Selenium Supplementation Using Se-Biofortified Forages Improves Cattle Health and Performance

Jean A. Hall, DVM, PhD, Diplomate ACVIM
Oregon State University

Background

Selenium (Se) has been recognized for years as an essential trace element for ruminant animals. Selenium deficiencies have been described in many species, including cattle, sheep goats, horse, swine, white-tailed deer, and elk. In general, the majority of livestock raised in low-Se regions do not receive sufficient dietary Se for optimum health. Severe Se deficiency in ruminants results in nutritional myodegeneration known as “white muscle disease” [1], whereas insufficient Se intake has been implicated as the cause of a group of Se-responsive disorders including unthriftiness, reduced weight gain, and immunosuppression [2]. The Se status of plants, animals, and humans varies markedly around the world as a result of different geological conditions. Animal health is affected by Se deficiency in the diet, which depends on the amount of bioavailable Se taken up by plants. In the US, a survey of state veterinarians and state veterinary diagnostic labs revealed that Se-deficiency diseases were diagnosed in 46 states and were reported to be an important livestock problem in regions of 37 states [3].

Livestock fed Se-deficient forages must receive Se supplements to ensure optimum health. In the United States, Se was approved as a feed additive in 1979 by the Food and Drug Administration (FDA) to respond to the documented deficiency of Se in animal feeds, first at a concentration of 0.1 mg/kg DM, and then after April 1987 at a concentration of 0.3 mg/kg DM [4]. For cattle, salt can be added to feed up to 120 ppm, but must not exceed a maximum intake of 3 mg Se/head daily (equivalent to 1.5 oz salt/head daily). For sheep, salt mineral mixtures can be added to feed up to 90 ppm, but must not exceed a maximum intake of 0.7 mg Se/head daily (equivalent to 0.25-0.33 oz salt/head daily). These amounts are for supplemental Se and do not take into account natural Se concentrations already present in feed.

There has been a significant decline in nutritional myodegeneration cases in ruminant species using the current FDA-allowed Se-supplementation regulations. Selenium supplementation is credited with improving animal health, e.g., reduced prevalence of retained fetal membranes, decreased severity and prevalence of clinical mastitis, decreased somatic cell counts in milk, decreased calf mortality, and increased mobilization and killing capacity of neutrophils (reviewed in [5-9]). Nonetheless, we have observed suboptimal blood-Se concentrations in ruminants offered Se supplements [10]. Reasons for this may include inadequate Se intake, or problems with Se bioavailability. Selenium bioavailability can be limited by dietary factors. For example, increasing dietary sulfur decreases Se bioavailability, and the presence of cyanogenic glycosides in certain legumes are also antagonistic to Se (reviewed in [11]).

There is also large variation in oral bioavailability between different chemical forms of Se. Most Se is supplemented in the form of inorganic sodium salts in mineral mixtures that are commonly left outside for several weeks for sheep or cattle to consume *ad libitum*. The primary form of Se in these supplements is inorganic sodium selenite because it is easier to purchase than sodium selenate, although sodium selenate is more stable than sodium selenite and has greater small intestinal absorption in nonruminants (reviewed in [12]). Selenium can also be supplemented as organic selenomethionine (SeMet). In the United States, organic Se was approved as a feed additive in 2003 by the FDA at the same supplementation rates as inorganic Se forms, even though there is a documented increase in bioavailability.

Rumen microorganisms (RMO) can also decrease Se bioavailability by reducing selenite into non-absorbable elemental Se, which is then excreted in the feces [13-15]. It is known that absorption of Se by ruminants is less compared with non-ruminants [16]. For example, researchers have shown that absorption of orally administered Se was 34% in sheep compared with 85% in swine [11]. Although enrichment of Se occurs in RMO compared with dietary levels [17,18], smaller amounts of inorganic sodium selenite or sodium selenate are incorporated into

RMO than SeMet, which is the primary form of Se found in Se-yeast [19,20] and high-Se grains and forages [12,21].

