Boric acids and mineral waters

Munteanu Constantin[1], *Dumitraşcu Mioara*[2]

[1] National Institute of Rehabilitation, Physical Medicine and Balneoclimatology
[2] SC BIOSAFETY SRL-D

All information known about this element is due to published results of scientifc research, experience of traditional use and expert opinion.

Boron is a metalloid –element with both properties metallic and nonmetallic. Is widespread in nature where is found in various caombination with oxygen. There are two main sources of boron: the natural (vulcanoes, geothermal steam)- recovered in mineral water and industrial – change the boron concentration in drinking water. Boric acid isn't a toxic waste and is not subjected to special law regarding to storage and transport. Beneficial or unwanted effects on the body are under investigation.

Pharmacodynamics: absorbtion and excretion complete; can be temporarily retained in the brain and kidney tract.

Efficiency:

Experimental studies performed in the laboratory in recent decades, that in vivo and vitro and clinical trials, have provided evidences considered insufficient on the following favorable effects (scientifc evidence of type C):

- **improvement of cognitive functions (coordination, attention, perception, memory)- preliminary studies on humans subjects;**
- **improvement of articular function with the preventing changes in arthrosis – observational cohort studies;**
- **improvement of bone metabolism, mainly of calcium, phosphorus and D vitamin, osteoporosis prevention- laboratory and experimental studies on human subjects;**
- **antiseptic, antibacterial and antifungal effects (candidal and non-candidal vulvovaginitis)- studies with debatable design; used in daily practice**
- **increasing of testosterone level (empirically used with the intention to mucscle mass increasing)**
- **reducing of menopausal symptoms by altering of estrogen level**
- **anticoagulant effects- in progress study, dispute;**
- **healing effect on skin lesions in psoriasis**

Aother effects: increasing of estrogen/ testosterone, D vitamin, calcium, copper, magnesium, thyroxine, levels; decreased of lcalcitonin, insulin, phosphorus levels.

Safety

FDA classifies products of boron in the class of herb and dietary suplements and doesn't regulate their use.

Adverse effects

- **allergy to boron and its compounds and various excipients that entering in different ingredients preparated with boron**
- **the accidental acute intoxication with boron as boric acid at which are exposed those who working in industrial sector .**
- **the exposure to boron or boric acid from dust: conjunctival irritation, dryness of mucous, coughing.**

Boric acids are of three types: orthoboric, metaborate and piroboric acid. In mineral waters (of course uncontaminated) are found various concentrations, usually small, of metaborate acid.

It is the case of mineral water from Romania. Boric acid and boron itself can be found in these waters.

Metaborate acid is a inactive compound and highly stable. It dissolves very little in water and doesn't decompose and transform into active products after ingestion.

There is no acute action on the body and no accumulation, because it is eliminated of 80% approximately as early as 10 hours. Elimination is primarly renal.

A possible effect of metaborate acid on laboratory animals could not be demonstrated. Also the study on humans (ingestion of mineral water with high content of metaborate acid) found any acute or cumulative effect.

In Romania, mineral water with high content of metaboric acid are found mainly in Harghita- Covasna, with Maria water representative in this regard, containing 296,3 mg/l. Studies conducted during the period 1984 – 2006 (observational and experimental) by INRMFB, on the effects of on patients treated with this water, who contain metaborate acid, not show any of the possible negative side effects on health, cited in the literature that would be possible if swallowed large amounts of boron.

Physico-chemical properties of boron

Boron (B) is a non-metallic element from group III of the periodic table and has oxidation state +3. it was discovered by Davy, Guy-Lussac and Thénard in 1808. it is exist as a mixture of two stable isotopes ^{10}B (19,8%) and ^{11}B (80,2%) (OMS, 1998).

Isotope ration ($^{10}B/^{11}B$), can be measured accurately (Vanderpool et al. 1994) using direct nebulization; ICP-MS can give a detection limit of 1 ng/g (Smith et al., 1991). At room temperature, boron exist as a solid, either as black crystals or yellow or brown amorphous powder when impure (WHO Guidelines for Drinking-water Quality, 1998).

