Copper and Selenium Metabolism and Supplemental Strategies for Grazing Beef Cattle

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Introduction

Trace minerals have long been identified as essential components in the diets of domestic livestock species. Chromium, cobalt, copper, iodine, iron, manganese, molybdenum, nickel, selenium, and zinc are included in the category of essential trace minerals (or microminerals). Trace minerals exist in cells and tissues of the animal body in a variety of chemical combinations, and in characteristic concentrations, depending on the trace mineral consumed and the tissue in which the trace mineral is metabolized (McDowell, 1992; Underwood and Suttle, 1999). Concentrations of trace minerals must be maintained within narrow limits in a cell (McDowell, 1989, 1992; Underwood and Suttle, 1999). Trace mineral deficiencies, toxicities, and imbalances require the animal to metabolically compensate for the nutrient deviation (McDowell, 1989, 1992; Underwood and Suttle, 1999). In doing so, certain metabolic diseases can manifest and overall animal production can be depressed, thus decreasing overall animal performance and health.

Supplementation of minerals to beef cattle has been shown to have positive effects on reproduction, immune status, disease resistance, and feed intake when specific trace minerals are deficient or imbalanced in the diet. Trace minerals have been identified as essential components for carbohydrate, lipid, protein, and vitamin metabolism, and have been shown to be involved in hormone production, immunity, and cellular homeostasis. In general, trace minerals function primarily as catalysts in enzyme systems within cells. Enzymes requiring trace minerals for proper function can be classified into two categories: 1) metal activated enzymes and 2) metalloenzymes. The requirement for a metal in metal-activated enzymes may or may not be absolute; however, the presence of a metal is typically required for optimizing enzyme activity. Metalloenzymes are enzymes that contain a tightly bound metal ion at or near the active site. The metal ions bound to metalloenzymes are actively involved in enzyme function and removal of the metal ion renders the enzyme non-functional. Enzymes associated with the electron transport, bone metabolism, immune function, oxidative stress protection, and gene expression require trace minerals for proper function (Underwood and Suttle, 1999). The specific functions of copper and selenium fall mainly into the catalytic and regulatory categories as described above. The intent of this review is to briefly discuss: 1) the functions of copper and selenium; 2) troubleshooting a potential

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trace mineral deficiency; 3) supplementation strategies, and 4) possible factors that may impact trace mineral requirements in ruminants.

**Functions of Copper and Selenium**

**Copper**: Copper is second only to zinc in the number of enzymes that require this metal for appropriate function (Underwood and Suttle, 1999). Copper is therefore essential to proper physiological function and is involved in an array of metabolic systems. These include iron metabolism, cellular respiration, cross-linking of connective tissue, central nervous system formation, reproduction, and immunity (McDowell, 1992).

In order for hemoglobin synthesis to occur, iron must be converted to the ferric form before being incorporated into the hemoglobin molecule. This process is accomplished by ceruloplasmin, which is a copper containing enzyme synthesized in the liver (Saenko et al., 1994). Copper is also an essential component in the enzyme cytochrome oxidase. This enzyme acts as the terminal oxidase in the electron transport chain and is essential to cellular respiration by converting oxygen to water (Spears, 1999). Cytochrome oxidase is also necessary for proper central nervous system function. Cross-linking of connective tissue is also facilitated by a copper-containing enzyme, lysyl oxidase (Harris and O'Dell, 1974).

The requirement for copper for optimal reproductive performance has also been widely documented, although a specific copper-linked enzyme that is responsible has not been identified. It is likely that an array of copper-containing or copper-activated compounds is involved in the reproductive process making this identification even more difficult. Corah and Ives (1991) noted that clinical signs of copper deficiency associated with reproduction include decreased conception rate, overall infertility, anestrus and pregnancy loss. Some of these problems may be associated with the function of a major enzyme: copper-zinc superoxide dismutase. This copper-containing enzyme functions as an antioxidant to protect cells involved in reproduction from oxidative stress. The same copper-zinc superoxide dismutase has also been implicated in contributing to proper function of the immune system as well (Miller et al., 1979).

