8 Selenium

Selenium (Se), a metalloid that shares many chemical properties with S, is predominantly present in cretaceous rocks, volcanic material, seafloor deposits, and glacial drift in the Great Plains.[409] It can be present in soil at levels sufficient to cause toxicity or low enough to result in deficiency in grazing animals. Either outcome can result in serious economic losses to livestock producers and illness and/or death in wildlife. Normal soil concentrations range from 0.1 to 2.0 µg total Se per gram of soil; however, in seleniferous areas such as Wyoming, soils can contain as much as 30-324 µg Se per gram of soil.[410] Plants grown on such soils tend to accumulate Se and, depending upon the species, may, in fact, bioconcentrate Se to concentrations in excess of 10,000 ppm.

Water in contact with seleniferous rocks and soils (e.g. irrigation wastewater) may also accumulate Se.[411,412] The most common form of Se in Wyoming surface waters is the selenate (SeO_4^{2-}) ion. "Normal" surface water is described as containing less than 2 µg Se/L[411], and it is thus not normally a major source of Se for livestock and mammalian wildlife; however, poisoning as a result of seleniferous water has occurred in horses and sheep.[413-415] Dissolved Se becomes concentrated in successive levels of the aquatic food chain and is a major concern for waterfowl that depend upon aquatic biota for food[411,416,417]; however, aquatic bioconcentration does not pose a hazard to large herbivores (e.g. cattle, elk) under normal conditions as their intake of algae and aquatic organisms is very small. Interestingly, bioaccumulation of Se in the aquatic food chain actually removes Se from the water column,[411,418] thus decreasing the risk to large mammals. Forages irrigated with seleniferous water contain elevated Se concentrations and can pose a risk to grazing animals.[411,412,418] While each of the preceding sources is important, this report is concerned specifically with the hazard posed to livestock and wildlife by Se in drinking water and will focus upon that source.

Essentiality

Selenium is an essential trace element. Most authorities agree that, worldwide, deficiency is a more common problem than toxicity, and, thus, for the last 40 years, much more research has focused upon the effects of inadequate dietary Se than too much. This research may still be useful for its insight to Se metabolism. Within the body, Se is a component of several enzyme systems, most involved in catalyzing oxidation-reduction reactions.[419,420] The Se-requiring system thought to be most responsible for damage in deficiency situations is glutathione peroxidase.[410,421] Selenium supplementation decreases the incidence of white muscle disease, a degenerative condition in muscle resulting from oxidant stress.[421-423] The FDA permits 0.3 ppm Se (total ration) as a feed additive, up to 0.7 and 3 mg Se per head per day as a feed supplement for sheep and beef cattle, respectively, and in fortification mixtures up to 90 and 120 ppm Se for sheep and cattle, respectively.[424] Deficiency is rarely a problem in Wyoming and northern Great Plains states.[425,426]

Metabolism

Selenomethionine is the main form of Se in common forages, even though it is not a major component of accumulator plant species.[427-429] It constitutes the majority of ingested Se, however, as accumulator plants are highly unpalatable and are usually avoided to the point of starvation.[430] Waterborne Se, usually selenite (SeO_3^{2-}) or selenate (SeO_4^{2-}) ions, normally comprises a relatively small portion of large herbivores' total exposure; however: 1) water concentrations sufficient to cause poisoning have been recorded in Wyoming[431,432]; 2) poisoning has occurred in livestock as a result of Se contamination associated with mineral extraction; and 3) Se-contaminated water has the potential to add to the already high background forage concentrations common to many parts of the Great Plains.

Dietary Se is absorbed from the small intestine in both ruminant and monogastric species. Selenocysteine and selenomethionine are transported across the intestinal epithelium by active amino acid transport mechanisms.[433] Selenite is absorbed passively by simple diffusion, but SeO_4^{2-} is accumulated via a Na-mediated carrier with sulfate (SO_4^{2-}).[419,434,435] To date, there is no evidence for homeostatic control of Se absorption as neither dietary Se concentration nor bodily Se status influences absorption

efficiency.[436,437] Absorption of Se *is* influenced by animal species and the form of Se ingested. Selenomethionine, the predominant form of Se in forage plants, is absorbed more efficiently than inorganic forms of Se, at least when the comparison is based upon tissue concentrations.[438] Selenate is better absorbed than SeO_3^{2-}, at least in laboratory rodents, and both are more efficiently absorbed than elemental Se.[419] Ruminants reduce Se to unabsorbable selenides in the rumen and are therefore, to some degree, protected against poisoning. It is not unusual to see selenosis in pastured horses, while cattle on the same pasture remain unaffected.[426] Because the reduction of Se by rumen microflora is heavily influenced by other dietary factors, ruminants also exhibit greater variation in Se absorption than monogastrics.[415,439]

