

Detailed Summary of the Panel Discussion on Copper-Associated Hepatopathy From the ACVIM Forum 2023

Sharon Center, DVM

Author Contact:

Sharon Center, DVM
Emeritus James Law Professor of Internal Medicine
College of Veterinary Medicine
Cornell University, Ithaca, NY
Email: sac6@cornell.edu

Abbreviations**CuAH****Copper-Associated Hepatopathy**

The ACVIM Forum 2023 included a panel discussion regarding the causal role of dietary copper in Copper-Associated Hepatopathy (CuAH), presenting concerns published in an open access commentary published in the *Journal of the American Veterinary Medical Association* (JAVMA) (1). This paper was written by veterinary specialists with expertise in liver disease (hepatologists) and nutrition. The prevalence of canine CuAH has increased contemporaneous with restructured American Association of Feed Control Officials (AAFCO) copper allowances enacted between 1993-1997. Increased disease incidence was recognized independently by veterinary hepatologists, internists, and pathologists. There is strong case-based evidence that allowances currently mandated for canine diets underlie the increased incidence of CuAH in pet dogs, including predisposed breeds (ie, certain Labrador Retrievers, Doberman Pinschers, Dalmatians, and others) and non-predisposed breeds (including giant breeds, medium-sized breeds, toy-sized breeds, and mixed breed dogs).

Modification of copper guidelines had been instituted based on a small study in juvenile (growing) dogs which investigated the bioavailability of copper oxide compared to copper sulfate (2). At that time, food grade copper oxide was conventionally used as a copper source in animal feeds. Copper oxide had already been shown to have low bioavailability in humans and in livestock feed compared to copper sulfate. An abstract—no peer reviewed manuscript was ever published—described a

decline in hemoglobin and serum copper concentrations after 16 weeks in growing dogs fed a base diet fortified with various concentrations of copper oxide compared to copper sulfate. Study details are sparse; the baseline diet composition and statistical comparisons between study parameters remain unpublished. Because serum copper does not correlate with systemic or liver copper concentrations, and growing dogs require ~2-fold higher copper provision compared to adult maintenance needs, using this study to change dietary recommendations for adult maintenance dog foods is problematic. The aforementioned veterinary specialists believe this change directly correlates with and is the cause of the increased incidence of CuAH described above.

The Forum presentation provided the historical perspective regarding liver copper concentrations in dogs from the advent of commercial dog food, graphically demonstrating progressive increases in average liver copper concentrations from ~50 µg/g dry liver weight (dlw) in the 1940-1950s to 435 µg/g dlw today. Notably, a human with >50 µg/g liver would be designated as having CuAH (known as *Wilson Disease*). During the 30 years of food grade copper oxide use, copper deficiency had never been reported in the peer-reviewed veterinary literature and never documented in a clinical patient by the group of concerned veterinary specialists authoring the *JAVMA* commentary; the clinical experience of these authors averaged 40 years.

Increased prevalence of CuAH is proposed to reflect injudicious copper allowances (copper sulfate and copper chelates/proteinates) currently endorsed by the FDA and AAFCO. Copper sources alternative to copper oxide have bioavailability ranging 2- to >5-fold higher. Additionally, premixes containing these more bioavailable forms of copper are advocated by AAFCO for addition to baseline dietary components to ensure sufficient dietary copper provision. However, use of premix supplements does not require consideration of baseline dietary copper content that varies from batch to batch due to different sourced dietary components (eg, liver, especially pork liver), making total copper levels variable. Indeed, wide-ranging copper concentrations have been documented in commercial canine diets from 2017-2021, summarized in graphic form in a final report formulated by the AAFCO working group that responded to the JAVMA commentary (3). Among more than 1,400 diets sampled during this time, median copper content was ~20 mg/kg dry weight diet (roughly 5.6 mg/1000 kcal), with some diets ranging as high as 140 mg/kg (roughly 39.8 mg/1000 kcal; assuming 4,000 kcal/kg and 12% moisture) (3). Relevantly, published research in Labrador Retrievers, one of the breeds predisposed to CuAH, has confirmed that chronic ingestion of a diet containing copper at 15 mg/kg dry weight diet can lead to pathologic liver copper accumulation (4, 5).

Because a maximum allowable level (the safe upper limit) of copper for commercial dog food has not been established, regulatory agencies are reluctant to set an upper limit standard. The veterinary hepatologists concerned about dietary copper over-supplementation suggest a range of 7-9 mg/kg dry weight diet as a safe upper tolerance level for dogs. This value considers that chronic use of a few copper-restricted canine diets (2 prescription diets that are also protein restricted and 3 adult maintenance diets that are not protein restricted) are commonly fed to large numbers of dogs. In dogs fed these diets, copper deficiency has not been documented by the concerned specialists or reported in the veterinary literature.

A labeling change for canine adult maintenance dog foods to designate restricted copper diets was also suggested by the concerned specialists. Currently, dietary copper content is usually not declared on a food label or manufacturer's website and is difficult to document even upon specific query to the manufacturer.

Finally, a proposal was made to address dietary copper allowances using an EPA-type study as employed to establish an oral copper tolerance limit for humans (3, 6-8).

Attendees were encouraged to contact hepatologists on the panel (and authors of the JAVMA commentary, reference 1) to participate in crowd-source data collection. Such data would include historical information from dogs with liver biopsies documenting CuAH, accompanied by a detailed dietary history including treats, supplements, name and manufacturer of the specific diet(s) fed, along with a label photograph. This information would further inform development of a safe upper copper allowance for adult maintenance dog food.

References

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