
Summary: International Symposium on the Health Effects of Boron and Its Compounds

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This symposium had two chairmen because of its wide-ranging concern with health, covering issues of boron reproductive toxicity at one extreme and boron essentiality at the other. Dr. Ernest Mastromatteo was asked to summarize the issues presented by the speakers, with a special focus on human effects. Dr. Frank Sullivan was asked to summarize the presentations with a special focus on implications for future research.

Summary of Issues

Many of you have seen me worriedly writing in the corner, sometimes furiously, trying to get down all the very important points that the conference speakers were making. It is now my task to try to sum up this conference and to give you my idea of the implications for human health on the basis of the latest information presented here. There was a wide range of papers, including the chemical and physical properties of the element and its compounds; their uses; the various methods for the analysis of boron in plants, animals, and humans, as well as in air, water and soil; the biochemical and pharmacological effects of boron in plants, animals, and humans; the effects of dietary boron in experimental animals; the effects of boron in human nutrition and human physiology; the toxicology of boric acid and borax, including developmental and reproductive toxicity; and the assessment of health effects among workers exposed to boric acid and borates in their

production and use.

We all learned that boron is ubiquitous in the human environment. Over the United States, atmospheric concentrations of boron average about 0.5 ng/m³ of air. Boron concentrations in the surface waters of the United States average less than 0.3 mg/l, but can range as high as 15 mg/l in regions draining boron-rich soils. A survey of 100 U.S. drinking water supplies showed a median boron concentration of 0.03 mg/l.

We received information about the boron content of foods, ranging from a low of 0.16 µg/g dry weight in red meat to about 160 ppm in quince. The average U.S. diet contains 2.5 to 3 µg/g of boron and provides a dietary intake in humans of about 1.5 mg boron/day.

The major uses of boron in our society are in the production of glass and ceramics, detergents, bleaches, fire retardants, disinfectants, alloys, specialty metals, preservatives, pesticides, and fertilizers. Since it is so ubiquitous in its distribution and use, the analysis of trace amounts of boron in biological and other samples is very important. But there are difficulties in sampling and analytic methods. Current analytic techniques include colorimetric methods, inductively coupled plasma atomic emission spectroscopy (ICP-AES), ICP mass spectrometry, and neutron activation analysis. Sample preparation is critical in much of the analytic work. And, of course, borosilicate glass must never be used as a sample container.

Too, we know that boron is an essential micronutrient for plant growth, but its actual biochemical function is not well understood in plant biochemistry. Recent studies have demonstrated that plants may require boron to stimulate ascorbate metabolism. These studies are consistent with the hypothesis that boron overcomes

aluminum toxicity to plants by increasing ascorbate supply.

Boron's effects in animals is equally compelling. *Drosophila* flies under increased dietary levels of boron experienced a 10% increase in their longevity. Boron recently has been demonstrated to overcome the effects of vitamin D deficiency in chickens and rats. It appears that boron, in combination with vitamin D₃, enhances the mineral content of bone, while boron alone enhances the maturation of growth cartilage. Boron is therefore beneficial to bone growth in animals. This was confirmed in another study in which boron supplementation to rats' diets, which were deficient in calcium and magnesium, produced an increase of serum calcium and serum magnesium to normal levels. The addition of dietary boron in animals increased femoral length, peak load bearing, and strength, as well as the peak load bearing and strength of the lumbar vertebra.

There were important findings reported from dietary studies in humans as well. These findings support the hypothesis that boron may well be essential for humans. Boron added to the diet of boron-deprived women decreased urinary excretion and plasma concentrations of calcium and magnesium; decreased the urinary excretion and plasma concentration of phosphorus in women who were fed a low boron and magnesium diet; and increased plasma testosterone and 17-β estradiol. In a subsequent human study of subjects maintained for 63 days on a low-boron and low-magnesium diet, supplementation with boron increased plasma-ionized calcium and serum 25-hydroxycholecalciferol and decreased the concentration of serum calcitonin, osteocalcin, and glucose. Urinary excretion of hydroxyproline indicated collagen turnover, and increased cyclic-AMP

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indicated new bone formation. These studies suggest that boron has a very important function in humans that involves macromineral and cellular metabolism at the cell membrane level.

Still another study with humans suggests that boron may have an important role in human brain function, but further study on this is needed. Boron given to male athletes in a separate study failed to demonstrate any effect in strength tests and in lean muscle mass. Female athletes given boron showed no effect on mineral density. Serum calcium and magnesium were increased and serum phosphorus decreased in athletes, but I could not be sure whether this was related to the effects of training or to the boron supplementation. It seemed that the first factor was far more important.

The symposium then turned its attention to toxicity of boron and boron compounds. Boric acid has a low, acute oral-toxicity of about 4,000 mg/kg of body weight in rats. It does not penetrate intact skin, but readily penetrates broken skin. The inorganic borates are absorbed readily following ingestion or inhalation, and are excreted mainly by the kidneys. Over 95% of absorbed boron is excreted by the kidneys, and its biological half-life is less than one day.