Following absorption, Se becomes associated with plasma proteins, mainly albumin and selenoprotein-P, for transport to tissues.[440] Selenomethionine is non-specifically substituted for methionine in protein[437] and only becomes available for either toxicity or nutrition as the protein turns over. Other forms are incorporated into essential selenoproteins and/or methylated to dimethylselenide and the trimethylselonium ion for elimination.[441] Both elimination and protein incorporation appear to involve metabolic activation to a reactive intermediate, which, when cellular defenses become saturated, is responsible for most of the toxic effects of Se.[419] Under normal conditions trimethylselonium is eliminated via urine and, to a lesser extent, bile, but as tissue concentrations increase to toxic levels an increasing percentage is eliminated via respiration as dimethylselenide.[419] Increased (i.e. potentially toxic) dietary Se also results in a shift of the distribution of Se between various proteins and body compartments[411,438,442] although both the physiologic and toxicologic significance of this observation is yet to be elucidated.

Selenium interacts with a number of other common dietary constituents, primarily at the pharmacokinetic (uptake, distribution, and elimination) level. These interactions modulate both the nutritional and toxic properties of Se. Arsenic (As) decreases Se toxicity by decreasing tissue Se concentrations.[35,38,443] Mercury decreases the toxicity of Se in birds[37,435] and possibly marine mammals.[411] Sulfur is thought to alleviate Se toxicity.[444] When sheep were given 2 mg of Se as sodium selenate (Na_2SeO_4), sheep receiving 0.05% dietary S showed a greater degree of Se toxicity when compared to sheep given 0.11, 0.17, or 0.24% S, mostly as added SO_4.[445] Dietary SO_4 decreased the Se balance in dairy cows fed Na_2SeO_4, reduced the true availability of nutritional levels of Se, and increased its excretion via feces in dairy cattle.[446] This interaction is hypothesized to occur as a result of S decreasing ruminal pH, altering Se metabolism to unavailable forms, as well as reducing the incorporation of dietary Se into ruminal bacteria.[445,447] Ruminal interactions, however, are not the only explanation for the inhibitory effect of S on Se toxicity. Added dietary SO_4 (0.29%) resulted in a 20% growth increase in rats fed 10 ppm Se; 0.58% SO_4 caused a 40% growth increase; and 0.87% SO_4 slightly prevented liver damage due to Se intoxication.[448] The interaction between SO_4 and Se is not universal, however. Three thousand mg SO_4^{2-}/L in drinking water failed to alter the uptake of sub-lethal dietary concentrations of sodium selenite (Na_2SeO_3) or selenomethionine in mallard ducks,[449,450] and more research is needed to elucidate the conditions under which the protective interaction occurs. Cyanogenic glycosides block uptake of Se and ameliorate Se toxicity[242,451] and have been investigated as a means of protecting livestock against selenosis. Copper and Cd have also been shown to reduce Se toxicity, though the mechanisms are not known.[37,452] Increased dietary protein has been suggested to reduce the severity of poisoning.[453] The type of feedstuff (alfalfa vs. grass hay) may influence the bioavailability of Se.[242] Even being Se deficient predisposes animals to Se toxicity.[454]

Toxicity

Although essential, Se exhibits a very narrow margin of safety. Toxic effects have occurred in livestock at dietary concentrations only 40-100 times larger than deficiency.[421] The form of Se administered influences tissue accumulation and thus toxicity.[455-460] The chemical species most common in water are the inorganic ions SeO_3^{2-} and SeO_4^{2-}. Selenium toxicity can be manifested in two forms, acute or chronic. Acute toxicity usually results in GI, liver, kidney, and heart damage, shock, and sudden death.[430,459,461] Selenium has also been implicated as a cause of hypertension and cardiac damage.[462] Reproductive deficits, including teratogenesis and embryonic mortality, occur in avian species[411,417,456,463]; however, there is no evidence Se is teratogenic in mammals.[464-466] Selenium may compromise reproduction in mammals.[467,468] Chronic selenosis ("alkali disease") in ungulates is manifested most obviously as epithelial damage (hair loss and cracked hooves) as a result of necrosis of the keratinocytes[450,469] and ill-thrift.