This element is widespread in nature, with a concentration of about 10 mg/kg in the earth's crust (5mg/kg to 100 mg/kg in shale; the average concentration in earth's crust is 10 ppm) and 4,5 mg/liter in the oceans (Woods, 1994). Boron is found in **soil** at concentration between 10 - 300 mg / kg (average 30 mg/kg), depending on soil type, amount of organic matter and rainfall. The largest deposits of boron are found in southern California, Nevada and Oregon, Turkey, Russia, Chile and China (Moore et al, 1997).

Boron doesn't presents significant values in the atmoshere (Sprahue, 1972), ranging from less than 0,5 ng/m^3 to about 80 ng/m^3, with an average of more 20 ng/m$^{3.}$ Boron is released into de air from the oceans, vulcanoes, geothermak steam and another natural sources (Graedel, 1978). Boron is also released from anthropogenic sources in a lesser extent.

Boron exists in **natural water** primarly as undissociated boric acid with some borate ions. Boron is dissolved in water as B $(OH)_3$ (aq) sau B $(OH)_4$ - (aq). Boron concentrations from surface water vary between 0,001-360 mg/liter and are dependent on factors such geochemical nature of drainage area, proximity to marine coastal regions and inputs from industrial and municipal dicharges.

Boron in groundwater is mainly as a result af leaching from rocks and soil containing borates and borosilicates. Boron concentration from groundwater globally vary widely from <0,3 la > 100 mg / liter. Boron was found to be geochemically mobile, with concentrations significantly correlated (α = 0,05) with the salinity of groundwater in alluvial and basin areas. The highest concentration of boron was detect in geoudwater about 3,32 Fg/L (Seidel, 2006).

The great concentrations of boron was found in southern Europe (Italy, Spain) and the least in northern Europe (Denmark, France, Germany, The Netherlands).

Boric acid and borates are used in the manufacture of glass (fiberglass, borosilicate glass, enamel, frit and glaze), soaps and detergents, flame retardants and neutron absorbers for nuclear installations. Boric acid, borates and perborates where used as light antiseptic, cosmetics, pharmaceuticals, pesticides and fertilizers for agriculture.

Boron is an essential element for vascular plant, but for vertebrates isn't considered essential. Boron was an essential element for cyanobacteria that dominated the middle period of the Precambrian (Bonilla et al., 1990). First discovered biomolecule with boron was **boromycin**, an antibiotc secreted by *Streptomyces antibioticus* (Hutter et al, 1967; Bonilla et al., 1990; Schunmer et al., 1994; Hunt, 2003).

Boron compounds have been used since the mid 1800's until 1900, to treat various diseases including epilepsy, malaria, infections of urinary tract, exudative pleuritis, etc. Boron is found in the body, mainly as undissociated boric acid which is uniformly distributed in the soft tissues and with some accumulation in bone. The human body contains about ***0,7 ppm of boron.*** The daily intake of boron is about 1,52 mg by Iyengar et al. (1998), 1,21 mg, after Anderson et al. (1994) originatating from : air-

0.44 µg/ day , drinking water- 0.2-0.6 mg / day and the rest from food. Average intake for male adults is about 1,5 mg/day. (*http://www.epa.gov/waterscience/*).

Boron in naturally found in fruits, vegetables, nuts and cereals at levels below the toxicity limit. The boron concentration from food is related to boron from soil for crops and shows some geographical fluctuations depending on the location (OIM, 2001). Hunt et al., (1991) reported taht bron is present in foods prepared at concentration ranging from undetectable to 26,9 micrograms/g or ml of product. Boron is also found in some animal products because it is present in feed (Moore, et al. 1997).

