

# Five causes why boron essentiality on humans has not been confirmed: A hypothesis

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## Abstract

On human nutrition, Boron (B) is classified in the category of possible essential elements; this means that its essentiality has not been proven and various causes have prevented it. The objective of this review was to analyze the next five causes that have possibly prevented to demonstrate the essentiality of B in humans: (1) Low daily requirement of B; (2) High number of sources to supply B in diet (3) Short life expectancy of humans (LEH); (4) Lack a method to diagnose B *in vivo* and; (5) Lack an area with low intake of B. Because the requirement of B in humans is very low (1.0 mg day<sup>-1</sup>), in trials of nutrition all sources of B should be controlled. Because a deficiency of B inhibits the synthesis of the active form of vitamin D, known as Calcitriol (1,25-(OH)<sub>2</sub>-D<sub>3</sub>) and assimilation of Ca on humans, osteoporosis (OST) and arthritis (ART) could be diseases associated with a deficit of B. In the past, the short LEH (47 years) prevented that OST and ART were identified as symptoms of B deficit; however today the LEH is 73 years, under this situation, is possible that the mineral reserve on bones is not sufficient to ensure the properly body function, therefore incidence of OST and ART on the population could be increasing, especially in areas with low intake of B. On the other side, B hair analysis is a usefully diagnostic tool which could be used in experiments to demonstrate B essentiality on humans; these experiments should be conducted in areas where the population has low intake of B along with high incidence of OST and ART.

## Introduction

The importance of boron (B) in plant nutrition was demonstrated in USA by Katherine Warington in 1923, and as soon as this occurred, also it began to study its essentiality in animals and human [1]. The first attempts to induce deficiencies of B in animals were conducted between 1939 and 1944 [2] and at the present its essentiality has been proven in diatoms, cyanobacteria, algae, actinomycetes of *Frankia* genus, fish and frogs [3-6] and although there are evidences of its beneficial effects on humans, its essentiality has still not been accepted [7]. Taking the lack of epidemiological evidence into consideration WHO (World Health Organization) put B in the possible essential elements category and this could be a sign that with a major number of studies, from a nutritional point of view, it could prove that B is an essential element [8]. This statement is associated to the fact that several researchers agree that an ingest a up to 2-6 mg B day<sup>-1</sup> helps to prevent arthritis (ART), osteoporosis (OST), osteoarthritis, cervical cancer, prostate cancer and cardiovascular diseases in people older than 45 years [7,9-13]. At the light of these evidences, several countries of the European Community (EC), England, Canada, USA and Australia where the B intake is lower than 3 mg day<sup>-1</sup>, have allowed the sale of B supplements; this as a way its population can meet their daily requirement of B [2]. Reviewing this topic, we founded that an agronomist wrote about the B importance on the human nutrition; why? Well, like many other people we were unaware the importance of B in human nutrition. It was until 2012 when I (the first author) had interest to study it; this because my rheumatism pain disappeared three months after I starting

to change my diet to increase the amount of B. As a man of science, I look for a scientific explanation for this event, so after analyzing the climatic conditions, food and water that I had consumed before (I was living in San Juan de Abajo Nayarit) and after I moved to San Quintin BC; for that time I also read the three articles published on the theme [14-16] I considered that a high amount of B present in my diet (mainly on water, fruits and vegetables) caused that my rheumatism disappeared. During the past 35 years, the B has been subject to an intense study to demonstrate its essentiality [1,2] and even though it has not been possible this, *in vitro* experiments and *in vivo* assays in animal and human have all shown that B is a bioactive element in nutrition and metabolism issues; certain amounts of B have important advantages on human health: bone growth, central nervous system function, alleviates arthritic symptoms, facilitates hormone action and moreover, its intake is associated with a reduced risk for some types of cancer [17]. Even with all this evidence, today most nutritionists do not consider the B an element essential; because of this, even though

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it has been established that B has beneficial bioactivity in humans, it generally has received limited attention or mention when dietary guidelines or intake recommendations are formulated [18]. Recently, to compare some studies related to B nutrition in animals and humans with those conducted to demonstrate the essentiality of Mo and Cl in plants [19,20] we found that many of the obstacles that prevented to demonstrate the essentiality of B on human's match with those that in the past preventing to prove the essentiality of the Mo and Cl in plants. Based on the aforementioned, the objective of this work review was to analyze five causes that possibly have prevented to demonstrate the B essentiality on humans: 1) Low daily requirement of B; 2) High number of sources of B in daily diet; 3) Short human life expectancy; 4) Lack a method to diagnose B *in vivo*; and 5) Lack of an area with low intake of B. It should be noted that the first two obstacles were extensively reviewed by researchers of Grand Forks Human Nutrition Research Center in North Dakota USA [21,22].