A single subcutaneous dose of 2 mg Se/kg BW given to pigs caused death after four hours.[470] Three hundred seventy six of 557 calves injected with a Na_2SeO_4 solution that contained 100 mg Se (0.5 mg/kg BW), rather than the 12 mg Se that was intended, died within five weeks.[471] Intramuscularly injecting 2 mg Se/kg BW as Na_2SeO_3 into four calves caused shock within three hours and death in 12 hours.[472] Ewes injected intramuscularly with doses from 0.4-1.0 mg Se/kg BW exhibited dyspnea, anorexia, colic, and a seromucoid nasal discharge. Doses less than 0.6 mg/kg BW were not lethal within 192 hours. The calculated LD_{50} was determined to be 0.7+/-0.035 mg/kg.[473] Injecting sheep intramuscularly with 0.68 mg Se/kg BW as Na_2SeO_3 produced death within 20 hours. Smaller doses took longer to be lethal, or they only caused reduced feed consumption and transient signs of intoxication.[473] Ninety µg Se/kg BW, given intramuscularly as Na_2SeO_4, produced no clinical signs in ewes. Three hundred fifty µg Se/kg BW was lethal in some ewes. Barium selenate ($BaSeO_4$), given similarly at rates of 0.225, 0.454, 0.908, 1.816, or 4.9 mg/kg BW produced no signs other than irritation at the injection site.[474]

Selenium fed as Na_2SeO_3 at rates of 22.3, 33.5, or 52.1 ppm dietary Se to rats for 359 days resulted in the deaths of five of nine, eight of nine, and all nine rats in the three treatment groups, respectively, as well as decreased fertility and anemia in the population as a whole.[475] An experiment focused on Se as a causative factor of tooth decay offered drinking water containing 3 mg Se/L as Na_2SeO_3 to rats for four weeks. Two of 15 rats died, and the others suffered significantly reduced feed consumption, water intake, and body weights.[476] Rations containing 6.4 ppm Se, as seleniferous wheat or Na_2SeO_3, resulted in significantly decreased growth and enlarged spleens in rats. Lower concentrations were without measurable effects. Higher concentrations resulted in decreased organ weights and anemia and were lethal in some rats.[477]

In one of the earliest controlled studies of Se dose-response, Miller and Williams[478] reported the single *oral* "minimum fatal doses" (which they defined as a dose large enough to kill 75% of the test group) were 0.68 mg Se/kg BW for horses and mules, 1.1-2.2 mg Se/kg BW for cattle and 2.2-3.6 mg Se/kg BW for swine, all given as Na_2SeO_3. Although the experimental protocol was not up to modern standards, more recent reports in cattle and horses usually agree within two- to five-fold. Depression, anorexia, hind limb ataxia, and sternal recumbency developed in 256 pigs in a commercial piggery after the pigs were exposed to feed containing 84 ppm Se.[479] Feed containing 8.1 ppm Se resulted in decreased feed consumption and paralysis in 54 feeder pigs.[480] Rations containing 14.75 ppm and 26.65 ppm selenium caused hair loss, reddening of skin, and hind limb ataxia in 80 of 160 pigs. Higher concentrations resulted in feed aversion.[481] Porcine diets fortified with approximately 25 ppm Se as Na_2SeO_3 resulted in hair and hoof lesions and weight loss. Higher concentrations produced feed aversion and poliomyelomalacia.[482] Corn, naturally contaminated with 10 ppm Se, fed for five months, resulted in two of five pigs developing alopecia and hoof lesions.[483] Pelleted rations containing 26.6 or 31.7 ppm Se, fed as Na_2SeO_3 or the Se-accumulator *A. bisulcatus,* respectively, and fed for several weeks, resulted in reduced feed consumption, alopecia, cracked hooves, and paralysis in pigs.[457]