Probabily, the body has a rezerve for boron, because there is evidence that is takes more than 21 days to induce changes on humans by feeding with a low concentration in the diet. The functions and the role of boron for humans and animals are mostly unclear, which is why the study of this element has advanced over the past two decaded, for its possible implications for human health. The first research conducted on the effects of boron for animal nutrition, have been published in the late '30 and early '40 (Hunt, 1994). Were performed numerous studies on the administration of various boron concentration in a series of animals, like mice, rats, rabbits, dogs, ruminants, invertebrates, etc. Boron is foudn in blood mainly as free B $(OH)_3$ (DRI, 2001). Normal concentration of boron in blood is about 0,1 - 0,2 pg / ml (Nielsen et al., 1986).

Boric acid and borate are absorbed at human and animals from gastro-intestinal and respiratory tract (Nielsen et al., 1986; Nielsen et al., 1988). More than 90% of administrated doses of these compounds are absorbed being evidenced by excretion in urine, which is fast and occurs within a few days. Boron pharmacokinetic seems to be quite similar in all species in the following aspects:

- ⇨ borates absorption is complete (about 95% on humans and rats), boron appear rapidly after ingestion, blood and body tissues in several mammals species.
- ⇨ boron distribution in mammals appears to occur by passive diffusion throughout the bdy fluids. In contrast to the soft tissues and blood, bones show a selective uptake of boron (> 4 times higher than in serum) and a significantly high retention time
- ⇨ elimination kinetics also appears to be similar for humans and rats.

In the discoveries until now it is considered that boron is a dynamic element that affect metabolism and use of other elements and substances: Ca, Mg, N, glucose, triglycerides and O_2 (OMS, 1998). Thus boron can affects mineral metabolism of bones, heart, cognitive functions, etc (Forrest & Nielsen, 2008; James & Penland, 1994).

Dietary variables affected by boron include calcium and magnesium concentrations from plasma and organs, plasma alkaline phosphatase and bones calcification. Boron compounds may represent potential anti-osteoporotic, anti-inflammatories anti-coagulats, anti-neoplasic agents, both in vivo and in vitro on animals (Benderdour et al, 1998)

There is some evidence from in vivo and in vitro studies that boric acid has an affinity for cis-hydroxyl gropups, this can be a mechanism that explains its biological effects. However, this attachament is known to be reversible (International Programme on chmemical Safety, WHO).

According to Rainey et al. (Rainey et al., 1999), the average of boron intake for an adults (men) from United States, Germany, England, Mexico, Kenya and Egypt was calculated as 1.11 ± 0.69, 1.72 ± 0.47, 1.30 ± 0.63, 2.12 ± 0,69, 1.95 ± 0.57 şi 1.31 ± 0,50 mg / day, respectively. Additionaly, for the adult women from the USA, Germany, England, Mexico, Kenya and Egypt the În plus, pentru femei adulte in SUA, Germania, Anglia, Mexic, Kenya şi Egipt, average of boron intake was about 0.89 ± 0.57, 1.62 ± 0,76, 1.14 ± 0.55, 1.75 ± 0.48, 1.80 ± 0.49 şi 1.24 ± 0,40 mg / day, respectively.

Because the chronic toxicicty of boron was inadequate studied or recognized, is difficult to set a threshold level of toxicity. Obvious signs of toxicity on animals generally occur only after the dietary boron concentration exceeds 100 µg / g.

Boron has a low toxicity when is orarlly administrated. Signs of chronic toxicity have been described on cow, dog, pig and rat (Nielsen et al., 1986).

As a result of boric acid exposure, were observed microscopic changes, especially on the kidneys (permeability changes of glomerular capillaries, cellular vacuolisation and cell elimination from tubular lumen) and nervous system (cell growth from spinal cord and gray matter of the cerebral cortex) on mice, rats and dogs (Pfeiffer et al., 1945). Have been reported two studies showing a response to boron deprivation.

Postmenopausal women from a metabolic unit, indicated that low level of boron in the diet (0,25 mg/2000 kcal) cause increased urinary excretion of calcium and magnesium (Nielsen et al., 1988).