Signs of copper deficiency in ruminants include anemia, bone and connective tissue disorders, neonatal ataxia, cardiovascular disorders, depigmentation of hair or wool, impaired immunity, and infertility. Copper deficiency can be produced by removal of copper from the diet but more often, under practical conditions, copper deficiency is produced by antagonists present in the diet or water. High concentrations of sulfur, molybdenum, iron, and zinc have been shown to inhibit the absorption of copper (Miltimore and Mason, 1971; Huisingh et al. 1973; Ward, 1978; Suttle 1974, 1975, 1991; Phillippo et al., 1987).

**Selenium**: Selenium was first identified in the 1930’s as a toxic element to some plants and animals. However, selenium is now known to be required by laboratory animals, food animals, and humans (McDowell, 1992; Underwood and Suttle, 1999). Selenium is necessary for growth and fertility in animals and for the prevention of a
variety of disease conditions. Rotruck et al. (1973) reported that selenium functions as a component of glutathione peroxidase, an enzyme that inactivates oxygen radicals such as hydrogen peroxide and prevents oxygen radicals from causing cellular damage.

Since the discovery by Rotruck et al. (1973), selenium has been shown to affect specific components of the immune system (Mulhern et al., 1985). Earlier research by Reffett et al. (1988) reported lower serum immunoglobulin (Ig) M (an antibody produced by B cells) concentrations and anti-infectious bovine rhinotracheitis virus (IBRV) titers in selenium deficient calves challenged with IBRV than when compared to selenium adequate calves. Polymorphonuclear leukocyte function was reduced in goats (Azizi et al., 1984) and cattle (Gyang et al., 1984) fed selenium deficient diets compared with controls receiving selenium-adequate diets. Some studies have shown increased T-lymphocyte proliferation following in vitro stimulation with mitogen while others have not (Spears, 2000). Bovine mammary endothelial cells growing in selenium deficient cell culture media were found to exhibit enhanced neutrophil adherence when stimulated with cytokines (Maddox et al., 1999; Spears, 2000). These findings indicate that selenium may impact neutrophil migration into tissues and subsequent inflammation.

Several other selenium containing proteins (selenoproteins) have been purified since Rotruck et al. (1973) reported selenium’s involvement in glutathione peroxidase. These include several glutathione peroxidase enzymes (1-4), iodothyronine 5’-deiodinase Type I, II, and III which are involved in thyroid hormone metabolism (conversion of T4 to T3), thioredoxin reductase, selenoprotein P (selenium transporter), and selenoprotein W (may serves as an antioxidant; Arthur and Beckett, 1994; Sunde, R. A., 1994; Underwood and Suttle, 1999).

Signs of selenium deficiency include white muscle disease, Heinz-body anemias, reproductive disorders (embryonic mortality, infertility, and retained placenta), impaired immune function, and growth impairment (Underwood and Suttle, 1999). The majority of these disorders are caused by a reduction in the antioxidant capacity of cells due to a reduction in selenium. Under practical conditions selenium deficiency can be induced by intake of low selenium diets, consumption of diets high in sulfur and possibly calcium (Harrison and Conrad, 1984; Miller, et al., 1988, NRC, 2000). Furthermore, since vitamin E is involved in oxidant protection within a cell, a vitamin E deficiency may increase the amount of selenium needed to prevent oxidative stress within a cell.

**Troubleshooting a Potential Copper and Selenium Deficiency**

As discussed by Arthington (2002), the first step in identifying trace mineral deficiencies is to attempt to rule out other more directly contributing factors that can be the cause of decreased animal performance (i.e. infectious diseases, other nutrient deficiency, etc.). For example, if average cow body condition score is below 5 (moderate), chances are far greater that decreases in reproduction and/or immune competence are a result of energy/protein deficiency rather than a trace mineral deficiency. Also be sure that appropriate trace mineral supplementation is being offered.
If other contributing factors such as disease or energy/protein deficiencies or imbalances are ruled out, it is then important to understand the trace mineral contribution from the available feedstuffs and water. Collect forage samples, being careful to select forage that the animals are actually grazing or consuming. Perform a standard trace mineral evaluation of the forage. Also, do not forget to analyze the drinking water, especially in drought-type conditions (Arthington, 2002). As mentioned previously, sulfur can decrease copper and selenium availability. Excessive levels of iron may also depress the utilization of copper. In some instances it may be important to confirm or disprove a potential copper and/or selenium deficiency by examining tissue status through blood and/or liver collection. Consider this option carefully before proceeding.

