ZINC, COPPER, MANGANESE, AND SELENIUM IN DAIRY CATTLE RATIONS

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Summary

The trace minerals zinc, copper, manganese, and selenium are components of a wide variety of enzymes and proteins that support metabolism, growth, production, and reproduction. Trace mineral supplements are added to dairy cattle rations to prevent mineral deficiencies, and supplementation has traditionally been provided in the form of inorganic salts. When these inorganic salts dissociate in the reticulo-rumen, omasum, and abomasum, the trace minerals can form indigestible compounds with other feed components which renders them unavailable for absorption in the intestines. Organic trace mineral supplements that are both stable in the digestive tract and available for intestinal absorption have the potential to be more available to the cow than inorganic supplements. However, measurement of bioavailability of trace mineral supplements is difficult, and studies comparing organic to inorganic trace mineral supplements do not consistently show increased bioavailability. Organic trace mineral supplementation has been shown to increase animal production response relative to inorganic trace minerals in some studies, with or without a concurrent increase in measures of bioavailability. Some studies have shown that trace mineral supplementation above predicted requirements improves animal health, likely due to the antioxidant functions of Zn, Cu, Mn, and Se. Supplementation of trace minerals during times of oxidative stress may enhance disease resistance.

Introduction

The importance of trace mineral nutrition relative to the maintenance of productivity and prevention of deficiency symptoms has been recognized for quite some time (Miller, 1981; NRC, 2001). However, scientists in industry and academia have shown a more recent interest in understanding factors influencing trace mineral requirements and digestibility. Specifically, goals of more recent work include: 1) determining the effect of trace mineral chemistry on mineral retention, and 2) measuring potential benefits of trace mineral supplementation above predicted requirements upon dairy cattle health and productivity (Nocek *et al.*, 2006; Siciliano-Jones *et al.*, 2008; Spears and Weiss, 2008). The objective of this paper is to summarize research related to zinc (Zn), copper (Cu), manganese (Mn), and selenium (Se) nutrition. After a brief summary of the functions of these nutrients, specific attention will be paid to the effect of trace mineral chemistry on mineral bioavailability and situations that may warrant trace mineral supplementation above predicted requirements.

Roles of Zinc, Copper, Manganese, and Selenium

Zinc is widely distributed throughout the body as a component of metalloenzymes and metalloproteins (Vallee and Falchuk, 1993). Zinc finger proteins play an integral role in regulating gene expression, consequently impacting a wide variety of body functions including cell division, growth, hormone production, metabolism, appetite control, and immune function (Predieri *et al.*, 2003; Vallee and Falchuk, 1993). Zinc has a catalytic, coactive, or structural role in a wide variety of enzymes that regulate many physiological processes including metabolism, growth, and immune function (Vallee and Falchuk, 1993). The coactive role of Zn in one such enzyme, superoxide dismutase (SOD), will be further discussed below. Because Zn is required for production of protective keratins in the hoof and teat, one area of recent attention has been evaluating the role Zn plays in maintaining structural integrity and health of the hoof and udder (Tomlinson *et al.*, 2004, 2008).

Copper and Mn function as components of metalloenzymes that take part in reduction reactions. These metalloenzymes are involved in multiple physiological processes including respiration, carbohydrate and lipid metabolism, antioxidant activities, and collagen formation (Andrieu, 2008; NRC, 2001; Tomlinson *et al.*, 2004). One of the Cu-containing enzymes, ceruloplasmin, binds up to 95% of circulating Cu, regulates iron availability, takes part in oxidation-reduction reactions, and may regulate immune function (Healy and Tipton, 2007). Like Zn, both Cu and Mn are important for keratin formation and are components of SOD (Tomlinson *et al.*, 2004).

Selenium functions as a component of at least 25 different selenoproteins (Andrieu, 2008). In these proteins, sulfur (S) is replaced with Se, which allows the proteins to donate hydrogen and take part in reduction reactions. Selenoproteins include the enzyme iodothyronine deiodinase which is important in regulating metabolism and glutathione peroxidase and thioredoxin reductase which are important components of antioxidant and immune systems (Andrieu, 2008; NRC, 2001).

Due to the diversity of proteins and enzymes containing Zn, Cu, Mn, and Se, these trace minerals are essential for a wide variety of physiological processes regulating growth, production, reproduction, and health. Deficiencies in these nutrients consequently lead to reduced performance, and dairy cattle diets are formulated with trace mineral supplements to prevent deficiencies (Miller, 1981; NRC, 2001). However, chemical composition of trace mineral supplements varies, and research is showing that some supplements are better available to support animal productivity and health than others.

