Viewpoint

Is it time to reconsider current guidelines for copper content in commercial dog foods?

Sharon A. Center DVM
Keith P. Richter DVM
David C. Twedt DVM
Joseph J. Wakshlag DVM, PhD
Penny J. Watson VetMD
Cynthia R. L. Webster DVM

From the Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853 (Center, Wakshlag); Veterinary Specialty Hospital of San Diego, San Diego, CA 92121 (Richter); Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80521 (Twedt); Department of Veterinary Medicine, University of Cambridge, Cambridge CB3 0ES, England (Watson); and Department of Clinical Sciences, Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA 01536 (Webster).

Address correspondence to Dr. Center (sac6@cornell.edu).

Over the past 15 to 20 years, we have seen what we believe to be an increased incidence of copper-associated hepatopathy in dogs. The onset of this increase appears to have coincided with a change in the type of copper used in premixes added to commercial dog foods. And, more recently, the increased incidence may have been exacerbated by consumer-driven desire for pet foods formulated with a high content of animal-based ingredients (eg, evolutionary diets), including certain organ meats, that might introduce additional copper and by trends favoring foods containing vegetables with a high copper content (eg, sweet potatoes). In light of the increased incidence of copper-associated hepatopathy in dogs, the association between dietary copper and hepatic injury, and the higher copper content of current commercial dog foods, compared with foods marketed prior to the revised guidelines for dietary copper, we believe that it would be prudent to reexamine dietary copper recommendations for dogs and reconsider current guidelines for copper content in commercial dog foods.

Copper Content of Commercial Dog Foods and Hepatic Copper Concentrations in Dogs

In agreement with suggestions by several previous authors,[1–7] we suspect that copper contents of many commercial dog foods are greater than the biologic requirement of dogs and exceed the tolerance limit for some of them. Guidelines for the nutrient content of commercial dog foods are overseen by the AAFCO, a voluntary association of local, state, and federal agencies that operates in a watchdog capacity to regulate the sale and distribution of animal feeds and animal drug remedies. The AAFCO guidelines[8] describe minimum and, for some nutrients, maximum allowable nutrient contents for foods formulated for dogs. These guidelines are developed from nutrient recommendations made by an NRC panel of experts on the basis of evidence-based scientific studies[9] and are periodically revised by canine and feline nutrition expert subcommittees appointed by the AAFCO.

In 1997, the AAFCO recommendation regarding copper in commercial dog food was revised on the basis of a study[a] that evaluated the relative bioavailability of feed-grade copper oxide, compared with that of copper sulfate. In that study, dogs fed a diet to which copper oxide (1.7 or 4.7 mg Cu/1,000 kcal) had been added had decreases in serum copper and hemoglobin concentrations within 16 weeks, which the authors interpreted to reflect insufficient copper intake. In contrast, dogs fed a diet to which copper sulfate had been added at a rate of 1.9 mg Cu/1,000 kcal did not develop anemia, and those fed a diet to which copper sulfate had been added at a rate of 2.7 mg Cu/1,000 kcal did not have any decrease in serum copper concentrations. Importantly, the baseline diet fed to dogs in that study was not specified, and a full description of the study details has not been published, to the authors' knowledge. Nevertheless, and despite the fact that there had been no evidence of widespread clinical copper deficiency in dogs prior to this study, recommendations for dietary sources of copper were subsequently modified. Specifically, a recommendation was made to replace feed-grade copper oxide in canine diet formulations with more bioavailable forms of copper, such as copper sulfate.[10,a]

Mean hepatic copper concentration in dogs has progressively increased from < 10 µg/g (measured on a dry-weight basis) in 1929 to 200 µg/g in 1982 and 453 µg/g in 1995,[1,4,11–21] and results of various studies suggest that high hepatic copper concentrations in dogs reflect high copper content in commercial dog foods. For example, a study[4] of Labrador Retrievers with and without chronic hepatitis found that hepatic copper concentrations were significantly higher after the recommendation to alter sources of copper in commercial dog foods than they had been before

