The Two Faces of Copper Nutrition in Sheep & Goats

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In most small ruminant circles, the mention of "copper" brings shivers of dread, but for different reasons with sheep and goat owners. Copper (Cu) is an essential micromineral required by all small ruminant species to maintain normal body functions when provided in appropriate amounts. However, Cu nutrition is a double-edged sword being associated with both deficiency and toxicity disease concerns with much variation among the small ruminant species. Although all microminerals are of importance, Cu is receiving more attention as a result of the potential toxicity concerns with sheep, llamas, and alpacas and for deficiency issues in goats. There is evidence of increasing Cu content in forages and feeding with other copper-containing supplements (pellets and mineral) may predispose animals to a greater risk for toxicity problems. However, the specter of animal health concerns related to Cu deficiency, even in sheep, is becoming more apparent. The objective of this article is to provide an overview of Cu nutrition by describing biologic functions and associated deficiency and toxicity disease conditions in sheep and goats.

Copper's Biological Roles

All trace minerals, including Cu, perform their biologic role as a component of a protein enzyme (i.e., metalloenzyme) in catalyzing a specific reaction. The measured activities of these mineral-specific enzymes are used to define a deficiency situation. Essentiality of Cu in animals was not discovered until 1928, though it had been discovered in animal and plant tissues much earlier. Copper performs many essential roles in the body as a component of Cu-containing enzymes that include ceruloplasmin, tyrosinase, lysl oxidase, cytochrome C oxidase, and superoxide dismutase (Table 1). Through the action of these metalloenzymes, Cu has been associated with iron regulation and red blood cell function, cellular respiration, bone and connective tissue formation, hair pigmentation, nerve tissue and cardiac development, and immune function.

Ceruloplasmin is a blood protein with multiple functions and contains seven copper atoms, thus accounting for a majority of copper in blood. Ceruloplasmin converts stored ferrous iron (+2) into the ferric (+3) state to be incorporated into hemoglobin or myoglobin for oxygen transport. Ceruloplasmin is a liver generated acute phase protein with an important role in the non-specific immune response and its blood concentration will be elevated in response to an infectious agent. Functional activity of most cell types responsible for the various immune system responses are influenced by Cu through superoxide dismutase activity.

Of interest to fiber producing small ruminants, Cu plays an important role in fleece coloration and quality. Tyrosinase is the enzyme responsible for the formation of melanin, a pigment responsible for hair and skin coloration. Hair or fleece would appear lighter in color or "bleached out" without the presence of melanin. Cross linkages of disulfide groups within the keratin structure of hair provide the physical properties of fleece and are dependent upon Cu. Wool from sheep with copper deficiency are described as having "steely wool" where the crimp has been lost and the fiber is straight.

Normal development of bone and connective tissue is dependent upon the copper-dependent enzyme lysl oxidase. This enzyme is responsible for modifying specific amino acids within the collagen protein structure that facilitates cross linkages between collagen fibers within connective tissue. These cross linkages impart properties of rigidity or elasticity to the collagen structure. Rigid connective tissue provides the scaffolding for mineralization in the development of bone. Elastic properties of collagen are seen in the large blood vessels such as the aorta, which must withstand wide fluctuations in pressure in circulating blood.

The cell's ability to generate energy through the transfer of electrons to the final receptor oxygen to form water is one of the functions of cytochrome C oxidase. Integrity of the nervous system is dependent upon the specialized phospholipid coating (myelin) around nerve fibers facilitating transmission of nerve signals. Myelin formation in the brain and spinal cord is related to cytochrome C oxidase activity. Besides the structural effects on nervous tissue, Cu is linked to nervous and cardiac tissue communications through its effect on production of neurotransmitters and heart muscle fiber (myofibril) development. Both cytochrome C oxidase and dopamine-β-monooxygenase are responsible for these biologic functions of Cu.

