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SELENIUM SUPPLEMENTATION FOR HORSE FEED

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History and current selenium regulations

Selenium (Se) was established as a dietary essential after it was demonstrated that a liver necrosis in rats fed torula yeast could be prevented by supplementing the yeast with Se (Schwarz and Foltz, 1957). Soon thereafter, practical problems relating to Se deficiency, e.g. white muscle disease of calves, lambs and foals, and exudative diathesis of poultry, were recognized. Burns Biotech Corp. was quick to develop injectable products (L-Se, Bo-Se, E-Se and Mu-Se) which gave veterinarians sources of supplemental Se (and vitamin E) for prophylaxis and therapy of these problems. The problem areas of the US became associated with regions of Se-deficient soils (Kubota *et al*, 1967). Ultimately, even human manifestations of Se deficiency (Keshan disease of children) in China became recognized (Keshan Disease Research Group, 1979).

The efforts to permit oral Se supplementation of livestock have been reviewed by Ullrey (1980, 1992a). The increasing prevalence of Se-responsive disease among US livestock through the 1960's prompted the American Feed Manufacturers Association (AFMA) to petition the Food and Drug Administration (FDA) for a GRAS (Generally Recognized as Safe) status for Se in March of 1970. The request was denied because the Director of the Board of Veterinary Medicine felt the AFMA petition did not show that food-producing animals would not be adversely affected by supplemental Se or that the Se residue in the products used for human food did not pose a carcinogenic risk. After AFMA supplied additional information on Se levels in typical livestock feeds, on background tissue Se concentrations, and on human Se intakes from Se-supplemented livestock, an official proposal to establish a food additive regulation governing the safe use of selenium in the feed of chickens, turkeys and swine was published in the Federal Register in June 1971. Almost 2.5 more years were required for sufficient data to be accumulated and/or generated to satisfy the FDA and United States Department of Agriculture (USDA) about the safety of Se supplementation of feeds for swine and poultry. On February 7, 1974, 17 years after the discovery that Se was an essential nutrient, it became legal to supplement swine and poultry (except laying hen) diets at 0.1 ppm (mg/kg).

It then took a special Selenium for Ruminant Animals Task Force, established in

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1975, two years to assemble published information and develop new data to prepare a petition to permit addition of Se to the diets of sheep and cattle at 0.1 ppm. These efforts culminated in FDA actions and Federal Register notices between March 1978 and January 1979, permitting Se supplementation at 0.1 ppm in the diets of sheep and cattle of all ages and sexes. In 1981, approval was granted for Se supplements of 0.1 ppm in diets of laying hens. In 1982, Se supplementation of swine prestarter and starter diets was approved at 0.3 ppm.

In 1983, the National Research Council (NRC) subcommittee on Se in Nutrition concluded that the dietary requirement of most animals was in the range of 0.05 to 0.3 ppm. This conclusion, in part, was the basis for the 1987 FDA approval for Se supplementation at 0.3 ppm in complete feeds of the major food producing animals, poultry (including ducks), cattle (dairy and beef), sheep and swine.

While the animal nutrition community generally agrees that 0.3 ppm is an appropriate and safe rate of Se supplementation, FDA is currently under pressure, particularly from environmentalist groups, to roll this rate back toward the 0.1 ppm. These groups claim, among other things, that the 0.3 ppm rate is contributing to Se contamination of recovered irrigation waters (as in the Kesterson Reservoir in California) sufficient to kill the water fowl and other aquatic life inhabiting these ponds. In actuality, when the variety of sources of environmental Se are calculated, it has been demonstrated that the 47.5 tons of Se which would be required annually to supplement the feed for all US livestock at 0.3 ppm, represent less than 0.5% of the Se in the environment originating from other anthropogenic and natural sources such as fuel combustion, industrial uses, rainfall and leaching of seleniferous rocks by ground water (Ullrey, 1992b).

It is important to note that horses, zoo animals, llamas and other pets were never included in any of the FDA regulations on Se supplementation. FDA probably elected not to include these species, in part, because they did not contribute to the human food chain (at least in the USA) and because the petitions for approval of Se supplementation did not include data on the benefits of dietary Se supplementation of these species. Unfortunately, this situation has created a dilemma for those trying to conduct sound feeding practices for these species. The burning question is: "Why should FDA restrict nutritionally sound Se supplementation practices for animals which will not affect the Se content of the human food chain?"