ABBREVIATIONS
AAFCO Association of American Feed Control Officials
NRC National Research Council

that change in formulation. A study[7] of 564 dogs of breeds with and without a predisposition for copper-associated hepatopathy came to the same conclusion. A small study[b] that compared hepatic copper concentrations in 9 healthy feral dogs from Malaysia and Nicaragua (presumably fed human food scraps and foraged foods) and 9 healthy purpose-bred dogs fed commercial dog food (23.4 mg of Cu/kg of diet, a concentration within AAFCO guidelines) found that the feral dogs had a significantly ($P = 0.004$) lower hepatic copper concentration (median, 152 µg/g; range, 69 to 370 µg/g) than did the purpose-bred dogs (median, 472 µg/g; range, 199 to 997 µg/g).

At the same time, there has been a growing body of evidence suggesting an association between high hepatic copper concentrations and the presence of histologic hepatic abnormalities. For example, a study[c] of hepatic biopsy specimens from dogs submitted to a diagnostic center between 2010 and 2015 found that of 2,149 samples, approximately 51% had hepatic copper concentrations > 400 µg/g (mean, 1,233 µg/g; range, 401 to 12,400 µg/g), with significantly higher concentrations in specimens with histologic evidence of inflammation. Similarly, one of the authors (CRLW) working at a different diagnostic center found that of 612 canine hepatic biopsy specimens submitted during a similar timeframe, 367 (60%) had copper concentrations > 400 µg/g, with 213 (58%) having inflammatory hepatic disease.

More recently, a study[22] examining hepatic copper concentrations determined with 3 different analytic methods (atomic absorption spectroscopy, inductively coupled plasma mass spectrometry, and digital image analysis of rhodanine-stained sections[23]) found that concentrations obtained with the atomic absorption spectroscopy and inductively coupled plasma mass spectrometry methods were significantly lower than concentrations obtained with digital image analysis. Significant differences between methods of copper quantification reflected the impact of nonhomogeneous distribution of copper across liver sections and the analysis of single versus multiple samples with spectroscopic-spectrometric and digital methods, respectively. Because hepatic copper concentrations in dogs have typically been measured in single liver samples by means of spectroscopic-spectrometric methods, it is probable that increases in hepatic copper concentrations over time are more extreme than acknowledged.

Copper Metabolism

Copper is a trace element essential for a wide range of biochemical processes; homeostatic balance depends on numerous membrane transporters, chaperones, and binding proteins, with copper ultimately eliminated in bile.[24] More than 30 copper-dependent metalloenzymes have a role in diverse metabolic pathways, including collagen synthesis (lysyl oxidase is essential for molecular cross-linking of collagen and elastin), mitochondrial energy generation (cytochrome c oxidase is essential for the electron transport chain that generates ATP), and antioxidation (copper–superoxide dismutase is responsible for the dismutation of superoxide anions that otherwise oxidatively damage local protein and lipid cell constituents).[25,26] Copper is absorbed in the upper portions of the small intestine and transported to the liver in free and protein-bound forms. After hepatocyte uptake, copper is added to designated transcriptional products, bound to metallothionein or other cupriproteins for storage, or shuttled to the canaliculus for biliary elimination.[24,27] Each step is critical for maintaining a neutral copper balance.

Hepatic Injury Association With Copper Accumulation

As a transition metal similar to iron, copper exists in an oxidized (cupric [Cu^{+2}]) or reduced (cuprous [Cu^{+1}]) state, allowing it to function as an electron acceptor or donor.[25,26] As such, copper participates in redox cycling reactions that promote generation of reactive oxygen species. Specifically, the Haber-Weiss/Fenton reaction[25] **(Figure 1)** generates superoxide ($\bullet O_2^-$) and hydroxyl ($\bullet OH$) radicals and other reactive oxygen species from hydrogen peroxide that can provoke DNA strand breaks, impair cell prolifera-

Chain reaction is initiated by the Fenton reaction:

$$Cu^{1+} + H_2O_2 \rightarrow Cu^{2+} + HO^- + \bullet OH \quad \text{(step 1: initiation)}$$