Chemical Structure of Trace Mineral Supplements

Traditionally, Zn, Cu, and Mn supplements have been fed as inorganic salts, for example zinc sulfate, cupric sulfate, or magnesium sulfate. In these salts, the trace mineral is associated with sulfate in a dry form but dissociates from the sulfate when hydrated in the rumen. Trace minerals are absorbed only minimally across the rumen epithelium and they cannot be absorbed by the animal until they reach the small intestine (Wright *et al.*, 2008). Dissociated trace minerals in the reticulo-rumen, omasum, and abomasum can form insoluble or indigestible compounds that pass into the manure. For example, minerals can bind with plant polyphenols and sugars to form indigestible complexes (McDonald *et al.*, 1996) and minerals can form insoluble complexes with other minerals that precipitate out of digesta (Spears, 2003). Formation of such compounds in the reticulo-rumen, omasum, and abomasum reduces mineral absorption in the small intestine.

A current trend is to feed “organic” forms of Zn, Cu, and/or Mn in place of inorganic salts. In organic Zn, Cu, and Mn, the mineral is bound to an organic (i.e. carbon-containing) molecule, typically an amino acid or protein. There are a wide variety of organic trace mineral supplements available. These supplements are classified as complexes, chelates, or proteinates based upon their chemical structure. In a complex, the minerals and organic molecules are associated, but not necessarily by covalent bonds (Spears, 1996). For both chelates and proteinates, covalent bonds exist between the minerals and organic molecules (Spears, 1996). For Zn, an example of a complex, chelate, and proteinate is Zn-methionine (ZN-met), Zn-methionine hydroxy-analogue (Zn-MHA), and Zn-proteinate, respectively.

Inorganic and organic forms of Se differ from those of Zn, Cu, and Mn. Selenites and selenates provide inorganic Se in the form of sodium salts while organic Se is provided by Se-yeast, a product made from growing yeast in media supplemented with Se (Weiss, 2005). Yeast incorporate Se into a variety of compounds, with the predominant compound being selenomethionine (Se-met; Schrauzer, 2000). In Se-met, Se is covalently bound to the amino acid and takes the place of S in the molecular structure.

What is Bioavailability?

The proposed benefit to feeding organic trace minerals is that they should undergo less dissociation in the reticulo-rumen, omasum, and abomasum than their inorganic counterparts. Organic trace minerals that remain intact in the upper gastro-intestinal tract are less likely to form insoluble and indigestible compounds than inorganic trace minerals, and availability of organic trace minerals for absorption by intestinal tissues should be enhanced. An ideal organic trace mineral supplement must be resilient enough to remain intact as the pH changes throughout the digestive tract but must still be available for absorption and metabolism by animal tissues (Andrieu, 2008). In reality, this ideal organic trace mineral does not exist. *In vitro* studies have shown that organic trace minerals are more effectively absorbed by gut tissues than inorganic trace minerals (Predieri *et al.*, 2005; Wright *et al.*, 2008). However, some extent of dissociation and loss of organic trace minerals in the upper gastro-intestinal tract is unavoidable (Cao *et al.*, 2000). Despite these inevitable losses, organic trace mineral supplementation can be of benefit to ruminant nutrition if they are absorbed to a greater extent than inorganic trace minerals and/or are better available to support production.

Comparison among different trace mineral supplements is difficult. There is no standard laboratory test to predict availability of one trace mineral source relative to another (Cao *et al.*, 2000), and comparisons must be conducted using tissue culture or animal feeding tests. As mentioned previously, *in vitro* studies of ruminal and intestinal tissues have demonstrated increased absorption of organic compared to inorganic minerals (Predieri *et al.*, 2005; Wright *et al.*, 2008). However, differences in absorption and availability are difficult to measure *in vivo*. Because absorption is not directly measured *in vivo*, potential benefits of organic trace mineral supplements are typically described relative to "bioavailability".

The meaning of the term bioavailability is fairly ambiguous, but it generally describes mineral absorption by and/or retention within the animal. Theoretically, a mineral supplement that is more bioavailable than another will provide a greater proportion of absorbed minerals to support animal production and health. An additional benefit of a more bioavailable mineral is that less can be fed to the animal, potentially reducing feed mineral use and mineral losses to the environment.