Copper Deficiency Diseases

With the number of biological functions attributed to Cu, a spectrum of disease entities has been associated with a deficient nutrient status (Table 1). A common Cu deficiency disease occurring in a wide range of animals is anemia. Anemia can be characterized by the size and pigment (hemoglobin) content of red blood cells. In older ruminants, Cu deficiency can induce a macrocytic, hypochromic anemia due to low ceruloplasmin activity, whereas in lambs

Table 1. Selected examples of biologic functions of copper as part of metalloenzymes and associated disease conditions.

Cu Metalloenzyme	Function	Biologic Actions	Disease Condition
Ceruloplasmin	Activation of Fe^{2+} to Fe^{3+}	Allows stored iron to be incorporated into hemoglobin in red blood cells. Acute phase protein that helps kill invading bacteria	Anemia, poor immune response
Cytochrome C oxidase	Terminal electron transfer – respiratory chain	Allows for electron transport in metabolism, Production of myelin sheath of nerves	Swayback in young animals, Enzootic ataxia
Dopamine-b-monoxygenase	Catecholamine metabolism	Production of metabolic regulators, heart function	Unknown association maybe abnormal heart development
Lysyl oxidase	Desmosine cross-linkages in connective tissue	Proper formation of structural components of bone, elastin, cartilage	Bone deformities similar to rickets in young growing animals; Rupture of large blood vessels
Peptidylglycine-a-monooxygenase	Elaboration of numerous biogenic molecules (e.g. gastrin)	Production of many different regulatory molecules impacting digestion, metabolism, reproduction	Unknown linkage to specific disease, but may be related to poor growth, reproduction
Cu-Zn Superoxide dismutase	Dismutation of 0_2^- to H_20_2	Antioxidant to protect against various oxidizing agents from metabolism or environment	May be associated with stillbirths or weak neonates, poor immune response
Tyrosinase	Conversion of tyrosine to melanin	Produces melanin pigment for skin and hair or wool	Decolorization of wool, hair, dark colors become "reddish" or lightened

the anemia is characterized as microcytic and hypochromic. Similar Cu-responsive anemia can be seen in goats.

Copper deficiency has been associated with neurologic degeneration in sheep and goats as a result of abnormal myelin formation with resulting disease signs of progressive muscular weakness of the legs and ataxia. Young lambs affected due to the pregnant animal being fed a low Cu diet is described as "swayback" whereas when older animals present with this disease process it is termed "enzootic ataxia".

Achromotrichia (loss of fleece pigmentation) and fleece structural changes is seen in sheep and other species with Cu deficiency. Bone development abnormalities (similar to rickets), blood vessel ruptures, and heart degeneration are other recognized Cu deficiency diseases, but these are not seen in all species. Copper deficient diseases will vary among animal species.

More recently sheep flocks, goat herds and beef cattle herds have been recognized with animal losses, poor reproductive performance and high losses of newborns with the only definitive finding of low Cu status. I have documented low liver Cu in aborted fetuses where no other potential cause could be found. In another study, stillborn calves have lower trace mineral status compared to healthy calves. One of our primary findings in sheep flocks experiencing low Cu is high stillbirth and death loss of newborn lambs. More research is underway to further characterize what is happening and why in these flocks.

The disease conditions discussed thus far are classified as clinical disease syndromes. Clinical disease is characterized as the "classical" disease processes associated with a specific nutrient and often described in various nutrition textbooks. In contrast to clinical disease is a less specific disease process termed subclinical disease. Subclinical disease is described as non-specific consequences of a nutrient being marginally deficient or toxic. Subclinical Cu deficiency is associated with impaired immune response and greater susceptibility to disease, reduced reproductive fertility, and poor growth or lactation. Clinical disease is more readily identified but is not near as prevalent as subclinical disease. With difficulties in assessing Cu status using blood concentrations, subclinical disease becomes a difficult process to diagnose.