### **Low daily requirement of B**

Currently, out of the 118 known elements, 93 are found in the nature [23], 59 are present in the human body, and in a person of 70 kg, there are about of 18 mg of B, that is 0.00003% of weight alive [24]. In accordance with Broyer *et al.* [19] the human requires ingesting at least 1.0 mg day<sup>-1</sup>, considering that on average, an adult man ingests 3.0 L water and 0.347 kg day<sup>-1</sup> of foods (dry basis) [25,26], the concentration of B in a regular diet is of 0.00003%; this value is difficult to manage in nutrition tests, especially when are evaluating intakes less than 1.0 mg B day<sup>-1</sup> [27]. To solve this situation, Hunt [21] recommended the use of water deionized, as well as filtering the air to eliminate B, using free borosilicate containers; and also, taking in account the B provided by products of hygiene and personal care. The suggestions made by Hunt, have been put in practice in experiments of B nutrition and as reference is the work made by Sutherland *et al.* [28].

### **High number of sources to supply B in the daily intake**

B is an element widely spread all over nature, it is present in any part of the environment [29,30] and the sources supplies are so varied that in tests of nutrition is difficult to control all of them [21]. The control of all sources to supply B on the diet is very difficult because, besides of the B contained in water, air, soil and food (plant and animal), it is in hygiene products and personal care such as detergents, soaps, shampoos, creams and toothpaste [22]; in addition, glass and ceramic utensils also contain B that easily integrates to hot liquid foods [21] as it occurs in the laboratory when the samples are contaminated to use material with a high content of borosilicate [31,32]. Due to the large number of sources that supply and the low requirement of B (1.0 mg day<sup>-1</sup>) to date have not been able to identify at least a symptom associated with its deficit, or well to demonstrate it participates in any reaction biochemical in the metabolism of the man [30]. However, several authors suggest the OST and ART are diseases could be related with a B deficit [14,17,33-35]; however, because Ca is 66% of the mass bone [36,37], currently OST are more associated with a deficiency of this element [38,39] that the B deficiency. The hypothesis that OST and ART could be related to a deficit of B is based considering people suffer these diseases present 50% less concentration of B in bones and blood than healthy people [14,34,35]; grounded on these evidences, since 22 years ago several physicians ha recommended the B supplementation as part of the OST and ART treatment [9,14,34,35,40]. There are no data to support that the assimilation of Ca and B occur at the same time but recently Jugdaohsingh *et al.* [36] reported that the accumulation and desorption pattern of both elements in bones through the life cycle of

rats is very similar. B presents high capacity to combine with hydroxyl groups, therefore, it can to participate in several biochemical reactions [41] and in the metabolism of humans, it participates in the reaction of the hydroxylation that occurs on the kidneys which gives rise to the active form of vitamin D known as Calcitriol (1,25-(OH)<sub>2</sub>-D<sub>3</sub>) [42]. When Newnham [43] developed the hypothesis that B could be essential, he considered that their assimilation is closely associated y both elements are accumulated mainly in the bones [36,44,45]. Apparently Newnham [43] had sense, because the adequate supply of Ca alone does not prevent OST and on countries such as USA, Canada and England where the intake of Ca is high, the population presents more incidence of OST than population of countries where the intake of Ca is lower [46,47]. Several factors are related with the assimilation of Ca on humans; however, from the point of nutritional view, the status of vitamin D is most important [47,48]; and more specifically could be the status of B, because in animals with hipovitaminosis besides of Vitamin D, the B is the only factor that can alleviate it and improve the assimilation of Ca [49,50]; This clearly suggests that in animals B could be the key in Ca assimilation [51]; today the recommendation is to supply B to prevent physiological disorders related to Ca deficiencies in humans such as OST and ART [11,52].