We previously showed that ewes receiving sodium selenite or sodium selenate by weekly oral drenching had decreased whole-blood and serum-Se concentrations compared with ewes receiving the same dosage of SeMet as Se-yeast [22]. To determine if RMO were responsible in part for these findings, we conducted an *ex vivo* experiment to evaluate the effect of sodium selenite, sodium selenate, and SeMet on Se uptake and elemental Se formation by RMO. Our results showed that organic Se as SeMet was incorporated to a greater extent into RMO than inorganic Se sources and resulted in less elemental Se formation. Thus, decreased bioavailability of inorganic Se compared with Se-yeast noted in our whole animal studies may be explained by these *ex-vivo* results showing increased elemental Se formation and decreased microbial incorporation of inorganic Se. In ruminants, the improved bioavailability of SeMet compared with inorganic Se may be the result of rumen-based reactions (increased incorporation of SeMet into RMO and decreased formation of elemental Se) rather than at the level of the small intestine (increased absorption efficiency). Consumption of Se-fertilized forage [23,24] as a source of organic Se provides an attractive alternative to inorganic Se supplements, because organic SeMet in forage is better incorporated into RMO and results in less elemental Se formation.

Methods of Se Supplementation

Several means of administering Se to deficient livestock are available. For example, there are a number of injectable preparations, which often include vitamin E. Selenium can also be added to feed, mineral, and protein supplements. Sustained-release boluses with a life of several months may be used. Because of their weight, these boluses stay in the rumen whereby they gradually release Se. Selenium supplemented by these methods is usually inorganic sodium selenite or selenate. One limitation of supplementing with inorganic Se in salt or feed is the apparent short duration of Se storage in the animal. If Se is removed from the diet, blood Se concentrations may become deficient if they were initially in the lower part of the normal reference interval. Seasonal grazing practices may result in limited access to Se-containing salt-mineral mixes for extended periods of time, and therefore, livestock may be Se deficient by the end of the grazing season.

Agronomic biofortification is defined as increasing the bioavailable concentrations of essential elements in edible portions of crop plants through the use of fertilizers. The potential for using Se-containing fertilizers to increase crop Se concentrations and, thus, dietary Se intake has been demonstrated in Finland, New Zealand, and Australia where it has been proven to be both effective and safe [25-27].

Functions of Selenoproteins

Selenium is incorporated into selenoproteins whose functions range from antioxidant, anti-inflammatory, and detoxification to thyroid hormone activation [28]. Evidence suggests that Se exerts its effects in part by enhancing innate and adaptive immune responses [29]. This is not surprising given that many selenocysteine (SeCys)-containing proteins are involved in regulating redox reactions, in removal of reactive oxygen species (ROS), and in other important cellular reactions (e.g., cell growth, apoptosis, and regulation of transcription) in a variety of tissues [29,28]. Levels of ROS influence inflammatory gene expression; thus selenoproteins can affect inflammatory responses by regulating the oxidative state of immune cells [30]. The selenoproteins involved in controlling oxidative stress include glutathione peroxidases (GPX) and thioredoxin reductases (TXNRD) [31]. In the GPX family, GPX1 acts as an antioxidant and uses glutathione as a cofactor to reduce hydroperoxides to their corresponding alcohols [32]. Hydroperoxides are non-radical ROS. The phospholipid hydroperoxide GPX4 is the major antioxidant enzyme that directly reduces phospholipid hydroperoxides within membranes and lipoproteins [32]. The TXNRD use NADPH in thioredoxin-dependent antioxidant pathways to reduce oxidized thioredoxins that are formed when oxidized proteins and lipids are detoxified [30]. Selenoprotein P (SELENOP) is important in the transport of Se to tissues, but also has antioxidant activity [33], as does selenoprotein W (SELENOW) [34]. Transcription factors such as FBJ murine osteosarcoma viral oncogene homolog (FOS; also a member of the activator protein-1 family) and nuclear factor kappa B (NFκB) are activated by ROS, and removal of these from cells by selenoproteins prevents induction and activation of pro-inflammatory signaling cascades (reviewed in

[35]). For example, overexpression of GPX4 inhibits the expression of NFκB target genes, and IL-1- dependent signaling of leukotriene and prostanoid biosynthesis is reduced [32]. Specific selenoproteins also have ROS-independent roles in modulating inflammatory responses [30]. Selenoprotein S (SELENOS) plays a role in the transcription of genes encoding pro-inflammatory cytokines [36,37]. The iodothyronine deiodinases (DIO) regulate the bioactivity of thyroid hormones by controlling levels of thyroxine (T4) and the active hormone, 3,3′,5-triiodo L-thyronine (T3). Whereas DIO2 is responsible for the conversion of T4 to the active hormone T3, DIO3 catalyzes the inactivation of T4 and T3. Although the role of thyroid hormones in inflammatory responses remains unclear, suppression of DIO2 has recently been shown to result in increased expression of inflammatory cytokine mediators [38]. Thus, several mechanisms are hypothesized for how Se affects immune responses, including protection against oxidative damage resulting in decreased inflammation and transcriptional regulation of genes encoding pro-inflammatory cytokines.