Toxicity Disease

In contrast to Cu deficiency, more emphasis is on the implications of excess Cu from the diet. Copper toxicity is the result of the highly reactive nature of the Cu ion when not protectively bound in tissues or blood. Copper like most minerals is a strong oxidizing agent that can damage cellular membranes and proteins. The liver is the body's primary trace mineral storage organ and contains special protein molecules capable of binding minerals and keeping them isolated from doing any damage to the surrounding tissues. Stored Cu is inefficiently excreted through bile produced in the liver and transported to the intestinal tract to be lost in fecal matter. The ability to excrete Cu is species dependent and accounts for the observed differences in sensitivity to Cu toxicity. Once the liver has become saturated with stored Cu, excess will spill out into the liver and blood reeking oxidative havoc. The challenge is being able to recognize disease risk early and initiate appropriate dietary changes as there is no treatment once the disease process has initiated.

In most situations Cu toxicity is a progressive disease process (e.g., weeks to months) where excess dietary Cu accumulates in the liver until the liver Cu storage proteins become saturated. Acute Cu toxicity (e.g., hours to days) can occur if the animal consumes excess highly soluble Cu sources such as copper sulfate. Sheep are well known to be extremely sensitive to excess dietary Cu (>10 mg/kg); however, llamas and alpacas do not seem to be as keenly sensitive but are prone

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to toxicity whereas goats seem more tolerant. However, goats can become Cu intoxicated just as well if they receive excess Cu in their diet or through copper wire boluses in treating parasites.

Clinical Cu toxicity in sheep is characterized by red blood cell breakdown (i.e., hemolysis) due to oxidative damage from the Cu ion released into the bloodstream. With hemolysis there is leakage of free hemoglobin into the blood (hemoglobinemia) and urine (hemoglobinuria). Hemoglobin in urine will damage the kidneys. The hemolytic crisis stage of the disease is nearly always fatal. The disease process is different in goats, llamas and alpacas as the "hemolytic crisis" has not been reported or seen in field cases. The common theme in goat Cu toxicity cases is the documentation of severe and widespread degenerative changes (necrosis) in the liver. Liver necrosis may or may not be associated with elevated blood enzyme activities assessing liver function. Affected goats will have highly elevated blood (>200 µg/dL) and liver (>600 µg/g dry weight) Cu concentrations as well as elevated kidney (>10 µg/g dry weight) Cu concentrations.

Typically blood and kidney Cu concentrations are not highly elevated until the final initiation of the disease process; therefore, they may not be useful in diagnosing potential risk. Additionally, kidney Cu concentrations are only determined in animals that have died. The difficulty in dealing with this disease is that animals may only show minimal signs of poor doing prior to the final demise. Stress factors or previous liver disease may precipitate the disease. Key to understanding and preventing Cu toxicosis is nutritional management practices.

Copper Requirements

Defining a "true" requirement, meaning how many milligrams (mg) per day to support a given physiologic state, for a trace mineral is difficult at best. Often a trace mineral requirement is described in terms of dietary concentration, namely parts per million (ppm). Ideally a trace mineral requirement would be defined in terms of how many mg of mineral was needed to support specific physiologic states such as maintenance, pregnancy, lactation, growth, and work/activity. Obviously to determine such needs, specific feeding trials must be completed. The recent National Research Council (NRC, 2007) publication for small ruminants has defined specific mineral requirements for sheep based on factorial models and for goats based on dietary concentration as there was insufficient data to generate predictive models. For sheep the suggested total dietary Cu concentration ranged from 5-8 mg/kg, while for goats the recommendation was 15-20 mg/kg. This would translate into a daily absolute Cu requirement between 5 and 22 mg/day for sheep depending upon body weight and physiologic state. On the other hand, the daily absolute Cu requirement for goats across body weights and physiologic states ranged from 12 to 50 mg/day. Clearly, supplements or mineral products cannot be formulated to meet the Cu requirements of both species appropriately. Unfortunately, Cu feeding is not this simple and is influenced by many dietary factors.

