Copper Toxicity in Sheep is on the Rise in Kansas and Nebraska
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Over the past two months, we at Kansas State University have received several phone calls from veterinarians and sheep producers across Kansas and Nebraska requesting information on ill and dead sheep describing signs consistent with copper toxicity. In many of these cases, toxic levels of copper have been documented in the tissues and we have become aware of a sheep-labeled feed that is at the center of this outbreak of cases.

There are two forms of copper toxicity: Acute copper toxicity results from ingestion of high copper feeds, copper salts, pesticides, poultry litter and other high copper substances. Acute copper poisoning can occur at copper intakes of 20-100 mg/kg in sheep and young calves, and 200-800 mg/kg in adult cattle. Chronic copper toxicity occurs when high levels of copper are ingested over a period of time, but at doses below the acutely toxic level. Sheep are the most susceptible species to chronic copper toxicity, because their liver cells have a high affinity for copper and they excrete copper into the bile at a very low rate, leading to a build-up of liver copper concentration over time. One of the most common causes of toxicity in sheep is the accidental feeding of feedstuffs intended for other livestock. Molybdenum reduces the accumulation of copper in the liver. The ratio of copper to molybdenum in the feed is, therefore, an important factor determining the risk of copper poisoning. Chronic copper toxicity typically involves the ingestion of feeds that have a high copper : molybdenum ratio. Any feed which tests to have copper levels > 25 ppm or has a copper : molybdenum ratio of >10:1 is considered potentially toxic for sheep.

Copper is a strong oxidizing agent. It binds to proteins in the liver cells and is stored in lysosomes within hepatocytes. As long as the copper remains stored in lysosomes it does not cause tissue damage. Copper can, however, be spontaneously released or released at times of stress, including shearing, weather extremes or transport. Chronic copper poisoning is, therefore, often described as a stress-related disease. When copper enters the blood it partitions into red cells, elevating red cell copper levels 15-20 times, while plasma copper levels only increase 2-3 times. It causes oxidative injury to hemoglobin, inducing Heinz-body formation and converting it to methemoglobin, which cannot bind O₂ or CO₂. The sulphydryl groups of the red blood cell membrane also undergo oxidative change, resulting in significant hemolysis and anemia. Finally, this massive release of hemoglobin can result in hemoglobinuric nephrosis and renal failure.

Many animals affected by copper toxicity are simply found dead. Necropsy findings will include icterus and “gun metal blue” kidneys (Figures 1 and 2). In the live animal, icterus, red or brown urine (Figure 3), anorexia, pallor, weakness and recumbency are common signs. Brown blood (Figure 4) or pink serum may be noted on blood collection and processing; anemia and, in some cases, evidence of red blood cell regeneration, will be present on blood work. Elevations in creatinine are expected in animals with renal involvement. Hepatocellular injury and bile duct occlusion occur as
the copper release and the enzymes AST and GGT have been shown to be elevated as far as 9 weeks prior to the development of clinical signs.

Once these clinical signs are recognized, the current feed for the flock should be withdrawn pending testing for both copper and molybdenum. Because copper may be stored in the liver for up to 18 months, it is common to find that the current feed is not the source. On necropsy, fresh samples of liver and kidney should be submitted to a diagnostic laboratory for copper levels. Serum copper levels are unreliable in live animals due to the primary storage in liver. If serum copper levels are elevated (> 2.0 ppm), this is diagnostic. If the levels are below this level, copper toxicity cannot be excluded because the elevation in serum copper concentration is often transient. Liver copper levels should also be interpreted with caution, because the release of copper from the liver during the disease process can significantly reduce liver copper concentrations.

Treatment is complicated by economic restrictions and antidote availability. For each drug, the current slaughter withholding for food animals is listed. Methylene blue (4-10 mg/kg slow IV; given to effect) is important in controlling the acute methemoglobinemia. Response is typically rapid with a noticeable effect expected within 15 minutes. The low end of the dose range may be repeated if additional doses are required. Methylene blue is a potential carcinogen, and because of the lack of residue studies that accounts for bound methylene blue in tissues, a slaughter withholding of 180 days has been recommended by the FDA in any species. Free methylene blue is not readily retained in the body and is virtually completely eliminated by 14 days, this being the current recommendation for withholding in cattle suggested by FARAD. Sodium thiosulfate (1000 mg per animal) is administered orally once daily for 3 weeks. This usually comes in an injectable form, which is administered orally. This drug is considered by FARAD to not be a concern for slaughter, but it is recommended to impose a slaughter withdrawal of 24 hours. D-penicillamine (26 mg/kg orally twice daily for 6 days) is a heavy metal chelator and increases copper excretion via urine. The recommended slaughter withdrawal is 21 days. Ammonium tetrahydroxoantimonate (1.7 mg/kg IV every other day for 3 treatments) decreases absorption of copper and increases removal from liver, decreasing liver copper within 6 days. A 10 day slaughter withdrawal is recommended. Vitamin C (500 mg subcutaneously) may also be useful in treating copper toxicity as ascorbic acid counters red blood cell oxidative damage. Supportive treatments, including blood transfusions and aggressive intravenous fluid therapy should be considered as indicated by clinical and economic parameters.

When addressing individual ill animals, it is also important to consider flock management. It is recommended that sodium thiosulfate, at the above listed dosage, be administered to all at-risk animals daily for 3 weeks to facilitate copper removal from the liver.

This disease is particularly concerning at this time of year with the extreme heat and exhibition of lambs. These stressors contribute significantly to the development of clinical disease and complicate therapeutic intervention in the individual animal and flock.

If you have any further questions regarding this or any other matter regarding livestock health, please feel free to call the Kansas State University Veterinary Teaching Hospital at 785-532-5700 or the Veterinary Diagnostic Laboratory at 866-512-5650.

Figure 1: Severe icterus in a sheep with copper toxicity.

Figure 2. Characteristic “gun metal blue” kidneys of a sheep with chronic copper toxicity.
Figure 3. Dark hemoglobin containing urine from a sheep with copper toxicity.
Figure 4. Blood from a sheep with copper toxicity and from a control sheep. Note that the blood from the affected sheep is much darker than the control and from the sample taken on day 4.