Adverse effects of boron

The most common symptoms of boron poisoning/ intoxication are vomiting, diarrhea and abdominal pai. Boric acid dose that cause clinical symptoms isn't yet determined, but is supposed to be between 100 mg and 55,5 g (Litovitz et al., 1988).

LD_{50} (dose at which mortality is 50%) for human is 6 g/kg corp; less than 2 g ins't considered toxic (Calvert, 2002).

Toxic phenomena occur at doses that vary by age and health status between 2 – 20 g boric acid in single acute administration.

Other adverse effects are based on results of studies from laboratory animals (mice) receiving the high dose in a short time; these results transfered to humans, described testicular toxicity with a decreased sper mtility and reduced fertility, hair loss, liver and kidney damages, anemia. Dosage: LD_{50} is currently considered 5,14 g/kgc for mice, 5-20 g/kgc on human, respectively. LD_{50} is for NaCl, 3,75 g/kgc (Index Merck). In conclusion, the effects on boron unhealthy on the body are rare, due to acute intoxication with large amounts that can get inti the body by simple ingestion of mineral water. Lowest level of boron that are observed adverse effects (LOAEL) on rats (a slight differentiation of fetal weight (ca. 5%) and rib abnormalities) is approximately 13 mg boron / kg body weight per day . As the dose increases may occur: effects onthe coast ,decreased fetal weight and increased fetal malf ormations in rabbits and cardiovascular severe testicular pathology in rats (approx. 25 mg boron / kg body weight per day), testicular atrophy and sterility in rats (approx. 55 mg boron / kg body weight per day) reduced fetal body weight in mice (approx. 80 mg boron / kg body weight per day).

The data show that exposure to boron is associated with short-term irritant effects on upper respiratory tract, nasopharynx, and eyes. However, they appear to be short term and reversible.

Any study as reported direct negative effect on fertility. The role of lifestyle and behavioral factors in health and fertility requires further study designed to identify potentially sensitive populations and better assess the effects on reproduction.

Subchronic and chronic exposure to boric acid or borax oral on laboratory animals have shown unequivocally that the male reproductive tract is a target of toxicity. Were observed testicular lesions on rats, mice and dogs who have been administered boric acid or borax in food or drinking water. (Truhaut et al, 1964;. Weir & Fisher, 1972; Green et al, 1973;. Lee et al, 1978;. NTP, 1987; Ku et al, 1993a).

Literature mentioneds several cases of boron poisoning or intoxication. In 1949 – there were 86 cases of borax and boric acid poisoning with a mortality rate of 48.8% (Hunt, 2007).

The clinical effects of boric acid or borax exposure on rats, mice and guinea pigs administered in large single doses, orally are depression, ataxia, occasional seizures, low body temperature and red-purple skin and all mucous membranes (Pfeiffer et al . 1945; Weir & Fisher, 1972).

Developmental toxicity was experimentally tested on rats, mice and rabbits. Tests show that boric acid and borax are not genotoxic. The long-term studies on mice and rats, show that boric acid and borax have caused no increased incidence of tumors (Guidelines for Drinking-water Quality, 2008).

The lowest reported lethal dose of boric acid was 640 mg / kg (Stokinger, 1981) oral 8600 mg / kg, dermal and 29 mg / kg by intravenous injection. Death occurred at concentrations of 5-20g of boric acid to adults and less than 5g to infants (Stokinger, 1981).

Based on reports with cases of boron intoxication, appeared over time, it was observed that the lethal dose for this element is between 3000-6000 mg for infants and 15.0000-20.000 mg for adults (Sakirdere et a., 2010).

Boron compounds are toxic for all species at high doses, but has been shown that haven' t mutagenic or carcinogenic effects. Testicular lesions were observed on mice, rats and dogs who have been administered borax or boric acid in food or drin king water (Truhaut et al., 1964,Weir & Fisher, 1972, Green et al., 1973, Lee et al., 1978, NTP, 1987, Ku et al., 1993).