Se Metabolism: Fate of Se in the Body after Uptake from the Diet
Regulation of Se metabolism is controlled by its availability. When the supply of Se is greater than needed for selenoprotein synthesis, excess Se is excreted. There are several cellular mechanisms that regulate Se use for synthesis of specific selenoproteins (reviewed in [39]. Some selenoproteins are favored over others for Se incorporation, creating a cellular hierarchy. For example, SELENOP is higher in the liver cellular hierarchy than GPX1. The liver secretes SELENOP into the plasma to supply other tissue with Se. SELENOP binds to the endocytic receptor apo ER2. Apo ER2 varies among tissues, creating an organ hierarchy for Se in SELENOP uptake. This is how the liver Se can maintain selenoproteins in other parts of the body. Human plasma contains most of its Se in two selenoproteins: GPX3, which originates in the kidney, and SELENOP, which originates in the liver. Plasma also contains unregulated SeMet in all of its methionine-containing proteins. Thus, plasma Se does not accurately mirror the regulated Se pool. Plasma GPX3 reflects kidney Se and SELENOP reflects liver Se. Plasma SELENOP may be the most accurate indicator of whole-body Se [39].

Selenium-Biofortification: Forms and Methods of Se Application, Uptake and Metabolism by Plants.
For over 20 years, research at Oregon State University has demonstrated the potential for using Se as a fertilizer to increase Se concentrations in forage for livestock feeds. Research in New Zealand, confirmed by OSU trials, found that sodium selenate is the form of Se most efficiently taken up by plants. The recommended level of application is 5 to 10 grams of actual Se per acre to achieve adequate levels of Se in forage. Sodium selenate is 41% Se. An application rate of 12 to 24 grams of sodium selenate per acre will provide the recommended 5 to 10 grams of actual Se per acre.

A pelleted material from New Zealand (called Selcote Ultra) contains sodium selenite that is 4.5 grams of actual Se per pound. This product is approved for use in Oregon by the Oregon Department of Agriculture and can only be mixed with fertilizer by a licensed fertilizer dealer. Recommended application rates of Selcote Ultra are 1 to 2 pounds per acre. Late winter or early spring applications are most effective; however, there is some evidence that a fall application will provide sufficient Se for plant uptake in the spring. Hay produced from Se-fertilized forage is another excellent source of organic Se.

Selenium is not an essential element for plants, and excess Se accumulation is toxic to most plants, most likely because the indiscriminate incorporation of SeCys and SeMet into proteins impairs their function [40].

Recent Studies that Show a Benefit for Feeding Se-Biofortified Hay

Hall JA, Harwell AM, Van Saun RJ, Vorachek WR, Stewart WC, Galbraith ML, Hooper KJ, Hunter JK, Mosher WD, Pirelli GJ. **Agronomic biofortification with selenium: Effects on whole blood selenium and humoral immunity in beef cattle.** *Animal Feed Science and Technology* 2011; 164:184-190.

The purpose of this study [24] was to evaluate Se supplementation strategies in mature beef cattle by measuring changes in whole-blood Se (WB-Se) status and humoral immune response to vaccination. Mature beef cows (n =