The most accurate way to measure bioavailability is by conducting animal feeding trials in which animals are fed different trace mineral sources and indices of mineral availability are measured. Indices of mineral availability include blood or liver mineral concentrations, blood or liver concentration of mineral-containing proteins, activity of mineral-containing enzymes, or mineral retention calculated as the difference between consumed and excreted minerals. Results of individual feeding trials are dependent upon test conditions (for example, feed ingredients, stage of lactation, environmental conditions) and the particular indices of bioavailability chosen. Due to these variables, conclusions from any one trial cannot be used to assign a bioavailability value to a given mineral supplement (Cao *et al.*, 2000).

Animal Responses of Organic versus Inorganic Trace Mineral Supplements

Animal Responses to Organic Zinc, Copper, and Manganese

Bioavailability of organic Zn, Cu, and Mn relative to inorganic salts has been evaluated in many studies and has been the subject of several reviews (Andrieu, 2008; Spears, 1996, 2003). Results of studies have been variable. For example, Zn-met was found to increase serum and liver Zn concentrations compared to zinc oxide in feedlot steers in one study (Chirase *et al.*, 1991). In another study comparing zinc sulfate, Zn-met, or a Zn-glycine complex, there were no treatment differences in plasma Zn concentration, although liver Zn concentrations were increased by Zn-glycine but not by Zn-met (Spears *et al.*, 2004). Similarly, organic Cu sources have been shown to be more bioavailable than inorganic Cu sources in some studies but not others (Spears, 2003). Although few studies have examined supplemental Mn sources, bioavailability of Mn-methionine was found to be greater than manganese sulfate or manganese oxide in lambs (Henry *et al.*, 1992).

Two recent large scale studies have examined effects of organic trace mineral supplements on bioavailability and performance. When 250 cows were fed Zn, Mn, and Cu as either sulfates or amino acid complexes, bioavailability (as measured by liver mineral concentrations) was not affected by treatment (Siciliano-Jones et al., 2008). Despite the lack of a difference in liver mineral concentrations, milk production and hoof health were improved by the amino acid complexes of trace minerals (Siciliano-Jones et al., 2008). Another study using 573 cows compared inorganic and complexed trace minerals at several supplementation levels fed over two lactations (Nocek et al., 2006). When supplemented at 100% of predicted Zn, Mn, Cu, and Co requirements, replacement of inorganic sulfate trace mineral salts with amino acid complexed trace minerals increased bioavailability as measured by liver Zn and Cu concentrations (Nocek et al., 2006). The complexed trace mineral also resulted in increased milk production in the first lactation and increased milk production and decreased SCS in the second lactation.

Despite the variable effects of trace mineral source upon bioavailability measures, studies generally point to improved animal production and health responses for organic versus inorganic trace mineral supplements. Benefits of organic trace minerals include improvements in growth, milk production, reproduction, and somatic cell score (Andrieu, 2008; Spears, 1996, 2003; Spears and Weiss, 2008). Improvements in animal production despite measured differences in bioavailability suggest that current measures of bioavailability are either not sensitive enough to detect differences or do not reflect actual pools of minerals available to support animal physiology.

Animal Responses to Organic Selenium

Mechanisms of absorption and metabolism of inorganic and organic Se differ substantially. Inorganic Se is recognized by the digestive tissues and is absorbed and converted into selenoproteins (Weiss, 2005). In contrast, organic Se in the form of Se-met is not believed to be recognized as Se-containing by mammalian cells (Behne and Kyriakopoulos, 2001). As a consequence, Se-met is absorbed and metabolized relative to methionine needs. If Se-met is broken down within the cell, Se will be released and recognized by the cell as a mineral, and will be processed according to the animal’s need for Se. However, if the cell does not break down Se-met, it will be incorporated into a wide variety of proteins that do not require Se.

Organic selenium is more digestible than inorganic selenium. Whether inorganic selenate or selenite is formed, selenite is the primary compound available for absorption because the reducing conditions of the rumen convert the majority of selenate to selenite (Weiss, 2005). In the rumen, about a third of selenite is converted to insoluble forms that are passed into manure (Weiss, 2005). Of the soluble selenite that reaches the intestine, less than 40% would be expected to be absorbed by the intestines (Vendeland *et al.*, 1994). This compares to roughly 80% intestinal absorption of Se-met (Vendeland *et al.*, 1994). As a consequence of these differences in solubility and absorption, digestibility of Se from selenite is around 50% in cows compared to roughly 66% for Se-yeast (Weiss, 2005).