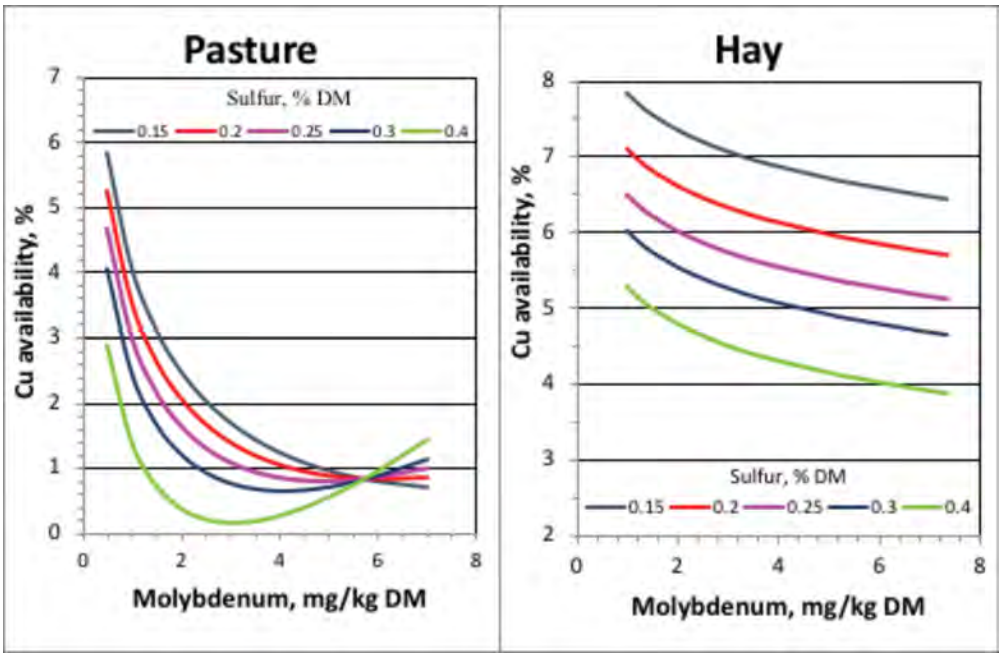
Copper Availability and Metabolism

In the more recent NRC publications, mineral requirements have been adjusted for variable availability from dietary ingredients. It has been shown that minerals within forages are not as available for absorption as from mineral sources. Compounds such as oxalates and phytates in forages can bind minerals reducing their availability. Copper availability in fresh pasture is lower than from hay (Figure 1). When the plant is harvested some breakdown of compounds facilitates the release of Cu making it more available. As with many other minerals, there are many documented interactions between minerals that can alter

availability. Relative to Cu, high dietary iron (Fe), zinc (Zn), and calcium (Ca) can reduce Cu availability. Iron is high in soil and soil consumed by grazing animals may contribute to the observed lower Cu availability from pasture.

Interactions affecting Cu availability have been well studied as a result of a unique situation in ruminant animals. Bacteria in the fermentation vat (rumen or camelid C-1) can combine dietary molybdenum (Mo) and sulfur (S) to produce thiomolybdate compounds. These thiomolybdates chelate or bind Cu in the fermentation vat and prevent Cu from being absorbed in the intestine (Figure 1). Even if absorbed, the chelated Cu is not available for use by tissues. For any ruminant animal, including sheep and goats, availability of dietary Cu will be significantly influenced by dietary Mo and S content. In this regard, often the Cu requirement is defined relative to dietary Mo as a Cu-to-Mo ratio. For sheep and camelids that are more sensitive to Cu, a suggested dietary Cu:Mo ratio of 6 to 8:1 is recommended whereas a range of 6 to 10:1 is suggested for goats and cattle. A Cu:Mo ratio of 16:1 or greater is often associated with Cu toxicity problems, especially if total Cu is well above requirements. A dietary Cu:Mo ratio less than 4:1 is associated with deficiency of Cu.