Further, subchronic feeding studies in mice and rats have demonstrated reproductive effects in males through testicular cell damage and atrophy. The testicular damage showed a threshold effect, and the threshold in mice seemed to be about 4,500 ppm as boric acid in the diet. There was no genotoxic effect. Studies have been made to determine the mode of action of boron-induced testicular damage in rats. It does not seem to result from the accumulation of boron in the testis, but may be caused by boron interference with DNA and RNA synthesis in germinal cells. The actual mechanism is not yet elucidated.

A retrospective standardized birth-ratio study of male workers exposed to sodium borate dust at levels in the order of 10 mg/m³ of air showed no evidence of any exposure-related effect on fertility.

Studies of developmental effects of boron have been carried out in mice, rats, and rabbits, and have shown that there are developmental changes. The no-observed-adverse-effect-level (NOAEL) for boric acid was found to be equal to or greater than 125 mg/kg for rabbits and 450 mg/kg for mice. In the rat, a lowest-observed-adverse-effect-level (LOAEL) of 78 mg/kg resulted in decreased fetal weight. The developmental abnormalities

noted, however, are found at or near the level that produce maternal toxicity.

The mammalian NOAEL and LOAEL for developmental effects appear to me to afford a wide margin of safety in terms of human exposure. I would invite your discussion on this conclusion.

Turning from animal studies to studies of man, a report was presented on workers in the borate-producing industry who were exposed to sodium-borate dust in mining and processing. Pulmonary function tests were done in 1981, and they were followed up in 1988. The only changes in pulmonary function were those attributable to aging and to cigarette smoking. There were no changes that could be attributed to exposure to the borate dust among the 303 workers who were tested at both times. Workers with a borate-dust exposure averaging 5.7 mg/m³ of air complained infrequently of cough and irritation of the eyes, nose, and throat, but more frequently than those with lesser exposures. Effects were considered mild and only elicited on repeated questioning of the worker. Their exposure level may be compared to the Occupational Safety and Health Administration (OSHA/MSHA PEL) of 10 mg/m³ and the CAL-OSHA PEL of 5 mg/m³. Another study involved the biological monitoring of 14 workers employed in packing and shipping in a plant where borax in its three commercial hydration states was handled. Airborne dust levels of these sodium borates ranged from 3.3 to 18 mg/m³. Expressed as boron, these were 0.5 to 2.67 mg/m³. Calculated doses, including dietary intake for the workers at the high end of the exposure range, averaged 0.38 mg boron/kg of body weight per day. In my opinion, this affords a large margin of safety over the NOAELs derived from animal data for impaired testicular function.

Now, I would like to present my quick overview of the health implications of boron. First, a comment on boron as an essential element for humans is needed. I think at this conference, we seemed to be moving nearer to the belief that boron may well be essential to humans. I asked our colleagues this question: Who makes the decision that boron is essential in humans? At present, the last scientific opinion is not in, so we must keep an open mind on boron's essentiality for humans.

In terms of the environment, the use of borates in detergents and the use of borate fertilizers and pesticides may result in some release of boron compounds to the environment. Most boron seems to come from

natural sources, because of soils and waters that are rich in boron. At any rate, I did not learn in this conference of any environmental health problems from boron exposure at levels present in the general environment. There are some local areas with high boron concentrations in the soil and natural waters. It might be interesting to conduct follow up studies on those areas. We heard repeatedly from one speaker of different parts of the world where they have such high levels, and it would be nice that these be studied in scientific detail.

In terms of occupational exposure, there does not seem to me to be a risk of cancer or of systemic poisoning at the boron levels that are encountered in our occupational activities. Similarly, I do not believe that there is a significant risk of reproductive effects in males or females, of developmental defects in pregnant women, or of allergic disease among workers engaged in the production and use of boron compounds.

The epidemiologic study reporting pulmonary function results and mild irritant effects does not provide any real evidence of adverse effect, although it was limited in its scope. Nevertheless, an exposure limit or a guideline of 10 mg/m³ appears applicable to boric acid and the borates.

The health effects of the boron fluorides, the boranes, and organic boron compounds have not been addressed in the present symposium and need to be assessed separately from those of the sodium borates and boric acid.

In regard to pharmaceutical use of boron, I talked briefly about the organoboron compounds under investigation for some uses in humans. We still must await further developments in clinical trials before we can judge these as effective therapeutic agents in humans. Inorganic boron compounds have been recommended by some for the prevention and treatment of various forms of arthritis and osteoporosis. Personally, I think we need further clinical study of such use before we can be assured of efficacy.

Implications for Future Research

I will briefly discuss some of the points which seem to me, as a relative outsider, to merit further research. It seems quite clear that for plants boron is an essential micronutrient, which at high concentrations becomes phytotoxic. The major question to be answered is whether this nutritive/toxic relationship also applies to mammals. If in mammals boron is an essential nutrient, are higher doses likely to

be toxic? In toxicology there is an old adage that there's no such thing as a toxic chemical; there is only a toxic dose. That adage very much applies to boron.