### **Short human life expectancy**

The life expectancy on humans (LEH) from 47 years in 1960 passed to 75 years in 2015 [53], and with a balanced nutrition could be 120 years [54]. The continuous improvement of LEH on the last 66 years suggests that in the past the LEH too short did not allow to detect the B relevance on the human nutrition. In 1963, when [43] hypothesized B could be essential, the LEH was 47 years; considering the pattern of loss of bone mass [37,55] at this age the mineral reserve accumulated in bones was still sufficient to ensure the proper functioning of the skeletal system, this explains why on this time the incidence of OST was quite low, and the high incidence of ART reported in some regions during this time could be related to B deficit [15], because under conditions of malnutrition, this etiology occurs before a subject could reach 37 years of life [56]. On the 90s decades, the LEH was 72 years and it was observed that the OST incidence increased so high it was recognized as main cause of fractures in adults over 50 years old. The impact of OST in the human health was so big, that in 1998 was funded the International Osteoporosis Foundation and one year after the Asociacion Mexicana del Metabolismo Oseo y Mineral [57,58] whose main goal was to study the origin and clinical management of diseases of the skeletal system. After 2010, the incidence of bone diseases had increased widely because the LEH became 75 years, the bone mineral reserve was not sufficient for ensure their properly function [59]. The tendency on the LEH indicates it will continue to increase, therefore quite sure the incidence of OST and ART will continue increasing too. This fact suggests that in the past was not possible to determine the essentiality of the B in the man because his biological cycle was shorter and paradoxically, to the actual did not allow to find response to B supplementation. But in the next few year, this will change because in order to demonstrate the essentiality of B, the long LEH actual could help to reproduce symptoms of deficiency of B on humans.

### **Lack a method to diagnosis B *in vivo***

The lack of a method to determine the concentration of B *in vivo* is a cause that has prevented to associate at least a symptom with B deficit on humans. According to Alexander *et al.* [45], because B is mainly accumulated in the skeletal system; the bones are the best tissue to diagnose the nutritional status of B on humans and animals.

Currently, the determination of B in bones is only done in animals and humans died [36,45]; this is because is no possible to collect samples of bones in ribs, femur, column and parietal *in vivo*. Two alternate methods to determine the B content *in vivo* are the analysis of blood and urine [34,35,60]; however, because both methods just can diagnose the nutritional status of 24 hours, is no possible to use them to identify etiologies associated with a deficit of B in the long term [61]. The homeostatic mechanism that regulates the concentration of B in humans is so dynamic that subjects who have different daily B intake present little variation in the content of B in blood and urine [62]. According to Vanderpool *et al.* [63], 95% of B ingested is absorbed in one hour, 50% is eliminated in the urine, and the rest is disposed between 72 and 96 hours [64]. Therefore, although the B present in blood and urine is related with the amount of B consumed [28], the metabolism regulates the amount of B present in the bloodstream, and for example, increasing the B intake 9 times (0.36 mg to 3.0 mg) only increases 1.5 times the B concentration in blood (5.72 to 8.79  $\mu\text{M}$  B L) [27]. Fortunately, the hair analysis is a technique currently used to diagnose the nutritional status of B on the long term [31,60]; According to Bass *et al.* [61]; this method is better than the urine and blood analysis because it reflects the nutrition status of B for several years; is more accurate, easy and secure to collect, store and analyze samples. In the future, the analysis of B in hair will be a tool that could help to determine the relationship of B nutritional status with and incidence of OST, ART another disease of the bones on humans.

