased in two times [38]. Since the use of Bais 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 Bacontents 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.

**References**

1. Nickel JC. Prostatitis. Can UrolAssoc J2011; 5: 306–315.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202001/>

1. [Lim](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lim%20KB%5BAuthor%5D&cauthor=true&cauthor_uid=29264223) KB. Epidemiology of clinical benign prostatic hyperplasia. [Asian JUrol](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5717991/) 2017; 4: 148–151.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5717991/>

1. Rawla P. Epidemiology of Prostate Cancer.[World JOncol](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6497009/) 2019; 10(2): 63–89.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6497009/>

1. Avisyn AP, Dunchik VN, Zhavoronkov AA, *et al*. Histological structure of the prostate and content of zinc in it during various age period. Archiv Anatomy, Gistology, and Ebriology (Leningrad) 1981; 81(11): 76–83.
2. Zaichick V. INAA and EDXRF applications in the agedynamicsassessment of Zncontent and distribution in the normal human prostate. J RadioanalNucl Chem 2004; 262: 229–234.

[https://link.springer.com/article/10.1023/B:JRNC.0000040879.45030.4f](https://link.springer.com/article/10.1023/B%3AJRNC.0000040879.45030.4f)

1. Zaichick V, Zaichick S. The effect of age on Br, Ca, Cl, K, Mg, Mn, and Na mass fraction in pediatric and young adult prostate glands investigated by neutron activation analysis. J ApplRadiatIsot 2013; 82: 145–151.

<https://www.ncbi.nlm.nih.gov/pubmed/23994740>

1. Zaichick V, Zaichick S. INAA application in the assessment of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fraction in pediatric and young adult prostate glands. J RadioanalNucl Chem 2013; 298:1559–1566.

<https://www.researchgate.net/publication/251091633_INAA_application_in_the_age_dynamics_assessment_of_Br_Ca_Cl_K_Mg_Mn_and_Na_content_in_the_normal_human_prostate>

1. Zaichick V, Zaichick S. NAA-SLR and ICP-AES application in the assessment of mass fraction of 19 chemical elements in pediatric and young adult prostate glands. Biol Trace Elem Res 2013; 156: 357–366.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Biological+Trace+Element+Research+156+(2013)%3A357-366>

1. Zaichick V, Zaichick S. Use of neutron activation analysis and inductively coupled plasma mass spectrometry for the determination of trace elements in pediatric and young adult prostate. Am J Analyt Chem2013; 4: 696–706.

<https://www.scirp.org/journal/paperinformation.aspx?paperid=40340>

1. Zaichick V, Zaichick S. Relations of bromine, iron, rubidium, strontium, and zinc content to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. Biol Trace Elem Res 2014; 157: 195–204.

<https://www.ncbi.nlm.nih.gov/pubmed/24435825>

1. Zaichick V, Zaichick S. Relations of the neutron activation analysis data to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. Advances in Biomedical Science and Engineering 2014; 1: 26–42.
2. Zaichick V, Zaichick S. Relations of the Al, B, Ba, Br, Ca, Cl, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, and Zn mass fractions to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. BioMetals2014; 27: 333–348.

<https://www.ncbi.nlm.nih.gov/pubmed/24554283>

1. Zaichick V, Zaichick S. The distribution of 54 trace elements including zinc in pediatric and nonhyperplastic young adult prostate gland tissues. Journal of Clinical and Laboratory Investigation Updates 2014; 2(1): 1–15.

https://www.jpmpress.com/wp-content/uploads/2018/05/JCLIUV2N1A1-Zaichick.pdf

1. Zaichick V, Zaichick S. Androgen-dependent chemical elements of prostate gland. AndrolGynecol: Curr Res2014; 2: 2.

<https://www.scitechnol.com/androgendependent-chemical-elements-of-prostate-gland-G1af.php?article_id=1902>

1. ZaichickV, Zaichick S. Differences and relationships betweenmorphometric parameters and zinc content innonhyperplastic and hyperplastic prostate glands.Br J Med & Med Res2015; 8: 692–706.

<http://www.sciencedomain.org/index.php?/abstract/9328>

1. Schwartz MK. Role of trace elements in cancer. Cancer Res1975; 35: 3481–3487.

<https://pubmed.ncbi.nlm.nih.gov/1104155/>

1. Zaichick V., Zaichick S. Role of zinc in prostate cancerogenesis. In: Mengen und Spurenelemente. 19. Arbeitstagung. Jena: Friedrich-Schiller-Universitat;1999.p. 104–115.