A single dose of 5 mg Se/kg BW, given orally as Na_2SeO_3, was acutely toxic in lambs.[484] Drenching 190 lambs with 6.4 mg Se/kg BW resulted in the death of 180 within 15 days.[485] Twenty lambs, four to 14 days of age and averaging 4.5 kg, were mistakenly given 10 mg Na_2SeO_3 (2.2 mg Se/kg BW) orally to prevent white muscle disease; seven died within 17 hours, and eight more experienced diarrhea as a result of acute toxicosis. As a follow-up experiment, an additional ewe was injected with 0.45 mg Se/kg BW, which resulted in death within eight hours.[486] Glenn et al.[464] fed ewes increasing dosages of Na_2SeO_4 for 100 days and concluded the "minimum lethal" dose was 0.825 mg Se/kg BW/day. One of a group of 12 adult ewes and their lambs, pastured in an area of seleniferous forage and water, died following 14 days; other animals were unaffected when removed after four weeks. The exposure from the combination of contaminated forage and water was calculated to be 0.26 mg Se/kg BW/day.[413] Sheep were lethally poisoned by grazing high Se forage (<49 ppm Se DM) and drinking high Se water (340-415 µg Se/L) for four weeks; however, a similar group on a neighboring pasture with forages < 13 ppm Se and normal water were unaffected.[413]

Steers gavaged with varying doses between 0.25 and 0.5 mg Se/kg BW as Na_2SeO_3 exhibited inappetence, depression, and death. Two of eight died within eight weeks, and four more died within 14 weeks.[487] Feeding 0.28 and 0.8 mg Se/kg BW (approximately 10 ppm and 25 ppm Se, respectively, under range conditions) as selenomethionine or 0.8 mg Se/kg BW as Na_2SeO_3 to yearling steers for four months resulted in overt clinical signs of alkali disease in one steer and histological lesions of dyskeratosis in several more.[458] Primary antibody response was

significantly impaired in the same dose groups.[488] A dose of 0.15 mg/kg BW (approximately 5 ppm Se in diet), fed as either selenomethionine or Na_2SeO_3, and 0.28 mg/kg BW as Na_2SeO_3 in the same experiments were without measurable effects.[458,488] Dosing calves with 0.25 mg Se/kg BW as Na_2SeO_3 via bolus for 16 weeks resulted in hair and hoof lesions typical of selenosis and indications of increased oxidant stress.[489] Decreased growth and anemia occurred in pre-ruminant calves fed 10 ppm as Na_2SeO_4 for 40 days, but no measurable effects occurred in calves fed 0.2-5.0 ppm Se.[490]

There is a relative paucity of *quantitative* data in horses, although horses are the species most commonly diagnosed with selenosis at the Wyoming State Veterinary Laboratory. Ponies dosed via stomach tube with 6 or 8 mg Se/kg BW as Na_2SeO_3 developed signs of acute selenosis within six hours; ponies given 2 or 4 mg Se/kg BW remained clinically normal for the 14-day experiment.[452] A 4-year-old gelding accidentally given 25 mg Se (0.055 mg Se/kg BW) orally as Na_2SeO_4 for five consecutive days developed a straw-colored exudate on its lips, prepuce, and anus. Within three weeks, its hooves had separated from the coronary band, and alopecia was present on the mane and tail.[491] This report did not investigate the Se content of the rest of the diet. Chronic Se toxicosis was diagnosed in seven horses consuming hay containing between 0.49 and 58 ppm Se (mean 22 ppm) in combination with a mineral supplement that contained 1.9 ppm Se.[492,493] Eight of 20 horses developed alkali disease after being fed alfalfa hay that contained 5.9-17 ppm (mean = 11.9 ppm) Se for several weeks.[494] Several horses were diagnosed with alkali disease in southeastern Idaho after being turned into a pasture where the only water supply contained approximately 0.5 mg Se/L.[495] Assuming water consumption of 10% BW, this works out to 0.05 mg/kg BW, but there was probably some additional Se from forage in the pasture. Feeding horses oats containing 96 ppm added Se (19.2 ppm of total ration) as Na_2SeO_3 for several months resulted in listlessness, loosening of hair, softening of the horny wall of hoof, and, ultimately, death.[496] A 9-year-old gelding developed a swollen prepuce, vesicles on its nostrils and mouth, and hoof lesions of alkali disease after receiving 153.4 mg Se per day in his feed (16.4 ppm DM) for several days.[497] In Queensland, Australia, horses and sheep were diagnosed with chronic and acute Se toxicity after grazing areas with vegetation containing 200-3,038 ppm Se and corresponding soil concentrations of 64-128 ppm Se.[498]

