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Barium

Barium (Ba), an alkaline earth element, oxidizes easily when exposed to air, and it is found as the Ba^{2+} ion in water. Barium found in surface and ground waters is predominantly derived from weathered rock and minerals. Common naturally occurring Ba minerals are insoluble barite (barium sulfate, $BaSO_4$) and somewhat more soluble witherite (barium carbonate, $BaCO_3$), while the Ba^{2+} ion is most common in natural waters.⁹⁵ Barium concentrations in water will likely be higher near drilling platforms than natural background concentrations as a result of drilling muds, cuttings, and produced water discharge containing Ba.⁹⁶ In water, soluble Ba may precipitate out of aqueous solution as insoluble salts (e.g. $BaSO_4$ and $BaCO_3$). At pH activity of 9.3 or below, the formation of $BaSO_4$ limits the Ba concentration in natural waters. Barium has a variety of uses: $BaSO_4$ is used in patients for digestive tract imaging and for oil drilling, and $BaCO_3$ is used in rodenticides.⁹⁶⁻⁹⁸

Essentiality

Barium is not an essential element for plants or animals.

Metabolism

Existing studies indicate Ba absorbed from the G.I. tract is primarily deposited in bones and teeth and excreted via feces and urine.⁹⁹⁻¹⁰³ The absorption efficiency of various Ba compounds given orally varies widely (0.7-85%) depending upon the chemical form, species, age, and fasting status of the animal.¹⁰⁴⁻¹⁰⁶ In general, more soluble forms of Ba such as barium chloride ($BaCl_2$) are more readily absorbed. Young rats absorb approximately 10 fold more $BaCl_2$ than adults.¹⁰⁶ Barium disappears from blood and milk with a half-life ($t_{1/2}$) measured in days;^{100,102} however, Ba deposited in bone has a $t_{1/2}$ measured in years, and disappearance from bone is generally dependent upon bone turnover.¹⁰⁷ These observations, together with the divalent cationic nature of Ba and the fact Ba is known to bind Ca-dependent enzyme systems in cells, suggest Ba metabolism utilizes Ca transport systems in the body.

Toxicity

Barium is toxic in water-soluble forms such as $BaCl_2$ and, to a lesser extent, $BaCO_3$. Barium sulfate is insoluble and is not considered hazardous to people or other monogastric animals. The specific toxic mechanism of Ba is a blockade of passive transmembrane potassium (K^+) conductance in excitable cells by the Ba^{2+} ion.^{97,98,108,109} Barium also competes with and/or mimics the functions of Ca in muscle contraction and in second messenger pathways.^{97,108} The characteristic systemic effect of Ba poisoning is "violent contraction of smooth, striated, and cardiac muscle."^{109,110} Clinically, this effect is manifested as arterial hypertension and premature supraventricular and ventricular contractions, followed by skeletal muscle contraction, salivation, vomiting, colic, and diarrhea.^{97,98,108,109,111,112} Subsequently, blood pressure drops precipitously and skeletal muscles exhibit flaccid paralysis. Finally, death results from arrhythmias and cardiac failure.^{104,112,113} The hypokalemia seen in Ba poisoning is thought to result from blockade of passive K channels and intracellular sequestration, as Ba has no proven activity on the Na^+K^+ ATPase pump.^{98,109,114}

Data on the toxicity of Ba in grazing animals is limited. Two ruminally fistulated dairy goats were infused with 5mM $BaCl_2$ at a rate of 60 ml/hr. The ruminal fluid Ba^{2+} ion concentration was estimated to be 0.4 mM assuming no absorption or precipitation occurred. After receiving Ba^{2+} for six hours, the animals exhibited weakness and paralysis, and they died later that night. The resulting oral lethal dose of $BaCl_2$ in the goat was determined to be less than 4.6 mg Ba^{2+} /kg BW.¹¹⁵ This Ba dosage would equate to approximately 23 mg/L in drinking water under conditions outlined in the Introduction. Ba poisoning occurred during two successive years in cattle that were trailed through an abandoned lead/silver mine site containing a Ba-contaminated pond.¹¹⁶ Affected animals exhibited protruding tongues, salivation, watery diarrhea, muscle tremors, and paralysis progressing to recumbency and death. Six of 30 animals died the first year and 16 of 20 the second. Liver and kidney tissues from affected animals contained elevated Ba concentrations, and other metals (Pb, As, Se, etc.) were within normal limits. Pond water contained 2.2 mg Ba^{2+} /L; however, clay found in