<https://www.tib.eu/en/search/id/BLCP%3ACN032910889/Role-of-zinc-in-prostate-cancerogenesis/>

1. Zaichick V., Zaichick S. Wynchank S. Intracellular zinc excess as one of the main factors in the etiology of prostate cancer. J Anal Oncol 2016; 5: 124–131.

<https://elibrary.ru/item.asp?id=27569119>

1. Zaichick V, Zaichick S, Rossmann M. Intracellular calcium excess as one of the main factors in the etiology of prostate cancer. AIMS MolSci 2016; 3: 635–647.

<https://www.aimspress.com/article/doi/10.3934/molsci.2016.4.635>

1. Fukuda H, Ebara M, Yamada H, *et al*. Trace elements and cancer. JMAJ 2004; 47(8): 391–395.

<https://www.med.or.jp/english/pdf/2004_08/391_395.pdf>

1. Chen QY, DesMarais T, Costa M. Metals and Mechanisms of Carcinogenesis.[Annu Rev PharmacolToxicol 2019; 59: 537–554.](https://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&retmode=ref&cmd=prlinks&id=30625284)

<https://pubmed.ncbi.nlm.nih.gov/30625284/>

1. Dunchik V, Zherbin E, Zaichick V, *et al*. Method for differential diagnostics of prostate malignant and benign tumours. Russian patent (Author’s Certificate No 764660, priority of invention 27.10.1977). Discoveries, Inventions, Commercial Models, Trade Marks 1980; 35: 13.
2. Zaichick V, Sviridova T, Zaichick S. Zinc in the human prostate gland: normal, hyperplastic and cancerous. IntUrolNephrol 1997; 29: 565–574.

<https://pubmed.ncbi.nlm.nih.gov/9413764/>

1. Zaichick V, Sviridova T, Zaichick S. Zinc in human prostate gland: normal, hyperplastic and cancerous. J RadioanalNucl Chem 1997; 217: 157–161.

<https://link.springer.com/article/10.1007/BF02034434>

1. Zaichick S, Zaichick V. Trace elements of normal, benign hypertrophic and cancerous tissues of the human prostate gland investigated by neutron activation analysis. J ApplRadiatIsot 2012; 70: 81–87.

<https://pubmed.ncbi.nlm.nih.gov/21975106/>

1. Zaichick V, Zaichick S. Ratios of selected chemical element contents in prostatic tissue as markers of malignancy. Hematol Med Oncol 2016; 1(2): 1–8.

<https://www.oatext.com/pdf/HMO-1-109.pdf>

1. Zaichick V, Zaichick S. Trace element levels in prostate gland as carcinoma’s markers. J Cancer Ther 2017; 8: 131–145.

<https://www.scirp.org/journal/paperinformation.aspx?paperid=74050>

1. Zaichick V, Zaichick S. Ratios of Zn/trace element contents in prostate gland as carcinoma’s markers. Cancer Rep Rev2017; 1(1): 1–7.

<https://oatext.com/pdf/CRR-1-105.pdf>

1. Sowden E.M. Trace elements in human tissue: 3. Strontium and barium in non-skeletal tissue. Biochem J 1958; 70(4): 712-715.

<https://pubmed.ncbi.nlm.nih.gov/13607431/>

1. Iyengar GV. Reevaluation of the trace element content in reference men. Radiat Phys Chem.1998;.51:.545–560.

<https://www.sciencedirect.com/science/article/abs/pii/S0969806X97002028>

1. Thang ND, Yajima I, Kumasaka MY, *et al*. Barium promotes anchorage-independent growth and invasion of human HaCaT keratinocytes via activation of c-SRC kinase. PLoS One 2011;6(10):e25636

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0025636>

1. Kato M, Ohgami N, Ohnuma S, *et al*. Multidisciplinary approach to assess the toxicities of arsenic and barium in drinking water. Environ Health Prev Med 2020;25(1):16.

<https://environhealthprevmed.biomedcentral.com/articles/10.1186/s12199-020-00855-8>

1. Kamlade P. Barium exposure of an invasive breast cancer cluster investigation – quantitative drinking water chemistry for carcinogen search. H2Open Journal 2019;2(1):168–183.