### **Lack an area with low intake of B**

At the present, has not been located a region where the B intake is less than 1.0  $\text{mg day}^{-1}$ , this situation has not permitted to find response in experiments with B supplementation. In the past, the poor knowledge of B in the human health conducted that [65] established a permissible level of B in drinking water of 0.3-0.5  $\text{mg B L}^{-1}$ , this value was so impractical that the European Community (EC) could not meet with this rule, and changed it to 1.0  $\text{mg B L}^{-1}$ , and permitted that their members countries to adjust it on basis of the quality of its water sources [66]. Germany had no problem to meet the standard [67]; England changed it to 2.0  $\text{mg B L}^{-1}$ , and Italy although adopted the English standard was flexible to regions like the Tuscany where the water contains between 4-8  $\text{mg B L}^{-1}$  could adjust it [68]. In order to take such decision, the EC is supported on studies conducted in Turkey where is found that the intake of 13-29  $\text{mg B day}^{-1}$  has not adverse effects on long term in humans [69-71]. It is evident to demonstrate the B essentiality we will need to operate the antithesis of the studies conducted in Turkey and the first step is to find a region where the B intake is less of 1.0  $\text{mg day}^{-1}$ . In accordance with the biogeochemical cycle of B [29], regions with low levels of B in the environment (air, water and soil) usually are far of sea, volcanoes, contaminated cities, industrial areas and located in high altitudes (at least 2000 meters above sea level). In Mexico, the municipality of San Felipe del Progreso, State of Mexico is a region that, besides to comply with the requirements aforementioned, 10% of its population exhibits arthritis to early age (37 years) [56]. As like as San Felipe del Progreso, the population of the municipality of Chankom Yucatán, also exhibits high incidence of arthritis (2.8 times more than the average national) and severe malnutrition [56,72,73]; Currently it is not known what is the B nutritional status in both population; but their low consumption of fruits and vegetables leads us to think that it is low. In theory the population of these two regions could be candidates to conduct experiments of B supplementation in order to confirm if ART is a disease related to B deficiency in humans. In order to try to demonstrate the B essentiality on the human nutrition, in the

next three years we will conduct a research project where will be to use all information discussed on this paper. Currently, the first steps to demonstrate the B essentiality were completed and the more important are: 1) The classification of B by WHO as possible essential element; (2) Demonstrate that the intake of 29  $\text{mg day}^{-1}$  has not an impact in health to long term; (3) Know that Australia, a country which initially declared toxic the consumption of B has now revoked this decision; (4) Achieve that even without their essentiality fully accepted, countries as USA, Canada, England and Australia allow the sale of B supplements. Based on all information previously presented, it is evident that the next studies should be directed to demonstrate the essentiality of B, to do so, the following points should be considered: a) All sources contributing to the B daily intake should be monitored, considering the low requirement of B; b) Taking in account OST and ART are probably caused by a deficit of B, the subjects to study must be living in regions with low intake of B and high incidence of ART and OST.; and (c) The use of hair analysis for B, will be valuable tool to diagnosis the nutritional status of B in a long term. Finally when I first read, 26 years ago the story how W. Reed discovered the agent transmitter of yellow fever virus; which certainly did not, but just confirmed that C. Finlay claimed several years before [74]; the question that arises from my mind is: will there be happening the same thing with B? about Newnham's hypothesis and that of Finlay hypothesis about Yellow Fever Virus resulted of an empiric assumption with no scientific data to support it, perhaps it could also be true, because the B deficit affecting negatively the production of vitamin D also inhibits the assimilation of Ca that could cause diseases of the skeletal system such as OST and ART, and other ones in a long term. There is no doubt that B essentiality will be demonstrated, the scientific bases were established by researchers as R. Newnham, F. Nielsen, C. Hunt, R. Scorei and many others that have not desisted in their attempt to prove that B is not only essential to plants and lower organisms; but it is also for higher animals and humans. The last step of this challenge will not be easy because we must experimentally replicate and scientifically explain what naturally occur in Italy, Cyprus, Israel, Spain and Australia, where the high intake of B [2,14,66] along with the long LE of its population (85 years) [75] is an unequivocal proof that B is important in human nutrition.

### **Conclusions**

Daily requirement of B is so low (at least 1.0  $\text{mg day}^{-1}$ ), that in experiments of nutrition with B on humans will be necessary to control all sources to supply this element on human diet. Because nutritional status of B on humans affect the synthesis of the vitamin D and assimilation of Ca, OST and ART could be associated with the deficit of B on humans. In the past, LE was less than 47 years, this avoided OST and ART as symptoms of deficit of B were expressed; however, today the actual LE is 75 years, so reserve of B and Ca on bones will not be enough to ensure their properly function and incidence of OST and ART diseases will increase, this fact will help to determine the beneficial effect of B on the human health on the short term. It is possible to use hair analysis as a diagnostic tool to determine the status of B on humans in experiments of supplementation with B to demonstrate its essentiality. These experiments could be conducted in areas where the low intake of B and the high incidence of OST and ART are common on the population.

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