both the abomasum of the dead cattle and in the pond contained 69,000 ppm Ba. The amount of Ba, if any, absorbed from the clay is presently unknown. X-ray diffraction analysis of the clay indicated the Ba was present primarily as insoluble BaSO_4 , with lesser amounts of $\text{BaCa}[\text{CO}_3]_2$ and BaCO_3 salts. Reagor¹¹⁷ fed BaCO_3 to steers at 0.4% and 0.8% of the dry matter diet to steers (0.28% and 0.56% Ba respectively). All three receiving the high dose died after a single day on feed; all three receiving the lower concentration remained healthy for the duration of the experiment. Clinical signs in the steers were similar to those reported in monogastrics.

Malhi et al.¹¹⁸ investigated the optimum concentration of BaCO_3 for a rodenticide and concluded 1.5 g of BaCO_3 per 100 g body weight (or 15,000 mg/kg) was the most efficient rat poison. There was no attempt to determine a minimum lethal dose. Mattila et al.¹¹⁹ administered BaCl_2 via the marginal ear vein of six rabbits instrumented with an electrocardiograph. Three to 5 mg Ba^{2+} /kg of BW caused dysrhythmias with and without convulsions. Rabbits receiving 3 mg Ba^{2+} /kg of BW survived, despite convulsions. Roza and Berman¹¹² observed anesthetized dogs after infusing them with 0.66-2.64 μmol Ba (as BaCl_2)/kg/min to identify mechanisms of Ba-induced hypokalemia and hypertension and to study the Ba-K interaction on the heart *in vivo*. They found rates greater than 4 μmol BaCl_2 /kg/min (~362 μg Ba^{2+} /kg/min) were fatal within a few minutes due to respiratory paralysis.

In humans, most acute oral toxicity data is derived from suicide attempts. Gosselin¹¹⁰ describes the oral lethal dose in humans as "1-15 g." A research chemist attempted suicide by ingesting a teaspoon (approximately 13 g) of BaCl_2 .¹²⁰ He was rushed to a hospital and survived after treatment with MgSO_4 and KCl . Seven members of a family were poisoned with Ba after ingesting fried fish accidentally breaded with powdered rat poison.¹¹⁴ The exact amount of BaCO_3 ingested was not determined, but the breading of the fish contained 105,000 ppm of Ba. Three of the family members displayed classic signs of Ba poisoning, while one developed rhabdomyolysis, respiratory failure, and hypophosphatemia. All patients survived with treatment. In another instance, a 26-year-old man consumed one can of "Magic Shave" containing 12.8 g of Ba^{2+} ion and 3 g of sulfide.¹²¹ Ipecac was given within three hours. He suffered respiratory paralysis, severe respiratory acidosis, and hypokalemia. His condition improved after he was given 206 meq of K over 19 hours.

Several studies have examined the chronic oral toxicity of low concentration BaCl_2 in drinking water to people because of Ba's recognized cardiac toxicity. Wones et al.¹²² concluded that drinking water concentrations of 5 and 10 mg Ba^{2+} /L did not affect any known modifiable cardiovascular risk factors. Eleven healthy men were given BaCl_2 in their drinking water for six weeks. For the first two weeks of the experiment, no BaCl_2 was added to their water. BaCl_2 was then added at rates of 2-5 mg/L for the next four weeks and 10 mg Ba/L for the last four weeks. The subjects were given 1.5 L of treated drinking water per day; any additional drinking water was distilled. Diets were controlled as well as other known causes of cardiovascular disease. Blood (plasma total triglycerides and HDL cholesterol), urine (Na, K, vanillylmandelic acid, and total metanephrines), blood pressure, and cardiac function were monitored throughout the study. They discovered no apparent changes in modifiable cardiovascular risk factors, but there was a trend toward slightly increased total blood Ca. Brenniman and Levy¹²³ conducted an epidemiological study to determine if mortality and morbidity rate were significantly increased in human populations drinking elevated Ba levels in their drinking water as compared to populations with little or no Ba exposure. Cardiovascular mortality rates were surveyed in communities with drinking water Ba concentrations that ranged between 2-10 mg/L. A morbidity study was also conducted in areas where mean Ba concentrations in drinking water were 0.1 and 7.3 mg/L. They found higher cardiovascular mortality rates in elevated Ba communities, but there were also several confounding variables. There were no significant differences in blood pressure, hypertension, stroke, and heart and kidney disease.