45) were balanced by age and randomly assigned to1 of 3 supplementation groups that received different chemical forms of Se or Se dosages compared to a standard (control) Se treatment. Supplementation treatment groups were provided limited access (6 weeks) to either sodium selenite (200 mg/kg Se; LSe) or Se-fertilized forage (FSe) and subsequently had no additional Se in their mineral supplement for the study duration. The LSe group cows grazed non-Se-fertilized forage. The control group grazed non-Se-fertilized forage and received continuous Se supplementation (CSe) from a free-choice mineral supplement (120 mg/kg Se from sodium selenite). Cows were bled pre and post grazing and then every 4 weeks thereafter for approximately 5 months to assess WB-Se concentration. All cows were immunized with J-5 Escherichia coli bacterin at the end of the 6-week supplementation period, and serum was collected for antibody titers 2 and 4 weeks after the third immunization. Covariate adjusted WB-Se concentrations were influenced ($P<0.0001$) by group, time and their interaction. Cows in the FSe group had higher ($P<0.0001$) WB-Se concentration (186±5 ng/mL) immediately post-grazing (42 days) compared to LSe (117±5 ng/mL) and CSe cows (130±5 ng/mL). WB-Se concentration in FSe cows remained higher ($P=0.02$ to $P<0.0001$) over the next 4 (CSe) and 5 (LSe) months. Higher ($P<0.05$) WB-Se concentrations were observed in CSe compared to LSe cows over the last 4 months of the study. Treatment group ($P=0.036$) and time post vaccination ($P<0.0001$) influenced J-5 E. coli antibody titers, with FSe cows having higher titers than LSe cows ($P=0.01$), although FSe and CSe cows were not different. Short-term exposure of cattle to Se-fertilized forage elevates WB-Se concentrations within several weeks and this exposure is sufficient to maintain adequate concentrations throughout grazing periods when there is limited access to Se supplements. Short term exposure to higher levels of inorganic Se supplementation is not equivalent to ongoing inorganic Se supplementation at lower rates.

Hall JA, Bobe G, Hunter JK, Vorachek WR, Stewart WC, Vanegas JA, Estill CT, Mosher WD, Pirelli GJ. **Effect of feeding selenium-fertilized alfalfa hay on performance of weaned beef calves.** *PLoS ONE* 2013; 8(3):e58188. doi: 10.1371/journal.pone.0058188.

Selenium (Se) is an essential micronutrient in cattle, and Se-deficiency can affect morbidity and mortality. Calves may have greater Se requirements during periods of stress, such as during the transitional period between weaning and movement to a feedlot. Previously, we showed that feeding Se-fertilized forage increases whole-blood (WB) Se concentrations in mature beef cows. Our current objective was to test whether feeding Se-fertilized forage increases WB-Se concentrations and performance in weaned beef calves [41]. Recently weaned beef calves (n = 60) were blocked by body weight, randomly assigned to 4 groups, and fed an alfalfa hay based diet for 7 wk, which was harvested from fields fertilized with sodium-selenate at a rate of 0, 22.5, 45.0, or 89.9 g Se/ha. Blood samples were collected weekly and analyzed for WB-Se concentrations. Body weight and health status of calves were monitored during the 7-wk feeding trial. Increasing application rates of Se fertilizer resulted in increased alfalfa hay Se content for that cutting of alfalfa (0.07, 0.95, 1.55, 3.26 mg Se/kg dry matter for Se application rates of 0, 22.5, 45.0, or 89.9 g Se/ha, respectively). Feeding Se-fertilized alfalfa hay during the 7-wk preconditioning period increased WB-Se concentrations ($P = 0.001$) and body weights ($P = 0.002$) depending upon the Se-application rate. Based upon our results we suggest that soil-Se fertilization is a potential management tool to improve Se-status and performance in weaned calves in areas with low soil-Se concentrations.

Hall JA, Bobe G, Vorachek WR, Hugejiletu, Gorman ME, Mosher WD, Pirelli GJ. **Effects of feeding selenium-enriched alfalfa hay on immunity and health of weaned beef calves.** *Biol Trace Elem Res* 2013; 156(1-3):96-110. doi: 10.1007/s12011-013-9843-0.