Blood is commonly used to determine an animal’s trace mineral status or to diagnose deficiency or toxicity because of ease of collection (Bull, 1980). Trace mineral-dependent enzymes have also been analyzed to determine trace mineral status since collection is easy and possible trace mineral contamination can be avoided (Bull, 1980). However, the most reliable method of diagnosing a mineral deficiency is to monitor an animal's response to the supplementation of a particular trace mineral (McDowell, 1992) by monitoring health and (or) production after supplementation, since conventional indices of trace mineral status (blood or liver concentrations) are only approximate measurements (Suttle, 1994). Because of the significant cost and time constraints of such experiments, the analysis of animal tissue (s) for trace mineral concentration is the most commonly used indicator of trace mineral status (McDowell, 1992).

**Copper:** Substantial storage of copper in the liver is possible (NRC, 2000), and therefore analysis of liver copper concentration is considered the best method of classifying copper status and to document changes in copper status (Hemken et al., 1993). However, determination of copper status via the analysis of copper dependent enzymes including ceruloplasmin and copper-zinc superoxide dismutase is also common. Analysis of serum copper concentrations to estimate mineral status is done, but the minimum liver copper concentration necessary to maintain normal plasma copper concentrations in ruminants is approximately 40 mg Cu/kg DM (Underwood, 1977), making serum evaluation a less valuable method to classify copper status, particularly if cattle are subclinically deficient. Analysis of blood samples alone for diagnosis of copper status can be misleading, and therefore should be accompanied by liver and forage analyses for copper concentration (Corah and Arthington, 1993).

**Selenium:** For several animal species, selenium concentrations in liver adequately portray selenium status (McDowell, 1992). Furthermore, tissue activity of glutathione peroxidase (a Se dependent enzyme) is a relatively good status indicator of selenium because tissue (i.e. liver tissue) and plasma glutathione peroxidase activity increase or decrease rapidly during selenium depletion or repletion (McDowell, 1992). However, glutathione peroxidase activity does not reveal the overall status within the tissue. Blood selenium concentrations indicate current selenium status but are difficult to use to determine selenium storage in the body (NRC, 1996).
Trace Mineral Supplementation Strategies for Grazing Beef Cattle

Prior to selecting a supplement strategy for trace minerals, it is important to try and estimate intake of the dietary essential trace elements from the pasture, water, and other protein/energy supplements being offered. This will require mineral analysis of all feed ingredients. It is also helpful to try and understand seasonal variations of minerals in forages and water that cattle are consuming. This requires feed and water sampling several times over the course of a year. Once it has been determined that a trace mineral (or trace minerals) are inadequate, a supplementation strategy should be developed. There are many different supplementation strategies for trace minerals which can include: 1) direct supplementation of the minerals needed. This type of mineral supplement would include free-choice lose dry mineral or compressed mineral blocks; 2) Energy and/or protein supplements fortified with minerals. These include protein blocks, lick tanks, range cake, etc.; and 3) injectable trace minerals.

Factors That Can Alter Trace Mineral Metabolism

Despite the involvement of certain trace minerals in animal production and disease resistance, deficiencies of trace minerals have not always reduced performance or increased the susceptibility of domesticated livestock species to natural or experimentally-induced infections (Spears, 2000). There are many factors that can affect an animal’s response to trace mineral supplementation such as the duration and concentration of trace mineral supplementation, physiological status of an animal (i.e. pregnant vs. non pregnant), the absence or presence of dietary antagonists, environmental factors and the influence of stress on trace mineral metabolism (Baker et al., 2003). For the purpose of this portion of the review, five areas deserve attention when discussing potential factors that may affect the trace mineral requirements of ruminants: breed, gestational status, stress, trace mineral antagonists, and age.