One interpretation of the FDA stand on this matter came in the form of a 1990 Notice of Adverse Findings from the Center of Veterinary Medicine to the President of Peninsular Products, a Lansing, MI manufacturer of MEGA-SEL. This product is a punch-like liquid labeled to contain 0.003% Se and 50 IU vitamin E/oz and promoted as a more satisfactory source of Se for horses than the standard Se-premixes designed to be mixed into concentrates. Even though the recommended dose of MEGA-SEL (1 oz/d/500 lb) would provide a 1000 lb horse with only 1.8 mg supplemental Se per day (equivalent to ~0.18 ppm if the horse consumed 10 Kg dry matter per day), the company was requested to cease marketing the product because there was no approved

food additive petition in effect (for horses) and no regulation permitting Se supplementation of equine diets. In contrast, a number of Veterinary Supply houses such as Butler Co., Vetpro Distribution Inc. and IDE Interstate, market a Se-containing oral supplement for horses (EQU SeE by Vet A Mix) and to my knowledge have not been requested to cease vending these products.

A petition for GRAS status for Se supplementation of equine diets was filed in May, 1991 by Real Selenium Inc. of Virginia. In July 1991, Real Selenium Inc. was notified that its petition could not be acted upon because it lacked the data and format required under section 21 CFR 5700.35 and the National Environmental Policy Act. At the time of writing, there is no new petition for GRAS status of Se as an equine dietary supplement.

Functions of selenium

It took about 15 years after the essentiality of Se was established, for investigators (Rotruck *et al.*, 1973) to determine one biochemical role of Se was as part of the enzyme, glutathione peroxidase (GSHpx). This is one of several cytosolic antioxidants which help protect cell membranes and organelles from oxidative damage. It is this antioxidant function which helps maintain muscle and vascular integrity and the competence of cells participating in the immune system. More recently, Se has been found to be a component of type I iodothyronine deiodinase (Beckett *et al.*, 1987; Behne *et al.*, 1992), a selenoenzyme which catalyzes the hepatic conversion of thyroxine (T4) to tri-iodothyronine (T3). This function would optimize utilization of thyroxine and/or formation of its tissue- active form (T3) if thyroid activity were limited by iodine deficiency. It is therefore possible that some clinical manifestations of hypothyroidism may be secondary to Se deficiency.

Clinical assessment of the selenium status of horses

Some of the first efforts to quantify the serum Se status of horses were conducted at the University of Kentucky (Stowe, 1967) using tedious Schoniger combustion flask technology for digestion, followed by fluorometric detection of the Se ion complex. Over time, several laboratories across the US have developed Se assay capabilities. Since 1982, the Clinical Nutrition Section of the Animal Health Diagnostic Laboratory (AHDL) at Michigan State University has provided serum and tissue Se analyses for diagnostic purposes on a fee for service basis and has generated a rather large Se data base on horses, food animals and exotic species. The expected or reference values developed from that data base for horses are as presented in Table 1. A summary of the 1990 - 1991 serum Se data (Stowe and

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Herd, 1992) from 599 adult horses (Thoroughbred, Standardbred, Quarter Horse) indicated their mean serum Se was 141 ± 35 ng/mL which is within the expected range for this age group and remarkably consistent with early estimates (Stowe, 1967).

Table 1. REFERENCE VALUES FOR SELENIUM IN SERUM, WHOLE BLOOD AND LIVER IN HORSES OF DIFFERENT AGES.^a

<i>Age (days)</i>	<i>Serum Se ng/mL</i>	<i>Whole blood Se^b g/mL</i>	<i>Liver Se ug/g DM</i>
1 - 9	70 - 90	98 - 135	1.2 - 2.0
10 - 30	80 - 100	112 - 150	1.2 - 2.0
31 - 300	90 - 110	126 - 165	1.2 - 2.0
301 - 700	100 - 130	140 - 195	1.2 - 2.0
<700	130 - 160	182 - 240	1.2 - 2.0

a Adapted from Stowe and Herd, 1992.

b Whole blood Se values for equine species are 1.4 to 1.5 x serum Se.

While GSHpx values, expressed usually as enzyme units/gram of hemoglobin (EU/g Hb), are expected to correlate well with Se intake and serum Se under well controlled conditions, GSHpx is not a preferred indicator of Se status for clinical diagnostic purposes. This is because the detected enzyme concentrations are subject to storage times and temperatures and to the kind of hemolyzing agent used in the assays. Additionally, a complete GSHpx response to Se supplementation requires some 80 - 90 days, equal to the life span of equine red blood cells. This is because the Se-containing GSHpx is incorporated in the red blood cells only during erythropoiesis, the time when the red cells are formed. Whole blood GSHpx values for the equine species assayed by MSU AHDL range from 40 to 160 EU/g Hb without a detectable age effect.