Previously, we reported that feeding selenium (Se)-enriched forage improves antibody titers in mature beef cows, and whole-blood Se concentrations and growth rates in weaned beef calves [41]. Our current objective was to test whether beef calves fed Se-enriched alfalfa hay during the transition period between weaning and movement to a feedlot also have improved immune responses and slaughter weights [8]. Recently weaned beef calves (n =60) were fed an alfalfa-hay-based diet for 7 weeks, which was harvested from fields fertilized with sodium selenate at 0, 22.5, 45.0, or 89.9 g Se/ha. All calves were immunized with J-5 Escherichia coli bacterin. Serum was collected for antibody titers 2 weeks after the third immunization. Whole-blood neutrophils collected at 6 or 7 weeks were evaluated for total antioxidant potential, bacterial killing activity, and expression of genes associated with selenoproteins and innate immunity. Calves fed the highest versus the lowest level of Se-enriched alfalfa hay had higher antibody titers (P=0.02), thioredoxin reductase-2 mRNA levels (P=0.07), and a greater neutrophil total antioxidant potential (P=0.10),whereas mRNA levels of interleukin-8 receptor (P=0.02), L-selectin (P=0.07), and thioredoxin reductase-1 (P=0.07) were lower. In the feedlot, calves previously fed the highest-Se forage had lower mortality (P=0.04) and greater slaughter weights (P=0.02). Our results suggest that, in areas with low-forage Se concentrations, feeding beef calves Se-enriched alfalfa hay during the weaning transition period improves vaccination responses and subsequent growth and survival in the feedlot.

Hall JA, Isaiah A, Estill CT, Pirelli GJ, Suchodolski JS. **Weaned beef calves fed selenium-biofortified alfalfa hay have an enriched nasal microbiota compared with healthy controls.** *PLoS ONE* 2017; 12(6):e0179215. doi: 10.1371/journal.pone.0179215.

Selenium (Se) is an essential trace mineral important for immune function and overall health of cattle. The nasopharyngeal microbiota in cattle plays an important role in overall respiratory health, especially when stresses associated with weaning, transport, and adaptation to a feedlot affect the normal respiratory defenses. Recent evidence suggests that cattle diagnosed with bovine respiratory disease complex have significantly less bacterial diversity. The objective of this study was to determine whether feeding weaned beef calves Se-enriched alfalfa (*Medicago sativa*) hay for 9 weeks in a preconditioning program prior to entering the feedlot alters nasal microbiota [42]. Recently weaned beef calves (n=45) were blocked by sex and body weight, randomly assigned to 3 treatment groups with 3 pens of 5 calves per treatment group, and fed an alfalfa hay based diet for 9 weeks. Alfalfa hay was harvested from fields fertilized with sodium selenate at a rate of 0, 45.0 or 89.9 g Se/ha. Blood samples were collected biweekly and analyzed for whole-blood Se concentrations. Nasal swabs were collected during week 9 from one or two calves from each pen (total n=16). Calculated Se intake from dietary sources was 3.0, 15.6, and 32.2 mg Se/head/day for calves consuming alfalfa hay with Se concentrations of 0.34 to 2.42 and 5.17 mg Se/kg dry matter, respectively. Whole-blood Se concentrations after 8 weeks of feeding Se-fertilized alfalfa hay were dependent upon Se-application rates (0, 45.0, or 89.9 g Se/ha) and were 155, 345, and 504 ng/mL ($P_{\mathrm{Linear}} < 0.0001$). Microbial DNA was extracted from nasal swabs and amplified and sequenced. Alpha rarefaction curves comparing the species richness (observed OTUs) and overall diversity (Chao1, Observed OTU, and Shannon index) between calves fed selenium-biofortified alfalfa hay compared with control calves showed that Se-supplementation tended to be associated with an enriched nasal microbiota. ANOSIM of unweighted UniFrac distances showed that calves fed high Se-biofortified alfalfa hay clustered separately when compared with control calves in the PCoA plot (R = 0.216, P= 0.04). The bacterial orders *Lactobacillales* and *Flavobacteriales* were increased in healthy control calves compared with *Clostridiales* and *Bacteroidales* being increased in calves fed Se-biofortified alfalfa hay. Although there were strong trends, no significant differences were noted for any of the bacterial taxa. Based upon these findings, we suggest that weaned beef calves fed Se-biofortified hay tend to have an enriched nasal microbiota. Feeding Se-biofortified alfalfa hay to weaned beef calves prior to entering the feedlot is a strategy for increasing nasopharyngeal microbial diversity.

Hall J, Bobe G. Effects of feeding cows Se-yeast or Se-enriched alfalfa hay on baby calves Se status and IgG titers. **11th International Symposium on Selenium in Biology and Medicine and 5th International Conference on Selenium in the Environment and Human Health.** 2017, Stockholm, Sweden.