Reaction chain propagates by means of two successive steps:

$$\bullet OH + H_2O_2 \rightarrow H_2O + \bullet O_2^- + H^+ \quad \text{(step 2: propagation)}$$

$$Cu^{2+} + \bullet O_2^- + H^+ + H_2O_2 \rightarrow Cu^{1+} + O_2 + \bullet OH + H_2O \quad \text{(step 3: propagation)}$$

Reaction chain is terminated when the hydroxyl radical is scavenged by a cuprous ion:

$$Cu^{1+} + \bullet OH + H^+ \rightarrow Cu^{2+} + H_2O \quad \text{(step 4: termination)}$$

The net reaction: $\bullet O_2^- + H_2O_2 \rightarrow \bullet OH + OH^- + O_2$

Figure 1—Initiation, propagation, and termination of the Haber-Weiss/Fenton reaction that orchestrates copper-mediated oxidative injury in copper-associated hepatopathy.

tion, cause endoplasmic reticulin stress and oxidative injury to cell and organelle (particularly mitochondrial) membranes, and initiate cell-death pathways.[25,26] Numerous studies[25–29] illustrate that copper-initiated oxidative injury first impacts mitochondrial membranes, disturbing their structure and the function of the electron transport chain. Because mitochondria provide approximately 90% of cellular ATP through oxidative phosphorylation, this damage has adverse cellular consequences. Concurrently, endoplasmic reticulin stress impairs protein synthesis, further compromising cell functions. Mitochondrial and endoplasmic reticulum injury explain the hepatocyte microvesicular lipid vacuolation often observed with severe copper-associated hepatopathy. Oxidative injury leads to consumptive depletion of hepatocyte and mitochondrial glutathione and α-tocopherol, permitting further oxidative damage.[26]

Glutathione is the most important of the numerous antioxidant and antioxidant enzyme systems in the liver and is essential for regulation of redox balance.[30] Glutathione maintains the redox status of protein sulfhydryl groups, quenches endogenous and exogenous oxidant species and electrophiles, assists in preservation of antioxidant enzymes (ie, glutathione peroxidase), and conjugates drugs and xenobiotics in a process catalyzed by glutathione S-transferases to facilitate their renal or biliary elimination.[30] Glutathione also assists in rejuvenation of α-tocopherol from the tocopheroxy radical that is generated when vitamin E terminates peroxidative membrane injury. Hepatocytes synthesize glutathione in their cytosolic compartment, and it then enters the mitochondria, which cannot generate glutathione de novo, and the systemic circulation. Copper-associated hepatic injury results in decreases in hepatic and plasma glutathione and vitamin E concentrations.[25,26,31–34] Because de novo hepatic synthesis of glutathione is the predominant source of plasma glutathione and plays a vital role in glutathione homeostasis, copper-associated hepatic injury can have widespread systemic consequences (eg, exacerbation of oxidative injury caused by concurrent illnesses).

Centrilobular hepatocytes are rich in cytochrome P450 oxidases and are the predominant site of xenobiotic biometabolism and detoxication. Because, in dogs, the centrilobular hepatic region is where copper accumulates, colocalization of copper and toxic metabolites or electrophiles magnifies the risk of regional cellular injury. Of additional concern is that centrilobular regions are the last zone to extract oxygen from sinusoidal blood. Consequently, these hepatocytes have a heightened risk for ischemic, hypotensive, or hypoxia-related oxidative injury. Thus, colliding factors may initiate sudden hepatocyte injury in dogs with substantial centrilobular copper accumulation. Examples of this so-called "2-hit phenomenon" include sudden dramatic increases in serum alanine transaminase activity in combination with severe hemolytic or blood loss anemia, hypoxemia, cardiac failure, hypotensive shock, gastric dilatation-volvulus, hypotension during general anesthesia, and administration of cytochrome P450–metabolized xenobiotics (eg, NSAIDs) that form oxidative adducts or electrophiles.