Unlike the variable bioavailability responses seen with organic Zn, Cu, and Mn supplementation, organic Se sources consistently lead to increased markers of bioavailability compared to inorganic Se. Serum and milk Se concentrations are consistently greater for animals fed Se-yeast compared to inorganic

Se (Weiss, 2005; Weiss and Hogan, 2005). However, some of the increase in blood and milk Se is due to Se-containing amino acids being processed as regular amino acids as described above. This is an important distinction because if a cow has a need for Se, her cells will not recognize that pool of Se as being available to support her needs (Weiss, 2005). Despite this distinction, Se-yeast appears to be more bioavailable than inorganic Se as measured by increased concentrations of blood selenoproteins (Weiss, 2005). However, the relationship between increased bioavailability and animal performance is unclear. In one cow trial, Se-yeast did not improve production or health measures compared to selenate (Weiss and Hogan, 2005).

Potential Benefits of Trace Mineral Supplementation above Predicted Requirements

There is some indication that supplementation of trace minerals above predicted requirements may improve dairy cattle health, particularly during the transition period or during other times of stress. One reason for this indication is the role that these trace minerals play in the antioxidant system as has been described in several reviews (Andrieu, 2008; Miller *et al.*, 1993; Tomlinson *et al.*, 2008). Oxidation is a normal process that produces free radicals, and the antioxidant system functions to neutralize these free radicals before they cause cellular damage. Zinc, Cu, and Mn are integral components in this system due to their presence in SOD which reduces the free radical superoxide to hydrogen peroxide. Selenium is a component of glutathione peroxidase which then converts hydrogen peroxide into water.

In a healthy animal, the antioxidant system reduces free radicals as they are produced to prevent them from damaging cells and metabolites. However, in times of stress, rate of free radical production can exceed rate of free radical neutralization by the antioxidant system and can lead to oxidative damage of lipids, carbohydrates, and proteins within cells (Miller *et al.*, 1993). Examples of such times oxidative stress include calving, infection, and heat stress (Bernabucci *et al.*, 2002; Miller *et al.*, 1993). Higher producing cows have also been shown to have greater concentrations of oxidatively damaged lipids than lower producing cows (Lohrke *et al.*, 2005). Trace mineral supplementation above predicted requirements during times of oxidative stress may reduce oxidative damage to cells and metabolites.

Free radical damage to the membrane of white blood cells may contribute to increased disease susceptibility during times of increased oxidative stress, such as occurs around calving (Miller *et al.*, 1993). White blood cells are particularly sensitive to oxidative damage because their membranes contain high concentrations of unsaturated fatty acids (Spears and Weiss, 2008). Oxidative damage to these membrane fats reduces the ability of white blood cells to defend the cow against disease challenges. If trace mineral supplementation reduces oxidative damage to white blood cells, it may reduce disease susceptibility in oxidatively stressed animals.

Epidemiological and disease challenge studies also suggest that trace mineral supplementation may improve disease resistance. For example, herds with marginal or deficient plasma concentrations of Zn or Cu were found to have increased risk of metritis, mastitis, and locomotion problems (Enjalbert *et al.*, 2006). Additionally, herds with higher serum Se concentration were found to have lower somatic cell concentrations (Weiss *et al.*, 1990). Finally, mastitis challenges have resulted in decreased serum concentrations of Zn and Cu (Erskine and Bartlett, 1993; Middleton *et al.*, 2004). Although it cannot be determined whether mastitis-induced decreases in blood mineral concentrations correspond to an increased physiological need for minerals, the data do support a potential role for trace minerals in disease recovery. However, no benefit to Zn supplementation was found in steers challenged with a respiratory virus or in immune measures of healthy calves (Chirase *et al.*, 1991; Kincaid *et al.*, 1997).

Conclusions

Zinc, Cu, Mn, and Se are important to a variety of biological processes. Organic forms of trace mineral supplements are generally more bioavailable than inorganic forms, although bioavailability measures vary substantially among trials. There is some evidence that organic forms of trace minerals improve production and health responses of dairy cattle relative to inorganic trace minerals. Supplementation of Zn, Cu, Mn, or Se during times of oxidative stress may reduce oxidative damage to white blood cells and increase disease resistance.

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