The single oral LD_{50} of BaCl_2 in rats was estimated to be approximately 264 mg Ba/kg BW.¹²⁴ Short-term (1-10 day) oral exposure to BaCl_2 at daily doses up to 138 mg Ba/kg BW produced no significant adverse health effects. Because of the link with cardiovascular disease in people, most chronic laboratory animal studies focus on cardiac effects. Barium acetate ($\text{Ba}(\text{CH}_3\text{COO})_2$), added to drinking water at 5 mg Ba^{2+} /L and fed to rats over their lifespan had little or no effect on growth, carcinogenesis, or longevity.¹²⁵ Rats drinking water with 100 mg Ba^{2+} /L as BaCl_2 for 16 months exhibited significant but varying increases in systolic blood pressure.¹²⁶ In a similar study, the average systolic pressure increased significantly after exposure to 100 mg Ba^{2+} /L for one month and after 10 mg Ba^{2+} /L for eight months. After 16 months, rats

exposed to 100 mg Ba²⁺/L had depressed heart rates and decreased cardiac function.^{127,128} Another experiment examined the effect of BaCl₂ in drinking water for 92 days on serum electrolytes, body weight, behavior, and fertility in rats and mice.¹²⁹ The no observed adverse effect level (NOAEL) for Ba, based upon depressed body weight gain and renal and lymphoid lesions, was estimated to be 1,120 mg Ba²⁺/L. Mortality was attributed to kidney damage. There appeared to be no adverse effects on reproduction and fertility, although there was a marginal reduction in pup weights. Tardiff et al.¹³⁰ studied acute oral and subchronic toxicity of Ba as BaCl₂ in rats. The acute oral LD₅₀ for weanling rats was 220 mg Ba/kg BW and for adults was 132 mg Ba/kg BW. Drinking 250 mg Ba²⁺/L for up to 13 weeks resulted in less water consumption than controls, but it did not cause any clinical signs of toxicity, nor was body weight affected. McCauley et al.¹³¹ found no significant lesions in rats exposed to up to 250 mg Ba/L drinking water for 68 weeks, nor were there measurable electrocardiographic changes when measured at five months; however, Ba-exposed rats were more sensitive to norepinephrine.

An anecdotal report of BaCl₂ ingestion in a man suggests Ba may damage kidneys, although the kidney lesions were likely the result of IV therapy with MgSO₄.¹²⁰ Chronic Ba exposure causes nephropathy in rodents. Male rats drinking 5 ppm Ba as the acetate salt in a life-time study developed proteinuria.¹²⁵ McCauley et al.¹³¹ identified kidney lesions in rodents administered 1,000 mg Ba/L in drinking water for 16 weeks. Dietz et al. identified kidney lesions in male and female mice receiving doses of 436-562 mg Ba²⁺/kg BW/day via drinking water for 92 days. Rats receiving the same water drank less, receiving only about one quarter of the dose and had much milder renal lesions.¹²⁹ In a subsequent two-year cancer bioassay, female and male rats receiving 75 and 60 mg Ba²⁺/kg BW/day, respectively, in drinking water gained less than controls but did not exhibit any Ba-related clinical signs. Mice in the same two-year study drank up to 160 (male) or 200 (female) mg Ba²⁺/kg BW/day and had significantly greater premature mortality due to kidney disease than did controls.¹³²

Most authorities indicate BaSO₄ is the least soluble and therefore least toxic form of Ba. A United Kingdom risk assessment of BaSO₄ described it as a low risk due to, among other reasons, low solubility.¹³³ Studies by Maglante et al.¹³⁴ and several decades use of BaSO₄ as radiographic contrast media support the premise BaSO₄ is relatively nontoxic in mammals.¹³⁴⁻¹³⁷ Ba sulfate-derived

Ba was poorly bioavailable in an environmental study and thus did not bioconcentrate between trophic levels in the food-chain.¹³⁸ One exception is a study suggesting ¹³¹Ba from BaSO₄ was nearly as bioavailable as BaCl₂.¹³⁹

There are a number of reports regarding the toxicity of inhaled Ba.¹⁴⁰⁻¹⁴³ Since the relationship between the toxicity of inhaled Ba and soluble Ba in feed or water is not fully understood, these studies were not included.