Figure 1. Relationships between dietary molybdenum (Mo) and sulfur (S) concentrations on copper (Cu) availability. Graphs are based on predictive models from Suttle, 2010. Green shaded areas represent the assumed range of Cu availability in NRC mode



Feeding Recommendations

With the requirement numbers presented, one needs to provide sufficient amounts of Cu from the diet without greatly exceeding this requirement and potentially inducing toxicity. The challenge here is remembering dietary Cu is contributed by every ingredient fed to some extent. This is where many people become confused with the daily Cu requirement on a dietary concentration basis ranging from 5 to 20 ppm. However, many feed ingredients can contain much higher Cu content, for example mineral supplements might contain between 30 and 600 ppm Cu. Does this mean these feed ingredients are toxic? Possibly, but only if they were fed as a sole feed source (not practical or realistic) or in combination with other feed ingredients with high Cu content. Each feed ingredient will contribute to the overall total dietary Cu content, but only to the proportion of the total diet the individual feed represents.

In Table 2, several examples are provided to demonstrate the concept of ingredient contribution to dietary Cu content. For these examples, three feed ingredients (hay, grain, and mineral) comprise the total diet. The same amount of hay (6.0 lbs/day), pellet (0.5 lb/day), and mineral supplement (0.015 lb/day or 0.25 oz/day) are provided in each example for simplicity and only Cu content is varied. In these examples hay provides the largest amount of dietary Cu even though it has the lowest Cu content. This is a direct result of hay being the largest proportion of the total diet. Example 1 shows Cu intake (18.8 mg/day) and dietary content (7.3 ppm) are in line with estimated requirements (10.4 mg/day; 5-9 ppm) for the maintenance ewe (see table legend). In example 2, the grain Cu content is increased from 10 to 46 ppm and a more typical forage Cu of 9 ppm are used. Dietary Cu intake and content are increased to a level that might be of concern. Example 3 shows the impact of higher Mo in the forage and generates a diet that potentially could lead to Cu deficiency. Of greatest concern is the situation in example 4 where hay Cu content increases from 9 to 18 ppm. In this situation, daily Cu intake and dietary content is greatly increased and, depending upon dietary Mo status, could potentially lead to Cu toxicity problems. Hay Cu content typically is between 4 and 14 ppm, though much higher Cu concentrations are being observed more frequently in many regions of the U.S. High forage Cu content may be the result of inappropriate fertilization practices, especially if poultry or pig manure are used. Dietary Cu is very high in poultry and pig diets, which accounts for the higher manure Cu content. Another concern is the use of copper sulfate footbaths on dairy cattle farms and the spread of this material on croplands. Given these situations, it is important for you to know just how the forages you purchase are raised or you need to test your forages to assess Cu status.

Given these dietary examples, it is imperative that all potential sources of Cu be accounted for in the diet to ensure adequate, but not excessive, Cu is consumed. As previously described, dietary Mo is an important factor to address in assessing dietary Cu status. From these examples both dietary ingredient Cu content and intake amount need to be considered. If testing feed ingredients for Cu content, one should also have Mo and S content determined. In feeding appropriately for Cu, one should first evaluate forage Cu content then match grain and mineral supplement accordingly. If your grain product contains more than 30 ppm Cu, then you may wish to use a mineral supplement with low (<60 ppm) Cu. If your hay has a Cu content greater than 15 ppm, then you may need to feed a grain with lower Cu content and a low Cu mineral. It must be remembered that high dietary Cu intake does not guarantee that a toxicity event will occur. The role of Mo is becoming more of an issue and needs to be addressed and measured in all feed ingredients to properly assess dietary Cu status relative to risk for deficiency or toxicity.

Monitoring Cu Status

With concerns for disease related to either Cu deficiency or toxicity, methods to assess Cu status are of interest. Copper can be directly determined in serum, plasma, or liver

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Table 2. Contribution of individual feed ingredients (hay, grain supplement, mineral salt) to total dietary copper (Cu) content. For comparison in the following examples daily Cu requirement for a 175 lb adult sheep at maintenance is between 7 and 10 mg/day. Dietary Cu content can vary from 5 to 9 ppm assuming a total intake of 2.2 and 2.0% of body weight, respectively.