Histologic Patterns of Copper-Mediated Hepatic Injury

Histologic features of copper-associated hepatopathy are well characterized and similar in all dogs. The first feature observed during histologic examination of H&E-stained hepatic sections is accumulation of refractile eosinophilic cytosolic granules in centrilobular hepatocytes, often colocalizing with lipofuscin (a tan-colored product derived from oxidized membrane lipids). Copper-mediated hepatocyte death initially appears as single random apoptotic cells, but with progression, distinct small pyogranulomatous foci, also known as copper granulomas, appear. These reflect the cellular response to dead or dying hepatocytes and are populated by macrophages containing phagocytized hemosiderin, copper, and lipofuscin-laden debris; fewer lymphocytes; and occasional neutrophils. These focal lesions typically abut copper-laden hepatocytes. Copper-associated liver injury can be confirmed with histologic examination of sections stained with rhodanine stain, which causes copper granules to appear as bright orange-red cytosolic inclusions.

With progression of centrilobular hepatic injury, lymphohistiocytic infiltrates accumulate at the interface of the perivenular adventitia (ie, the central vein supportive structure) and regional hepatocytes, typically described as centrilobular or periacinar hepatitis. Progressive injury extends into midzonal regions and later involves portal regions where inflammation provokes a cholangiocyte ductular reaction. Eventually, hepatocytes in all zones may display cytosolic copper aggregates and scattered copper granulomas appear. Macrophages in portal and central regions often sequester iron as a result of phagocytosis of heme-laden cellular debris. At this stage, the liver often appears grossly normal, but serum biochemical assessments disclose fluctuating alanine transaminase activities, with activities 5 to 10 times the upper reference limit common.

Progression of copper-associated hepatic injury leads to centrilobular parenchymal collapse, obscuring acinar structures and profiles of central veins. Severe injury results in obstruction of sinusoidal flow through hepatic venules. Parenchymal remodeling and fibrosis associate with formation of regenerative nodules. At this stage, portal regions bridge with central regions and become amalgamated within the inflammatory process; this may be histologically misinterpreted as portal hepatitis. Regenerative nodules populated by newly replicated hepatocytes display comparatively few copper inclusions, and biopsy of regions with large numbers of regenerative nodules

will underestimate the severity of hepatic copper accumulation. At this stage, the liver may be normal or small in size and have a finely irregular surface or obvious macroscopic nodularity and a firm, fibrotic texture.

The most advanced stage of copper-associated hepatopathy is characterized by loss of acinar structures with areas devoid of viable hepatocytes (ie, parenchymal extinction). These regions vary widely in size and distribution and have a paucity of stainable copper. The liver at this stage is grossly small, pale, and firm with innumerable nodules.

Rarely, some dogs develop acute, severe panlobular hepatic necrosis associated with massive release of copper from damaged hepatocytes that may cause markedly increased circulating copper concentrations and hemolysis. On gross examination, the liver appears normal or plump and may have soft pale-yellow foci delineating necrotic areas.

An acquired Fanconi syndrome (euglycemic glucosuria reflecting acute proximal tubular injury) is occasionally encountered in some dogs, typically those with advanced disease. Rhodanine staining of renal biopsy specimens demonstrates copper accumulation in proximal renal tubular epithelium.[35] It is surmised that this syndrome reflects renal tubular copper accumulation secondary to a high circulating copper concentration alone or in conjunction with other causes of proximal renal tubular injury (eg, NSAID exposure or leptospirosis).[35,36] Dogs with this syndrome can recover with intensive supportive care.[35–37]

Treatment of Dogs With Pathological Hepatic Copper Accumulation

Several studies[1,3,15,16,22,38,39] of dogs document wide variations between the extent of hepatic injury and the severity of hepatic copper accumulation. Histologic evaluation of hepatic biopsy specimens from dogs with pathological copper accumulation can reveal a marked diversity in the extent of hepatic injury. The most vulnerable dogs develop copper-associated hepatopathy with hepatic copper concentrations as low as 600 µg/g. It is likely that individual susceptibility reflects a complex interplay of genetic and environmental factors, coexisting diseases, and exposure to toxins and xenobiotics. Currently, clinical observations are at odds with a previous suggestion based on work in Bedlington Terriers and West Highland White Terriers to treat dogs with hepatic copper concentrations > 2,000 µg/g.[3,19] In fact, it is now recommended by the authors to initiate chelation in dogs with hepatic copper concentrations as low as 600 µg/g if histologic lesions are seen in association with hepatocyte copper accumulation or if fluctuating serum alanine transaminase activities are seen with no plausible alternative cause. With this current standard of care in mind, many pet dogs are now subjected to general anesthesia and liver biopsy out of an abundance of caution so that preclinical copper-associated hepatopathy will not be overlooked. In addition to the costs of surgery and anesthesia for these dogs, there is the potential cost of treatment (eg, copper chelation and antioxidants) and lifelong need to feed a copper-restricted diet.