Summary

The acutely toxic effects of Ba are similar in monogastrics and ruminants. This argues that 1) Ba is a valid water quality concern for livestock and wildlife, and 2) subacute and chronic effects are probably similar, if not identical, between these species. The putative toxic mechanism(s) of the Ba²⁺ ion in rodents and human beings involve physiologic mechanisms that are highly conserved (i.e. very similar) throughout terrestrial mammals; therefore, any species-specific differences in toxicity logically derive from species-specific differences in the toxicokinetics of Ba. In monogastric mammals, the oral toxicity of Ba compounds correlates with their water solubility. Less soluble forms of Ba (notably BaSO₄) are poorly absorbed and are thus considerably less toxic than more soluble salts such as BaCl₂, barium nitrate (Ba(NO₃)₂), or barium hydroxide (Ba(OH)₂).¹⁰⁵ There is no equivalent data in ruminants. Theoretically, reduction of the SO₄ salt to sulfide by rumen microflora *might* result in increased bioavailability of the Ba²⁺ ion. There *is* some precedent for differences in metabolism of Ba between monogastrics and ruminants¹⁴⁴, but much more needs to be done. As a practical matter, however, this theoretical effect would be significant only in solid feedstuffs as insoluble forms of Ba (i.e. BaSO₄) will presumably not be present in drinking water in any significant concentration.

The long-term effects of Ba, especially on reproduction, have been incompletely investigated in any species. A single Russian report of Ba inhalation toxicity describes reproductive lesions in both male and female rats¹⁴⁵ whereas more recent rodent studies did not note alterations in reproductive tissues or reproductive function following acute-, intermediate- or chronic-duration exposure to Ba.^{129,131,132} Kidney damage *was* observed in laboratory rodents following two-year exposure to 200 mg Ba/kg BW and in long-term (91-day) oral exposure to 450 mg Ba/kg BW, but it was not seen after administration of 250 mg Ba/kg BW for 36-46 weeks.^{131,132}

The only *quantitative* data available in cattle indicates 138 mg Ba/kg BW, as BaCO₃, in dry feedstuffs was acutely toxic to steers, whereas 69 mg Ba/kg BW was not.¹¹⁷ Assuming water consumption of 20% BW, this translates to 690 mg Ba²⁺/L in drinking water as being acutely toxic or 345 mg Ba²⁺/L as the NOAEL. This contrasts with the report of Richards et al.¹¹⁶ that 2 mg soluble Ba²⁺/L water, plus some undetermined amount of Ba from sediment, was immediately toxic to cows and calves. It is also much higher than the toxic dose reported in goats, where 7 mg/kg BW BaCl₂ (4.6 mg Ba/kg BW) was lethal.¹¹⁵ It is likely that BaCO₃ in feed is not as bioavailable as the Ba²⁺ ion in water. The acutely lethal dose in the goat study translates to 23 mg Ba²⁺/L under the assumptions outlined in the Introduction.

Obviously, much more research needs to be done with Ba in ruminants, but, given the current state of knowledge, soluble Ba²⁺ concentrations should be held to well below 23 mg/L to avoid acute toxicity. There is absolutely no data on chronic Ba²⁺ ion toxicity in any of our species of interest. This, plus the limited and conflicting data from chronic studies in other animals, makes it impossible to postulate a long-term “safe” level of the Ba²⁺ ion in drinking water for domestic livestock and/or wildlife species with any degree of certainty.

We do not recommend using water containing more than 10 mg Ba²⁺/L even for short periods. Until there is better data, it is impossible to make any recommendations regarding chronic exposure.