Example 1	Forage	Grain	Mineral	Total Diet
Intake, lb/day	6	0.5	0.015	6.52
Cu, ppm	7.0	10	30	7.3
Cu, mg/day	16.6	1.9	0.19	18.8
Mo, ppm	1.0	0.5	2.0	0.96
Cu:Mo ratio	7:1	20:1	15:1	7.6:1
Example 2	**Higher pellet Cu content**			
Intake, lb/day	6	0.5	0.015	6.52
Cu, ppm	9.0	46	30	12.31
Cu, mg/day	21.1	8.9	0.19	31.7
Mo, ppm	1.0	0.5	2.0	0.96
Cu:Mo ratio	9:1	92:1	15:1	12.8:1
Example 3	**High Forage Mo content**			
Intake, lb/day	6	0.5	0.015	6.52
Cu, ppm	9.0	10	30	9.1
Cu, mg/day	21.1	1.9	0.19	23.5
Mo, ppm	3.5	0.5	2.0	3.23
Cu:Mo ratio	2.6:1	20:1	15:1	2.8:1
Example 4	**Higher forage Cu content**			
Intake, lb/day	6	0.5	0.015	6.52
Cu, ppm	18	10	30	17.33
Cu, mg/day	36.85	1.9	0.19	44.6
Mo, ppm	2.0	0.5	2.0	1.87
Cu:Mo ratio	9:1	20:1	15:1	9.3:1

samples. Serum or plasma Cu concentrations are most easily obtained and determined, though interpretation relative to dietary status is confounded. Only very low (<0.1 µg/ml) or very high (>5 µg/ml) blood Cu concentrations are diagnostic. Values within the normal reference range (0.3 to 0.8 µg/ml) could also be associated with marginally deficient or excessive dietary Cu intake. Liver Cu concentration is considered the best measure of dietary Cu status but requires a liver biopsy to obtain a sample. If an animal dies from unknown causes, a sample of liver and kidney should be obtained for Cu concentration determination. Liver Cu concentrations below 25 ppm (dry weight basis) or above 500 ppm (dry weight basis) are suggestive of deficiency or toxicity, respectively. Kidney Cu concentrations below 10 mg/kg (dry weight basis) are considered normal. Elevated kidney Cu is highly supportive of Cu toxicity and is the preferred sample for analysis.

Summary

Copper is an essential micromineral for all small ruminant species, though differences in the species Cu requirement results in differential risks for deficiency or toxicity disease. Sheep and camelids are more prone to copper accumulation from an over supplemented diet thus predisposing them to greater risk for toxicity problems. Goats have a much higher tolerance for Cu and have higher requirements compared to other small ruminants and are more prone to present with deficiency disease. A common problem in the feed industry is the lack of recognition for the difference in copper requirement between sheep and goats with many products labeled for their use being formulated for low Cu content relative to sheep requirements. Proper Cu dietary supplementation requires that all feed ingredients be analyzed not only for their Cu content, but the content of important interfering substances to Cu availability such as iron, molybdenum, and sulfur. Ongoing monitoring of animal Cu status is a necessary component of a small ruminant health program.

Suggested Resources:

McDowell LR: *Minerals in Animal and Human Nutrition*, San Diego, CA, Academic Press, 1992, pp 176-204.

National Research Council: *Nutrient Requirements of Small Ruminants, Sheep, Goats, Cervids, and New World Camelids*. Washington, D.C., National Academy Press, 2007.

Suttle NF: *The Mineral Nutrition of Livestock, ed 4.* Cambridge, MA, CAB International, 2010, pp 255-305.

The objective of this article is to address pertinent aspects of copper metabolism, nutrition, and disease concerns relative to small ruminant feeding programs. Clinical manifestations of copper deficiency are associated with a critical decline in activity of a specific copper-dependent metalloenzyme. Though any disease process may occur in all small ruminant species, there seems to be some species differences in presentation of copper diseases. Goats tend to have greater problems with copper deficiency due to their higher requirements compared to other small ruminants. Copper toxicosis results from the accumulation of copper from the diet culminating in uncontrolled copper ion release from storage and subsequent oxidative damage. Toxicosis is of concern for sheep, llamas, and alpacas and less so for goats, though clinical presentation is not equivalent across the species. All dietary ingredients need to be accounted for in addressing sheep and goat dietary copper management to prevent copper-related disease risks.

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