In goats, daily oral doses of 5-160 mg Se/kg BW administered via capsules were uniformly lethal within 31 days. Daily doses of 0.11-0.45 mg Se/kg BW were given for 225 days with no toxic effects.[499] Elevated levels of selenium in the soil (1.45-2.25 ppm Se) and forage (40.32-80.64 ppm Se) in West Bengal, a state in India, have been blamed for a gangrenous condition ("Deg Nala") in grazing buffaloes exhibiting hoof cracks, malaise, abdominal pain, laminitis, and edema on the tails and ear tips.[500] Feeding captive pronghorn antelope grass hay that contained 15 ppm Se for 164 days did not result in any overt clinical signs but did decrease primary antibody response to a challenge with hen egg albumin.[501]

The foregoing notwithstanding, feeding steers seleniferous wheat, seleniferous hay, or a control diet with supplemental Na_2SeO_4 to supply 12 ppm dietary Se (65 µg Se/kg BW/day) for 100 days did not produce any *obvious* evidence of selenosis.[442,502] Ellis et al.[503] fed adult Holstein cows up to 50 mg Se/head/day (approximately 87 µg Se/kg BW/day) as Na_2SeO_3 for 90 days, followed by 100 mg Se/head/day (approximately 175 µg Se/kg BW/day) for another 28 days with no apparent health effects. Ewes tolerated 24 ppm dietary Se from Na_2SeO_3 or 29 ppm Se from *A. bisulcatus* for 88 days[504] or 10-15 ppm dietary Se through two pregnancies.[505] Cristaldi et al.[506] fed wether lambs Na_2SeO_3 at dietary Se concentrations up to 10 ppm for one year with no effect on rate of gain, serum enzymes, or pathology and concluded "≤10 ppm dietary Se as selenite is not toxic." The same research group fed 4, 8, 12, 16, and 20 ppm dietary Se as Na_2SeO_3 to adult ewes for 72 weeks with no effect upon body weight nor other evidence of poisoning.[507]

Summary

Although the NRC[421] suggests that horses are about as sensitive to oral Se as cattle, sheep, and goats, our research indicates that species sensitivity is horses > cattle > sheep and goats. Experience at several regional diagnostic labs indicates horses may be poisoned while ruminants using the same forage and water remain unaffected.[426,508,509] With the exception of one study in antelope, there is insufficient dose-response data upon which to base safety recommendations in large mammalian wildlife. That said, there are reports of elk and deer sharing pastures with horses, sheep, and cattle, where the horses developed alkali disease, without any measurable ill-effects in the elk and deer.[510] *Thus, water that is safe for horses should be safe for other livestock and ruminant wildlife species.*

The effects of water-borne Se are, like many other elements, additive with feed content. The chemical form of Se in surface waters is predominately SeO_3^{2-} or SeO_4^{2-}, which is fortunate as these ions are the forms most thoroughly researched. In theory, relatively small concentrations of Se in water may be sufficient to push animals on moderately high Se forages over the edge of toxicity. Unfortunately, the Se content of forage and hay in this region varies from marginally deficient to downright toxic, and other dietary factors such as protein, vitamin E, or cyanogenic glycosides may modify the effects of a given concentration of dietary Se. For purposes of this report, we assumed a "typical" forage containing 1 ppm Se (mostly as selenomethionine), normal protein, vitamin E, and other trace element concentrations. The threshold for chronic poisoning in horses from the literature is 0.05-0.1 mg/kg BW/day. This agrees with unpublished observations from our laboratories. Thus, water that contains 0.25 mg Se/L, consumed at a rate of 10% BW, combined with "average" Se forage, would constitute a potentially hazardous dose. In extremely hot weather, working horses drinking 20% BW of 0.125 mg Se/L water (a *very* conservative assumption) would receive a hazardous dose.

In areas where forage Se concentrations are higher, or if horses are receiving dietary supplements that contain Se, safe water concentrations will have to be adjusted downward, but under normal conditions, 0.1 mg/L should not cause problems.