<https://iwaponline.com/h2open/article/2/1/168/70195/Barium-exposure-of-an-invasive-breast-cancer>

1. Zaichick V. Medical elementology as a new scientific discipline. J RadioanalNucl Chem 2006; 269: 303–309.

<https://link.springer.com/article/10.1007/s10967-006-0383-3>

1. Hunter P. A toxic brew we cannot live without. Micronutrients give insights into the interplay between geochemistry and evolutionary biology. [EMBORep](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2246629/). 2008; 9(1): 15–18.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2246629/>

1. López-Alonso M. Trace minerals and livestock: Not too much not too little. International Scholarly Research Notices 2012; 2012: Article ID 704825.

<https://www.hindawi.com/journals/isrn/2012/704825/>

1. Bhoelan BS, Stevering CH, Van der Boog ATJ, *et al*. Barium toxicity and the role of the potassium inward rectifier current. Clin Toxicol (Phila) 2014;52(6):584-593.

<https://pubmed.ncbi.nlm.nih.gov/24905573/>

1. Kravchenko J, Darrah TH, Miller RK, *et al*. A review of the health impacts of barium from natural and anthropogenic exposure. Environ Geochem Health 2014;36**:**797–814.

<https://link.springer.com/article/10.1007/s10653-014-9622-7>

1. Ohgami N, Mitsumatsu Y, Ahsan N, *et al*. Epidemiological analysis of the association between hearing and barium in humans. J Expo Sci Environ Epidemiol 2016;26(5):488-493.

<https://www.nature.com/articles/jes201562?proof=t>

1. Mohammed AT, Ismail HTH. Hematological, biochemical, and histopathological impacts of barium chloride and barium carbonate accumulation in soft tissues of male Sprague-Dawley rats.Environ SciPollut Res Int 2017;24(34):26634-26645.

<https://pubmed.ncbi.nlm.nih.gov/28956246/>

1. Zakutinsky DI, ParfyenovYuD, Selivanova LN. Data book on the radioactive isotopes toxicology. Moscow: State Publishing House of Medical Literature; 1962.
2. Tipton IH, Cook MJ. Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys 1963; 9: 103–145.

<https://journals.lww.com/health-physics/Abstract/1963/02000/Trace_Elements_in_Human_Tissue_Part_II__Adult.2.aspx>

1. Forssen A. Inorganic elements in the human body. I. Occurrence of Ba, Br, Ca, Cd, Cs, Cu, K, Mn, Ni, Sn, Sr, Y and Zn in the human body. AnnalesmedicinaeExperimentalisetBiologie (Finland) 1972; 50(3): 99-162.

<https://europepmc.org/article/med/5081903>

1. Schroeder H.A., Tipton I.H., Nason A.P. Trace metals in men: strontium and barium. J Chron Dis 1972; 25: 491-517.

<https://www.sciencedirect.com/science/article/abs/pii/0021968167900021>

1. Jaritz M, Anke M, Holzinger S. Der BariumgehaltverschiedenerOrgane von Feldhase, Wildschwein, Damhirsch, Reh, Rothirsch, Mufflon and Mensch. In: Mengen- und Spurenelemente. 18. Arbeitstagung. Jena: Friedrich-Schiller-Universität;1998. S. 467-474.
2. Zaichick V, Nosenko S, MoskvinaI. The effect of age on 12 chemical element contents in intact prostate of adult men investigated byinductively coupled plasma atomic emission spectrometry. Biol Trace Elem Res 2012; 147: 49–58.

<https://pubmed.ncbi.nlm.nih.gov/22231436/>

1. Zaichick V, Zaichick S. [Determination of trace elements in adults and geriatric prostate combining neutron activation with inductively coupled plasma atomic emission spectrometry](http://www.scipublish.com/journals/BIOC/papers/701). Open Journal of Biochemistry 2014; 1(2): 16–33.
2. Zaichick V, Zaichick S, Davydov G. Differences betweenchemical element contents in hyperplastic and nonhyperplastic prostate glands investigated by neutron activation analysis. BiolTraceElem Res 2015, 164, 25-35.

<https://pubmed.ncbi.nlm.nih.gov/25519178/>

1. Zaichick V. The variation with age of 67 Macro- and microelement contents in nonhyperplastic prostate glands of adult and elderly males investigated by nuclear analytical and related methods. Biol Trace Elem Res 2015; 168: 44–60.

<https://pubmed.ncbi.nlm.nih.gov/25940729/>

1. Zaichick V, Zaichick S. Age-related changes in concentration and histological distribution of 18 chemical elements in nonhyperplastic prostate of adults. World Journal of Pharmaceutical and Medical Research 2016; 2(4): 5-18.