Introduction: Selenium (Se) is an essential trace mineral important for immune function and overall health of cattle. Two methods of Se-delivery to pregnant cows are organic Se-yeast supplementation and agronomic Se biofortification, whereby the Se content of hay is increased through the use of Se-containing fertilizer amendments. Our objective was to evaluate the effect of these two Se-delivery methods in cows on passive transfer of IgG to calves.

Methods: Se-Yeast Supplementation: During the last 8-wk before calving, dairy cows were fed either 0 (n=17) or 105 mg Se-yeast once weekly (n=20), in addition to Na-selenite at 0.3 mg Se/kg DM in their ration [43]. The Se-

yeast dosage was calculated to provide 15 mg of Se/d (5× the maximal FDA-permitted level). After birth, calves were fed pooled colostrum from control or supranutritional Se-yeast supplemented cows. Concentrations of whole-blood (WB)-Se and serum-IgG were measured at birth, 48-h, and 14-d of age.
Agronomic Biofortification: During the last 8-wk before calving, beef cows were fed alfalfa hay fertilized with 0 (calculated Se intake: 8.3 mg Se/head/d; n=15), 45.0 (27.6 mg Se/head/d; n=15), or 89.9g Se/ha (57.5 mg Se/head/d; n=15). Concentrations of colostrum-Se and IgG1 were measured at birth, and concentrations of calf WB-Se and serum-IgG1 were measured at birth and 12, 24, 36, and 48-h of age [44].
Chemical Analysis: Concentrations of IgG1 were quantified by ELISA, and Se concentrations by an inductively coupled argon plasma emission spectrophotometry method by commercial laboratories (Michigan State University, East Lansing, MI, for the WB-dairy cow samples and Utah Veterinary Diagnostic Laboratory, Logan, UT, for all other samples).

Results and Discussion: Se-Yeast Supplementation: Calves born to Se-yeast supplemented cows had higher WB-Se concentrations at birth (280±7 vs. 190±9ng/mL; P<0.0001), 48h (323±11 vs. 221±14; P<0.0001), and d14 (238±7 vs. 184±9; P<0.0001), and higher IgG absorption efficiency (40±4 vs. 23±4% at 48 h; P=0.004), resulting in higher serum-IgG concentrations (20.8±1.8 vs. 12.3±2.0mg/mL at 48 h; P=0.003 and 6.8±0.5 vs. 4.8±0.6mg/mL at 14 d; P=0.01) and higher serum-IgG content (58.1±4.5 vs. 31.5±5.0g at 48 h; P=0.0004 and 23.4±1.6 vs. 15.5±1.7g at 14 d; P=0.002), compared with calves born to control cows.

Agronomic Biofortification: Colostral Se concentrations increased with Se-fertilization from 119±51(0g Se/ha) to 504±51(45.0g Se/ha), and 1,336±51 ng/mL(89.9g Se/ha), and IgG1 concentrations from 107±5(0g Se/ha) to 167±34(45.0g Se/ha), and 198±51 ng/mL(89.9g Se/ha). Calf WB-Se concentrations at birth increased with Se-fertilization from 138±37(0g Se/ha) to 279±37(45.0g Se/ha), and 429±37 ng/mL(89.9g Se/ha), but Se-fertilization had no effect on serum IgG1 concentrations during the first 48 h of age. Thus, feeding Se-biofortified alfalfa hay promotes the accumulation of Se and antibodies in colostrum, but a physiologic limitation of small intestinal epithelial cells to absorb additional antibodies may have limited our ability to observe differences in serum antibody concentrations in these calves.

Conclusion: Both Se supplementation strategies for cows during the dry period were effective for maximizing WB-Se and serum-IgG concentrations in calves. The more economical alternative is agronomic biofortification because it involves less labor and costs.

Conclusions
As beef producers enter into niche markets with grass finished beef and restricted use of antibiotics, more knowledge on alternative practices to enhance cattle health and prevent diseases is important. Results of these studies provide evidence for hay producers in Oregon to adopt the practice of Se-fertilization of forages to provide an enhanced quality of hay, which will then be used to benefit performance and health of beef cattle. This is an innovative and economically viable way of supplementing Se to cattle in our Se-deficient state that we hope will be adopted by hay and cattle producers.

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