What is the feed industry doing about Se supplementation of equine feeds?

It is my understanding that at least some formulators and manufacturers of equine concentrate (grain) mixes are incorporating a Se source sufficient to create ~0.3 ppm Se in the total dry matter consumed by horses, particularly for growth, performance and brood mares. Thus, if the grain mix comprises 50% of the dry matter intake, a reasonable Se concentration in the grain mix would be 0.6 ppm because diluting it 50% with Se-deficient roughage would result in a Se concentration

of the total dry matter of ~0.3 ppm. This is the concentration FDA permits for food animal species and equine nutritionists have reason to believe that it is sound feeding management for horses as well, particularly when the Se status of the animals is monitored via serum or whole blood Se assays.

If the horse owner is unable to obtain Se-supplemented concentrates, appropriate quantities of Se could be provided by top-dressing Se premixes on the concentrate portion of each horse's daily ration and/or by providing access to a loose trace mineral salt mix with appropriate Se content.

So how much Se per day is reasonable? Assume a growing 200 kg (440 lb) horse consumed 3% of its body weight in dry matter daily, the total dietary dry matter would be 6 kg. (0.03 x 200 kg). It would take 1.8 mg (6 kg x 0.3 mg/kg) of Se to supplement that diet at 0.3 ppm Se. If Se 90/200 is the Se source, each ounce of that supplement contains 5.5 mg Se. So approximately 1/3 ounce (1.8 mg/5.5) of Se 90/200 would be an appropriate amount of Se supplement to top dress daily for a growing horse of that size.

Selenium toxicity and toxic reactions to injectable Se/vitamin E products

The maximum tolerable level (MTL) of dietary Se for horses is believed to approximate 2 ppm (NRC, 1980); therefore, there is a considerable margin of safety between the practiced 0.3 ppm rate of supplementation and the MTL. When Se was established as the element causing blind staggers and/or alkali disease in horses in the plains states in the 1930's (Franke, 1934), the affected horses had consumed products of seleniferous soils and/or plants capable of concentrating Se in their aerial parts to levels of several hundred ppm. Chronically affected horses developed cracked and very sore hooves, as well as impaired hair development, particularly of the mane and tail.

In 1991, the AHDL diagnosed Se toxicity among a group of 20 horses used in a feedlot operation in Nebraska. An initial serum sample taken from one affected horse had the highest serum Se concentration ever assayed in horse serum by the AHDL (928 ng/mL). The horses' hay, grown in western Nebraska and the primary nutrient source for these horses, was found to contain 20 ppm Se. As in the early cases of Se toxicity of horses, these horses experienced impaired hoof and hair development. Serum Se concentrations in these horses declined to the 250 - 325 ng/mL range within 8 weeks after the toxic hay was replaced by normal hay, and all but one of the horses recovered over time.

Untoward responses to injectable Se/vitamin E products have been observed in several species, and animal owners should be advised of the potential fatal effects of these products, even when used at recommended doses. The response is an immediate, usually fatal, anaphylactoid reaction. The reaction is not to the Se or vitamin E in the

product but apparently to an emulsifying agent or preservative present in the product. An immediate injection of epinephrine or antihistamine into the horse experiencing the anaphylactoid reaction may save the animal but often is of no help. If the reaction is not fatal, the horse may develop a generalized edema and/or apparent blindness for a period of time. None of these untoward reactions is observed from oral administration of Se at appropriate rates.

Summary

“Determination of nutrient essentiality or of the quantitative requirements is not a political act” (Ullrey, 1980). The FDA, however, has assumed the authority to regulate essential Se additions to animal diets and now permits 0.3 ppm supplemental Se in the diets of poultry, sheep, swine and cattle. While horses are not included in this list, it is gratifying to know that feed manufacturers are providing appropriate options to people to meet the Se requirements of their horses on a scale comparable to that permitted in the food animal species. I would like to think that FDA will remain tolerant of these options because they are conducive to equine health and do not pose a threat to the human food chain. In the interim, it would be prudent for the equine industry to assemble a task force, as did the ruminant industry, to prepare a new petition or assist Real Selenium Inc. in resubmitting its petition for GRAS status of Se in equine feeds. The Equine Nutrition and Physiology Society might wish to play a role in this task.

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