Among the adverse effects of boron compounds were observed: inhibition of spermatogenesis, degeneration of the reproduct ive system of mice, rats and dogs (Sakirdere et a., 2010). The inhibition of sperm production was observed at concentrations of 3000-4500 ppm, and testicular atrophy at doses of 6000-9000 ppm (Ku et al., 1993).

At a daily intake of over 5 g of boric acid the human body is clearly negative affected, causing nausea, vomiting, diarrhea and blood clotting problems. Quantities exceeding 20 gthreatening the life. Boric acid irritates the skin and eyes. Quantitative data about doses on adults with acute oral exposure ranged from 1.4mg B/ kg to a high of 70 mg B / kg (Culver and Hubbard, 1996). In cases where ingestion was less than 3.68 mg B / kg, subjects were asymptomatic.

Culver and Hubbard (1996) have studied the effects of boron for epilepsy at doses ranging from 2.5 to 24.8 mg B / kg-day for many years. Signs and symptoms reported on patients treated with 5 mg B / kg-day and above were indigestion, dermatitis, alopecia (hair loss) and anorexia. A patient with epilepsy who received 5.0 mg B / kg / day for 15 days showed indigestion, anorexia, and dermatitis, but the signs and symptoms disappeared when the dose was reduced to 2.5 mg / kg /day.

Saylor et al. (2003) obtained information on reproduction, through a questionnaire administered to 191 workers in a borate unit, all of them were considered people exposed to boron. In addition, the investigators obtained information on reproduction without an interview on subjects that included 712 other office workersand general management, employees active at the borates, and former workers in the environment with borates. Percentage of infertility among workers in environments borates was similar to that of the general population.

Although these studies appeared to confirm previous results, who showed that exposure to boron did not affect reproduction among people, lack of specific data about the interview for most people, in all studies and statistical population size limits the use of these studies for the risk assessment.

Yazbeck et al. (2005) found no difference in birth rates in three areas of France where the concentration of boron in drinking water was ≥ 0.3 mg / L than in areas where the concentration was between 0.1-0.29 or 0.00-0.09 mg / L. The percentage of the baby female was slightly, but significantly higher in areas where boron concentration was ≥ 0.30 mg / L than in other areas.

Oral LD50 values of boric acid or borax on mice and rats are in the range of about4 00-700 mg of boron per kg of body weight (Pfeiffer et al, 1945;. Weir & Fisher, 1972). Oral LD50 has values about 250-350 mg in the range of boron per kg of body weight for boric acid or borax exposure have been reported for guinea pigs, dogs, rabbits and cats (Pfeiffer et al, 1945;. Verbitskaya, 1975). Signs of acute borax and boric acid toxicity in animals given in large single doses include ataxia, seizures, and death. Kidney degeneration and testicular atrophy are also observed (Larsen, 1988) after short term exposure. In a study of 13 weeks, the mice (10 per sex per dose) were fed with diets containing boricacid at about 0, 34, 70, 141, 281, or 563 mg of boron per kg of body weight per day. At the highest dose was observed a increased mortality. Degeneration or atrophy of the seminiferous tubules was observed at 141 mg of boron per kg of body weight per day. In all dosage was seen a extramedullary hematopoiesis from the minimal to mild severity of the spleen (NTP, 1987).

A 2-year study on mice (50 per sex per dose) who received approximately 0, 275, or 550 mg boric acid per kg of body weight per day (0, 48, or 96 mg of boron per kg of body weight per day) in the diet (NTP, 1987, Dieter, 1994) demonstrated that body weight was 10-17% less at high dose for males after 32 weeks and on females after 52 weeks. Increased mortality rates were statistically significant for

males mice, with significant lesions in the testicles and not significant on female mice with non-neoplastic lesions. In a 2-year study, rats were fed with doses of boron normalized by weight of 0, 5.9, 18, or 59 mg / kg of body weight per day in the diet (Weir & Fisher, 1972). High doses of boron were determined to animals coarse hair coats, scaly tails, hunched posture, swelling and flaky areas on the feet, toenails abnormally long, shrunken scrotum, inflamed eyelids.