Breed: Although species differences in trace mineral metabolism have long been recognized, differences been between breeds within a species have only recently been noted. Differences in trace mineral metabolism between breeds of dairy cattle have been reported. In an experiment by Du et al. (1996), Holstein (n = 8) and Jersey (n = 8) primiparous cows and Holstein (n = 8) and Jersey (n = 8) growing heifers were supplemented with either 5 or 80 mg of copper/kg DM for 60 days. At the end of the 60 day experiment, Jerseys had higher liver copper concentrations relative to Holsteins across both treatments. Furthermore, liver copper concentrations increased more rapidly and were higher in the Jerseys supplemented with 80 mg of copper/kg DM compared to Holsteins supplemented with 80 mg of copper/kg DM by day 60 of the experiment. Overall serum ceruloplasmin oxidase activity was higher in Jerseys than Holsteins. Additionally, Jersey cows and heifers had higher liver iron and lower liver zinc concentrations than did Holstein cows and heifers at day 60 of the experiment. These data indicate that Jerseys and Holsteins metabolize copper, zinc, and iron differently.
Ward et al. (1995) conducted a metabolism study in which Angus (n = 8) and Simmenthal (n = 8) steers were placed in metabolism crates to monitor apparent absorption and retention of copper. At the end of the 6-day metabolism experiment, plasma copper concentrations and apparent absorption and retention of copper were higher in Angus relative to Simmenthal steers. The authors indicate, from their data as well as from others, that Simmenthal cattle may have a higher copper requirement than Angus cattle and that these different requirements may be related to differences in copper absorption in the gastrointestinal tract between breeds. Furthermore, it has also been suggested that these breed differences in copper metabolism may not be due solely to differences in absorption, but also to the manner in which copper is utilized or metabolized post-absorption. Gooneratne et al. (1994) reported that biliary copper concentrations are considerably higher in Simmenthal cattle than in Angus cattle. It is apparent that differences in copper metabolism exist between Simmenthal and Angus cattle both at the absorptive and post-absorptive levels.

An extensive study comparing the mineral status of Angus, Braunvieh, Charolais, Gelbvieh, Hereford, Limousin, Red Poll, Pinzgauer, and Simmenthal breeds consuming similar diets has also been conducted (Littledike et al., 1995). This work compared not only copper, but also zinc and iron status between all previously mentioned breeds of cattle. In adult cattle, it was shown that Limousin liver copper concentrations were higher than all other breeds, except for Angus. This same trend was not seen for zinc or iron; with very little breed differences observed except for lower liver zinc concentrations in Pinzgauer when compared to Limousin. Serum zinc and copper concentrations did not differ by breed.

**Gestational Status:** Although little data have been published examining the effects of gestational status on trace mineral metabolism in cattle, several experiments have been conducted using laboratory animals and humans that indicate trace mineral metabolism is altered during pregnancy. Studies using rats have shown that the overall maternal body stores of copper increase during pregnancy and then decrease during lactation (Williams et al., 1977). Vierboom et al. (2002) reported that pregnant cows tended to absorb and retain more copper than non-pregnant cows and sheep. These data indicate that certain physiological and/or metabolic parameters are altered in pregnant cows that enhance the apparent absorption and retention of certain trace minerals.

The above data indicate that copper metabolism is altered in pregnant vs. non-pregnant animals. Further research is required to determine the metabolic mechanisms that enable pregnant animals to alter copper metabolism as well as an animal’s specific metabolic requirement for both maintenance and fetal development. Additional research to determine the effects of gestational status on the metabolism of other trace minerals as well as if breed differences exist relative to trace mineral metabolism and gestational status is needed.

**Stress:** As mentioned earlier, minerals such as copper and selenium are involved in immune responses. Deficiencies and/or imbalances of these elements can
alter the activity of certain enzymes and function of specific organs thus impairing specific metabolic pathways as well as overall immune function.

Stress and its relationship to the occurrence of disease have long been recognized. Stress is the nonspecific response of the body to any demand made upon it (Selye, 1973). Stressors relative to animal production include a variety of circumstances such as infection, environmental factors, parturition, lactation, weaning, transport, and handling. Stress induced by parturition, lactation, weaning and transport has been shown to decrease the ability of the animal to respond immunologically to antigens that they encounter. Furthermore, research has indicated that stress can alter the metabolism of trace minerals. Stress in the form of mastitis and ketosis has been shown to alter zinc metabolism in dairy cattle. Orr et al. (1990) reported an increase in urinary copper and zinc excretion in cattle inoculated with IBRV. Furthermore, Nockels et al. (1993) reported that copper and zinc retention was decreased in steers injected with adrenocorticotropic hormone (ACTH, a stressor), in conjunction with feed and water restriction.