We have used the term "boron-deficient diet" quite extensively during the conference, and that implies that there were participants who think that boron is an essential micronutrient in mammals. But the question that has not been answered, and thus one of the areas for future research, is whether there is a clinical condition of boron deficiency. Several speakers have reported that when subjects were put on boron-supplemented diets, they have shown changes in various parameters. However, the changes all seemed relatively small, and I am not very convinced that this is good evidence that boron is an essential micronutrient. And of course, there are ethical problems about working with normal volunteers, which limits the studies that can be performed.

Among the conference presentations were discussions about arthritis, particularly from Dr. Newnham and others. This is an important area; and if it is true that boron deficiency leads to inflammatory disease and other illnesses, then it is crucial that this should be investigated. Study is particularly important because most advances in therapeutics are made by drug companies; since boron is not a patentable compound, it is unlikely that any drug company will spend the money necessary to develop compounds like borates for promoting health. Boron's nonpatentable status poses the problem of how this whole topic could be studied and developed, and if necessary, findings made available for use by the public.

These are compelling areas for research, and I think that some questions that need to be answered are the following: Is boron essential, and if so, for what is it essential? How much boron is required? Participants here have mentioned needs for 1 mg, 3 mg, or 10 mg of boron per day; and studies are required to answer this. Another important question is, at what level does boron become harmful? There is an inverted, U-shaped curve where increased doses bring about beneficial effects, but further increased doses bring about toxic effects. It is important to try to establish some parameters on this, and it does seem that there are many natural experiments out there. We have had discussions about Chile,

Australia, New Zealand, and other countries where people are exposed either to very high levels or very low levels of boron, and it would be a good research project to study people living in those regions.

Still another important area for research is into assay methods. The available methods are extremely sensitive, but it is not known how much boron is lost or gained during extraction of samples. Therefore, it is not known exactly what the normal blood-boron level in humans really is. There is obviously a need for interlaboratory comparisons. Since most of the concerned research experts in the world attended this conference, why not reunite to agree on a program for standardization and quality control of methodology for the sake of consistency?

I foresee other needs that arose from this conference. I was disappointed that in this meeting we did not really get any indication of what the chemical species is in the blood. After discussions about borax, borates, and boric acid, no one defined exactly what is measured in the blood. Do all of these produce the same substance in blood and tissues?

Another important consideration is the medicinal use of borates and boron compounds. The paper on carboxyboranes showed that they have a wide range of actions. This is not surprising if these compounds are acting through prostaglandins and interleukins, since these would influence a very wide range of diseases, from arthritis through allergies and immunology. These are such fundamental body systems, there is no reason these drugs could not have a very wide range of effects. However, with a complex of substances like carboxyboranes, one would need good evidence that boron is a key factor. There has also been discussion about effects of boron on calcium metabolism, osteoporosis, and membrane function. These are all of very fundamental importance in medicine and biology, and constitute an area of research that would well merit investigation.

Still another area of discussion that merits research is agricultural use of boron. There are clear advantages for agriculture from improving or increasing boron levels, and there was an interesting contribution to the discussion about the large number of soil samples in the United States that are boron-deficient. However, as we add more boron into agriculture, more gets into the

plants, and thus the food chain, which gets into people. Work on agriculture cannot be divorced from the work on human medicine and human toxicology, because they are all closely tied. Research is very important to ensure that boron's use in agriculture is not a potential source of harm.

Finally, I want to comment on the toxicology studies. The reproductive toxicology falls into two divisions—the effects on fertility and the effects on pregnancy. The animal studies make clear that at high doses, these compounds are reproductive toxins. However, the effects on fertility in animals are not of concern, because we have a series of human studies that I think are unique inasmuch as they have examined probably the most continuously-exposed worker population. Workers have been studied from the perspectives of exposure, absorption, blood and urine-boron levels, fertility, and so on. It does seem that, in this highly exposed population of workers, there is no adverse effect on their fertility as assessed by the number of children, or evidence of infertility. These people are exposed to sodium borate dust levels of up to 28 mg/day of boron, and so I feel that we need not be concerned with the antifertility effects of boron.

However, there may be cause for concern in the developmental toxicity data. It is extremely difficult to get data on chemical exposures of women during pregnancy. The animal data are not excessively worrying, because there is a reasonably high safety margin; nevertheless, a researcher is never very comfortable in this kind of study without having human data. An effort should be made to identify whether there are populations of women exposed to borates.

Consider, for instance, that women have been using borax and perborate in washing powder for 100 years, and if there were any important effect there, it is likely it would have been noticed. However, until some studies have been carried out, we cannot be confident that there is no effect on pregnancy.

Finally, there was mention in the symposium of various populations exposed to high concentrations of boron in drinking water. Studies on the fertility and pregnancy outcome in these populations may be worthwhile, although the difficulties of conducting such studies should not be underestimated.