<https://www.wjpmr.com/home/article_abstract/102>

1. Zaichick V, Zaichick S. The comparison between the contents and interrelationships of 17 chemical elements in normal and cancerous prostate gland. JPS Open Access 2016; 1(1): 1-10.

<https://www.longdom.org/abstract/the-comparison-between-the-contents-and-interrelationships-of-17rnchemical-elements-in-normal-and-cancerous-prostate-gla-14091.html>

1. Zaichick V, Zaichick S. Prostatic tissue level of some major and trace elements in patients with BPH. J JNephroUrol 2016; 3(1): 1-10.
2. Zaichick V, Zaichick S.Distinguishing malignant from benign prostate using content of 17 chemical elements in prostatic tissue.Integr. Cancer SciTherap2016; 3(5): 579-587.

<https://oatext.com/pdf/ICST-3-208.pdf>

1. Zaichick V, Zaichick S. Chemical element contents in normal and benign hyperplastic prostate. AnnMens Health Wellness 2017; 1(2): 1006.

<https://www.jscimedcentral.com/MensHealth/menshealth-1-1006.pdf>

1. Zaichick V. Differences between 66 Chemical Element Contents in Normal and Cancerous Prostate. J Ana Oncol2017; 6: 37-56.

<https://www.researchgate.net/publication/316633646_Differences_between_66_Chemical_Element_Contents_in_Normal_and_Cancerous_Prostate>

1. Zaichick V, Zaichick S.Comparison of 66 chemical element contents in normal and benign hyperplastic prostate. Asian J Urol 2019; 6: 275-289.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6595161/>

1. Isaacs J.T. Prostatic structure and function in relation to the etiology of prostatic cancer. The Prostate 1983; 4(4): 351–366.

<https://pubmed.ncbi.nlm.nih.gov/6866850/>

1. Leissner KM, Fielkegard B, Tisell LE. Concentration and content of zinc in human prostate. Invest Urol 1980; 18: 32–35.

<https://pubmed.ncbi.nlm.nih.gov/6157652/>

1. Woodard HQ, White DR. The composition of body tissues. Br J Radiol 1986; 59: 1209–1218.

<https://pubmed.ncbi.nlm.nih.gov/3801800/>

1. Arnold WN, Thrasher JB. Selenium concentration in the prostate. Biol Trace Elem Res 2003; 91(3): 277–280.

[https://link.springer.com/article/10.1385/BTER:91:3:277](https://link.springer.com/article/10.1385/BTER%3A91%3A3%3A277)

1. Schroeder HA, Nason AP, Tipton IH, Balassa JJ. Essential trace metals in man: Zinc. Relation to environmental cadmium. . Chron Dis 1967; 20: 179–210.

<https://www.sciencedirect.com/science/article/abs/pii/0021968167900021>

1. Saltzman BE, Gross SB, Yeager DW, Meiners BG, Gartside PS. Total body burdens and tissue concentrations of lead, cadmium, copper, zinc, and ash in 55 human cadavers. Environ Res 1990; 52: 126–145.

<https://pubmed.ncbi.nlm.nih.gov/2394204/>

1. Zaichick V. Sampling, sample storage and preparation of biomaterials for INAA in clinical medicine, occupational and environmental health. In: Harmonization of Health-Related Environmental Measurements Using Nuclear and Isotopic Techniques. Vienna: IAEA;1997. p. 123–133.

<https://inis.iaea.org/search/search.aspx?orig_q=RN:29019688>

1. Zaichick V. Losses of chemical elements in biological samples under the dry ashing process. Trace Elements in Medicine (Moscow) 2004; 5(3): 17–22.
2. WHO, World Health Organization. Barium and barium compounds.Concise International Chemical Assessment Document 33. Geneva: WHO; 2001.

<http://www.inchem.org/documents/cicads/cicads/cicad33.htm>

1. WHO, World health Organization. Barium in drinking water. WHO/SDE/WSH/03.04/76, Geneva: WHO**;** 2004.

<https://www.who.int/water_sanitation_health/water-quality/guidelines/chemicals/barium-background-jan17.pdf>

1. Pappas RS. Toxic elements in tobacco and in cigarette smoke: Inflammation and sensitization. [Metallomics 2011; 3(11): 1181–1198.](https://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&retmode=ref&cmd=prlinks&id=21799956)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542087/>

1. Chaudhary S, Aggarwal A, Avasthi R. Acute severe poisoning by barium carbonate (rat poison). Journal, Indian Academy of Clinical Medicine 2008;9(2):133-135.