Hematocrit and hemoglobin were significantly lower than controls. Absolute and relative testes weights were significantly lower, but the relative weight of thyroid and brain were higher than in controls. On animals of small and medium-dose groups there were no significant effect on the general appearance, behavior, growth, food consumption, hematology, stereochemistry or histopathology.

NOAEL (No observed adverse effect level) represents the level of exposure of an organism to a substance, experimental or observational determined in which there are no statistically significant biological effects, such as morphological or functional alterations, the capacity for growth and development or life, increases in frequency or severity of any side effects in humans exposed by comparison with the corresponding control group. Toxic dose is derived by dividing the NOAEL boron (9.6 mg / kg of body weight per day) who develop the critical effect and to which is affected the development (decrease in fetal body weight in rats), by an appropriate uncertainty factor , which is considered to be 60. The 10 variation between species (animals to humans) was adopted because of lack of toxicokinetic and toxicodinamic data to allow deviation from this default value. However, available toxicokinetic data do not support the reduction of default uncertainty factor of intraspecific variation 10-6 (WHO, 1994). Direction that was most intense approached on the effects of boron in bone mineral metabolism shows that boron intake influence the composition and functional properties of bone. A review of experimental studies concerning the biological effects of boron on apendicular system and axial bones on animal models suggests that numerousinfluences, known and unknown, affect the responsiveness of bone to boron. Skeletal response to boron are modified by other dietary variables that include calcium, magnesium, D vitamin and fluoride.

The consumption of foods with vegetable origin and thus boron is often higher in countries with a lower incidence of osteoporosis. However, there are no comprehensive epidemiological studies establishing the relationship between boron intake and osteoporosis. Because the effects of boron chronic toxicity has not been clearly defined, it remains uncertain whether there are areas in the world where people can be affected by the intake of boron.

A diet supplementation with 50 mg boron / kg has contributed to increased the bone mineral content and density, trabecular volume and strength to rats (Rico et al., 2002).

Numerous studies have used very different doses of boron to observe the body's response to this element. Nielsen and colleagues have found that by supplementing the diet with 3 mg of boron per day occurs a reduction in Ca and Mg excreted in the urine to postmenopausal females. Qualitative and quantitative differences of the body's response to boron suggests that there is unidentified factors until now which are involved in the determining effects of boron at different levels.

A new direction that has aroused a particular interest is the use of boron in the treatment of prostate cancer. Boric acid concentration of 60-100 M suppresses the cell reproduction in prostate cancer (Barranco & ckhert, 2004).

Some studies have tried to determine if there is a correlation between boron concentration in groundwater and incidence of prostate cancer. A team from Texas found from their research that between boron concentration in water, prostate cancer and mortality there is an inverse correlation (Wade etal., 2007). A number of studies have confirmed the hypothesis that boron influence the cognitive performance to humans (James & Penland, 1994).

More recent studies have shown that boron is involved in the immune response (Hunt & Idso, 1999, Armstrong et al., 2001; Nielsen, 2002). Some research has shown

that dietary supplementation with boron humoral may increase the immune response (Bai et al., 1997) and reduces the inflammatory response (Hunt & Idso, 1999, Armstrong & Spears, 2003).

Boric acid added to human fibroblasts may increase TNF-α secretion and mRNA TNF-α on the culture medium (Benderdour et al., 1998). Some evidence suggests that boron may also reduce, tissue damage from inflammation by destroying reactive oxygen species by increasing activities of keyantioxidant enzymes (Hunt and Idso, 1999).

Supplementation with 2 mg B / kg diet (0.1 mg B / kg) reduced paw swelling of ratswith adjuvant induced for arthritis, suggesting that boron has an impact on the inflammatory response (Hunt & Idso, 1999). Aren't completely identified the mechanisms and cellular processes to be carried out in the presence of boron in the body's immune response, but apparently involving one or more biomolecules or processes: Fc receptor expression, IL-6, TNF-a, and concentrations Apna that affect pain and fever, activating lymphocytes and killer cell concentrations.