**Trace Mineral Antagonists:** Many element-element interactions have been documented (for an in depth review see Puls, 1994). These include zinc-iron, copper-iron, copper-sulfur, copper-molybdenum, and copper-molybdenum-sulfur interactions and interactions between elements and other dietary components. Peres et al. (2001) used perfused jejunal loops of normal rats to characterize the effects of the iron:zinc ratio in the diet on mineral absorption. When the iron:zinc ratio in the diet was held below 2:1, no detrimental effects on absorption were observed. However, once concentrations were increased to yield a ratio between 2:1 and 5:1, zinc absorption was decreased. Similar effects have also been seen for copper absorption, with depressed copper uptake in the presence of excess iron (Phillippo et al., 1987).

The best known of mineral interactions that can cause a reduction in copper absorption and utilization is the copper-molybdenum-sulfur interaction. However, even molybdenum or sulfur alone can have antagonistic effects on copper absorption. Suttle (1974) reported that plasma copper concentrations were reduced in sheep with increasing concentrations of dietary sulfur from either an organic (methionine) or inorganic (Na₂SO₄) form of sulfur. In another experiment, Suttle (1975) demonstrated that hypocupraemic ewes fed copper at a rate of 6 mg copper/kg of diet DM, with additional sulfur or molybdenum, exhibited slower repletion rates than sheep fed no molybdenum or sulfur. However, when both molybdenum and sulfur were fed together, copper absorption and retention was drastically reduced. Current research would support these findings and suggest that in addition to independent copper-sulfur and copper-molybdenum interactions, there is a three way copper-molybdenum-sulfur interaction that renders these elements unavailable for absorption and/or metabolism due to the formation of thiomolybdates (Suttle, 1991).

Ward (1978) investigated the independent effect of molybdenum on copper absorption and concluded that elevated molybdenum intake reduces copper availability and can lead to a physiological copper deficiency. Based on this and previous
experiments, it appears that the ratio of the antagonistic elements seems to be more important than the actual amounts. Miltimore and Mason (1971) reported that if copper:molybdenum ratios fall below 2:1, copper deficiency can be produced. Huisingh et al. (1973) further concluded, in their attempt to produce a working model of the effects of sulfur and molybdenum on copper absorption, that both sulfur (in the form of sulfate or sulfur-containing amino acids) and molybdenum reduce copper absorption due to the formation of insoluble complexes. They also noted that sulfur and molybdenum interact independently and suggested that they may share a common transport mechanism.

Mineral to mineral interactions are not the only possible inhibitors of mineral absorption. Other dietary components can also inhibit or enhance the amount of mineral that is absorbed. Protein containing sulfur-containing amino acids is an example of a dietary component that can affect mineral metabolism. Snedeker and Greger (1983) reported that high protein diets significantly increase apparent zinc retention. In contrast, diets high in sulfur-containing amino acids have been shown to decrease copper absorption, most likely due to the formation of insoluble copper-sulfur and potentially copper-molybdenum-sulfur complexes (Robbins and Baker, 1980).

In his review, O'Dell (1984) also noted the potential for carbohydrate source to affect copper absorption. This is attributed to phytate as well as oxalate concentrations in the diet. Fiber can also act as a mineral trap due to its relatively large negative charge that serves to bind the positively charged divalent metal cations rendering them unavailable for absorption (van der Aar et al., 1983).

**Age:** Age has also been shown to affect the mineral of cattle. Trace mineral requirements have been reported to vary with age of dairy cattle (NRC, 2001). Wegner et al. (1972) reported that dairy cattle in their second to fifth lactations had higher serum zinc concentrations than either first lactation or bred heifers. This change in mineral needs over time is most obvious in young growing animals.

**Summary**

The interactions between trace minerals, animal production and stress are extremely complex. Many factors can affect an animal’s response to trace mineral supplementation such as the duration and concentration of trace mineral supplementation, physiological status of an animal (pregnant vs. nonpregnant), the absence or presence of dietary antagonists, environmental factors, and the influence of stress on trace mineral metabolism. Prior to formulating a trace mineral supplementation strategy, it is important to understand (to the best of your ability) mineral intake from grazed forages and water. Future research is needed to better understand the mechanisms by which trace minerals are absorbed and metabolized in beef cattle.
References