<https://www.researchgate.net/publication/289187110_Acute_severe_poisoning_by_barium_carbonate_rat_poison>

1. US EPA, U.S. Environmental Protection Agency. Toxicological review of barium and compounds (CAS No. 7440-39-3).Washington, DC: US EPA; 2005.

<https://iris.epa.gov/static/pdfs/0010tr.pdf>

1. Filippini T, Tancredi S, Malagoli C, *et al*. Dietary estimated intake of trace elements: Risk assessment in an Italian population. Expo Health 2020;12**:**641–655.

<https://link.springer.com/article/10.1007/s12403-019-00324-w>

1. Dallas CE, Williams PL. Barium: rationale for a new oral reference dose. J Toxicol Environ Health B Crit Rev 2001;4(4):395-429.

<https://pubmed.ncbi.nlm.nih.gov/11695044/>

1. Turconi G, Minoia C, Ronchi A, *et al*. Dietary exposure estimates of twenty-one trace elements from a Total Diet Study carried out in Pavia, Northern Italy. Br J Nutr 2009;101(8):1200-1208.

<https://pubmed.ncbi.nlm.nih.gov/19007448/>

1. Rose M, Baxter M, Brereton N, *et al*. Dietary exposure to metals and other elements in the 2006 UK Total Diet Study and some trends over the last 30 years. Food AdditContam Part A Chem Anal Control Expo Risk Assess 2010;27(10):1380-1404.

<https://pubmed.ncbi.nlm.nih.gov/20628929/>

1. González-Weller D, Rubio C, Gutiérrez AJ, *et al*. Dietary intake of barium, bismuth, chromium, lithium, and strontium in a Spanish population (Canary Islands, Spain). Food Chem Toxicol 2013;62:856-858.

<https://pubmed.ncbi.nlm.nih.gov/24416776/>

1. Gimou M-M, Pouillot R, Charrondiere UR, *et al*. Dietary exposure and health risk assessment for 14 toxic and essential trace elements in Yaoundé: the Cameroonian total diet study. Food AdditContam Part A Chem Anal Control Expo Risk Assess 2014;31(6):1064-1080.

<https://pubmed.ncbi.nlm.nih.gov/24684161/>

1. Pearson AJ, Ashmore E. Risk assessment of antimony, barium, beryllium, boron, bromine, lithium, nickel, strontium, thallium and uranium concentrations in the New Zealand diet. Food Additives &Contaminants: Part A 2020;37(3): 451-464.

<https://www.tandfonline.com/doi/full/10.1080/19440049.2019.1704445>

1. Parekh PP, Khan AR, Torres MA, Kitto ME. Concentrations of selenium, barium, and radium in Brazil nuts. J Food Compos Anal 2008;21(4):332–335.

<https://www.researchgate.net/publication/223715605_Concentrations_of_selenium_barium_and_radium_in_Brazil_nuts>

1. Lima AMS, Santos LO, David JM, *et al*. Mineral content in mustard leaves according to the cooking method.[Food Chemistry](https://www.sciencedirect.com/science/journal/03088146) 2019; [273](https://www.sciencedirect.com/science/journal/03088146/273/supp/C)(1):172-177.

<https://www.sciencedirect.com/science/article/pii/S0308814617320046?via%3Dihub>

1. Ong GH, Yap CK, Mahmood MM, *et al*. Barium levels in soils and*Centellaasiatica.* [Trop Life Sci Res.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3799414/) 2013;24(1):55–70.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3799414/>

1. Plant JA, Breward N, Simpson PR, *et al*. Regional geochemistry and the identification of metallogenic provinces: examples from lead-zinc-barium, tin-uranium and gold deposits. [Journal of Geochemical Exploration](https://www.sciencedirect.com/science/journal/03756742) 1990;39(1-2):195-224.

<https://www.sciencedirect.com/science/article/abs/pii/037567429090074K>

1. Dashtizadeh M, Kamani H, Ashrafi SD, *et al*. Human health risk assessment of trace elements in drinking tap water in Zahedan city, Iran.J Environ Health SciEng 2019;17(2):1163-1169.

<https://pubmed.ncbi.nlm.nih.gov/32030182/>

1. Kato M, Kumasaka MY, Ohnuma S, *et al*. Comparison of barium and arsenic concentrations in well drinking water and in human body samples and a novel remediation system for these elements in well drinking water. PLoS ONE 2013;8(6):e66681.