Another direction is the use of boron in the body's response to insulin. Research shows that on rats the boron administration increased the plasma insulin concentration without change that of the glucose (Bakken & Hunt, 2003).

References:

1. Cayton M. T. C. (1985). Boron toxicity in rice. IRRI Research Paper Series. Nr. 113. Manila. Philippines.
2. Shiotsuki I., Terao T., Ogami H., Ishii N., Yoshimura R., Nakamura J. 2008. Drinking Spring Water and Lithium Absorption: A Preliminary Study. German Journal of Psychiatry.
3. McCoy Harriett, Kenney Mary Alice, Montgomery Catherine, Irwin Amy, Williams Louise, and Orrell Rhonda. (1994). Relation of Boron to the Composition and Mechanical Properties of Bone. Environ Health Perspect 102(Suppl 7):49-53.
4. Bakirdere S., Örenay S., Korkmaz M. (2010). Effect of Boron on Human Health. The Open Mineral Processing Journal, 3, 54-59.
5. Drinking Water Health Advisory For Boron. (2008). Health and Ecological Criteria Division Office of Science and Technology Office of Water U.S. Environmental Protection Agency Washington, DC 20460. Document Number: 822-R-08-013.
6. Xu F. et al. (2007). Boron as a dietary factor for bone microarhitecture and central nervous system function. Advanced in plant and animal boron nutrition. 277-290. Springer.
7. Hunt C. (2007). Dietary boron: Evidence for essentiality and homeostatic control in human and aniumals. Advanced in plant and animal boron nutrition. 251-267. Springer.
8. SCOTT. R.B. (2007). Effect of Dietary Boron on Immune Function and Disease Resistance to Bovine Herpesvirus Type-1 in Growing Steers. (A thesis submitted to the Graduate Faculty of North Carolina State University in partial fulfillment of the requirements for the Degree of Master of Science). North Carolina.
9. Curtiss D. Hunt. (2007). Dietary Boron: Evidence for Essentiality and HomeostaticControl in Humans and Animals. *Advances in Plant and Animal Boron Nutrition,* 251-267.
10. Hunt C. (2003) Dietary Boron: An Overview of the Evidence for Its Role in Immune Function. The Journal of Trace Elements in Experimental Medicine 16:291–306 DOI: 10.1002/jtra.10041.
11. Armstrong T. A. and Spears J. W.. (2001). Effect of dietary boron on growth performance, calcium and phosphorus metabolism, and bone mechanical properties in growing barrows. *J ANIM SCI* 2001, 79:3120-3127.
12. Harder H. (1970) Boron content of sediments as a tool in facies analysis. Sediment. Geol., 4 153-175.
13. Guidelines for drinking-water quality, 2nd ed. Addendum to Vol. 2. *Health criteria and other supporting information.* World Health Organization, Geneva, 1998. Maximum limits for boron and fluoride in natural mineral water should be in line with drinking water regulations. (2006). BfR Opinion No. 024/2006.
14. http://www.scribd.com/doc/26960203/Curs-Balneologie
15. http://www.scribd.com/doc/32413194/Perspectivele-Turismului-Balnear-in-Romania
16. http://www.mendeley.com/research/salt-craving-the-psychobiology-of-pathogenic-sodium-intake/#page-1
17. http://www.sciencedirect.com/science/article/pii/S0304395907004307
18. http://www.sciencedirect.com/science/article/pii/0006899377910502
19. http://physrev.physiology.org/content/85/4/1271.full.pdf+html
20. http://physrev.physiology.org/content/86/1/155.full.pdf+html?sid=9624a6e8-366f-4cb0-8476-eaf5012de37a
21. http://physrev.physiology.org/content/86/1/155.full.pdf+html?sid=9624a6e8-366f-4cb0-8476-eaf5012de37a