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0066681>

1. Goddard SL, Williams KR, Robins C, *et al*. Determination of antimony and barium in UK air quality samples as indicators of non-exhaust traffic emissions. Environ Monit Assess 2019;191(11):641.

<https://pubmed.ncbi.nlm.nih.gov/31586255/>

1. Aziz HA, Ghazali MF, Hung Y-T, *et al*. Toxicity, source, and control of barium in the environment, In: [Handbook of Advanced Industrial and Hazardous Wastes Management](https://www.taylorfrancis.com/books/handbook-advanced-industrial-hazardous-wastes-management/10.1201/9781315117423?refId=56ea47e0-713f-471e-9b73-9c715397100e). 3rd ed. CRC Press; 2017.

<https://www.taylorfrancis.com/chapters/toxicity-source-control-barium-environment-hamidi-abdul-aziz-miskiah-fadzilah-ghazali-yung-tse-hung-lawrence-wang/e/10.1201/9781315117423-14>

1. Yan G-W, Deng J-F, Bhetuwal A, *et al*. A case report and literature review of barium sulphate aspiration during upper gastrointestinal examination. Medicine (Baltimore) 2017;96(47):e8821.

<https://pubmed.ncbi.nlm.nih.gov/29381987/>

1. CDC, Centers for Disease Control and Prevention. Barium toxicity after exposure to contaminated contrast solution--Goias State, Brazil, 2003. MMWR Morb Mortal Wkly Rep 2003;52(43):1047-1048.

<https://pubmed.ncbi.nlm.nih.gov/14586298/>

1. Su J-F, Le D-P, Liu C-H, *et al*. Critical care management of patients with barium poisoning: a case series.Chin Med J (Engl) 2020;133(6):724–725.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190221/>

1. Payen C, Dellinger A, Pulce C, *et al*. Intoxication by large amounts of barium nitrate overcome by early massive K supplementation and oral administration of magnesium sulphate. Hum ExpToxicol 2011;30(1):34-37.

<https://pubmed.ncbi.nlm.nih.gov/20354061/>

1. Łukasik-Głębocka M, Sommerfeld K, Hanć A, *et al*. Barium determination in gastric contents, blood and urine by inductively coupled plasma mass spectrometry in the case of oral barium chloride poisoning. JAnalToxicol 2014;38(6):380-382.

<https://pubmed.ncbi.nlm.nih.gov/24794066/>

1. Poddalgoda D, Macey K, Assad H, *et al*. Development of biomonitoring equivalents for barium in urine and plasma for interpreting human biomonitoring data. [Regulatory Toxicology and Pharmacology](https://www.sciencedirect.com/science/journal/02732300) 2017;86:303-311.

<https://www.sciencedirect.com/science/article/pii/S0273230017300818>

1. MoskalevYuI. Mineral metabolism. Moscow: Meditsina; 1985.
2. Nguyen J, Crawford D, Howarth D, *et al*. Ex vivo quantification of lanthanum and gadolinium in post-mortem human tibiae with estimated barium and iodine concentrations using K x-ray fluorescence.PhysiolMeas 2019;40(8):085006.

<https://pubmed.ncbi.nlm.nih.gov/31422953/>

1. Hung Y-M, Chung H-M. Acute self-poisoning by ingestion of cadmium and barium. Nephrology, Dialysis, Transplantation 2004; 19(5):1308–1309.

<https://pubmed.ncbi.nlm.nih.gov/15102970/>

1. Vernadsky VI. Living matter.Moscow: Nauka; 1978.
2. Zaichick V, Ermidou-Pollet S, Pollet S. Medical elementology: a new scientific discipline. Trace Elem. Electroly. 2007; 24(2): 69–74.

<https://www.researchgate.net/publication/289100419_Medical_elementology_A_new_scientific_discipline>

1. Johnson CA, Piatak NM, Miller MM. Barite (Barium), chap. D. In*:* Schulz KJ, DeYoung JH, Jr, Seal RR, II, Bradley DC, editors. Critical mineral resources of the United States—Economic and environmental geology and prospects for future supply: U.S. Geological Survey Professional Paper 1802; 2017. p. D1– D18.

<https://pubs.usgs.gov/pp/1802/d/pp1802d.pdf>

1. Nanda N, Hauser B, Heatley D, *et al*. An unwitnessed case of foreign body aspiration of barium from an unknown source. Int J PediatrOtorhinolaryngol2020;138:110355

<https://pubmed.ncbi.nlm.nih.gov/33152958/>