Potential Causes of Pathological Hepatic Copper Accumulation

Three potentially synergistic factors are often considered when pathological hepatic copper accumulation is diagnosed in a dog: genetic factors, chronic hepatic disease altering hepatic copper homeostasis, and long-term dietary copper intake exceeding homeostatic regulatory mechanisms. The authors believe that neither genetic factors nor decreased biliary elimination is responsible for the perceived increase in copper-associated hepatopathy in dogs and that dietary factors are most important.

Genetic causes of copper-associated hepatopathy

Bedlington Terriers have a genetic form of copper-associated hepatopathy resulting from homozygous deletion of exon 2 in the *copper metabolism domain containing 1* (*COMMD1*) gene, resulting in complete absence of this essential copper-transporting protein.[40,41] This protein facilitates function of ATP7β, the defective protein causal to Wilson disease in humans.[42] The ability to genotype dogs has permitted genetic-based selection of breeding Bedlington Terriers that has dramatically reduced the incidence of this hepatic disease. Preliminary genotyping studies in Labrador Retrievers, Doberman Pinschers, and Bedlington Terriers have also identified single nucleotide polymorphisms potentially associated with risk for copper-associated hepatopathy.[43–46] However, interpretation of such findings must consider that linebreeding of dogs to establish certain breed characteristics increases risk for propagation of single nucleotide polymorphisms. In some cases, these occur near disease-causing mutations, regardless of whether they are causally related to disease. This reflects transfer of DNA in blocks rather than simply as single genes, resulting in naïve selection of single nucleotide polymorphisms near determinants of breed characteristics (so called hitchhiking genes) and sometimes disease-causing mutations. This phenomenon probably contributes to the vulnerability of some dogs to high dietary copper intake and could influence any of a number of proteins or transcriptional elements influencing copper homeostasis.

Cholestasis and chronic hepatic disease

Cholestasis and cirrhosis are often cited as potential causes of hepatic copper accumulation in dogs. Hepatic copper accumulation can, in fact, occur in humans who survive for many years after the onset of cholestasis or cirrhosis.[3] However, comparable long-term survival in dogs with chronic cholestasis or cirrhosis is extremely rare.

Comparatively, cats with slowly progressive cholangitis can develop periportal copper accumulation secondary to cholestasis, contrasting with dogs, in which pathological hepatic copper accumulation is centrilobular.[47]

Previous studies[48,49] along with observations of one of the authors (SAC) further suggest that cholestasis is not a common cause of hepatic copper accumulation in dogs. In one of those studies,[48] chronic (≥ 2 months) extrahepatic bile duct obstruction in dogs did not result in clinically relevant hepatic copper accumulation unless copper was administered IV (0.5 mg/kg [0.23 mg/lb], q 48 h for 27 to 87 days), whereupon hepatic copper concentration significantly ($P \leq 0.003$) increased (median, 1,473 µg/g; range, 817 to 3,273 µg/g), compared with concentration in healthy dogs (median, 185 µg/g; range, 102 to 342 µg/g) and dogs with extrahepatic bile duct obstruction without IV copper administration (median, 291 µg/g; range, 122 to 371 µg/g). Notably, median hepatic copper concentration in dogs with extrahepatic bile duct obstruction without additional IV copper administration was not significantly different from that in healthy dogs. In the other study,[49] 6 dogs with evidence of extrahepatic bile duct obstruction (as determined by means of ultrasonography, clinicopathologic testing, and histologic examination) had no (n = 2) or only mild (4) hepatic copper accumulation when qualitatively assessed with a rubeanic acid–based method. Finally, of 32 dogs evaluated by one of the authors (SAC) between 2015 and 2020 that had hyperbilirubinemia with chronic (> 2 weeks) gallbladder disease and high serum alkaline phosphatase activity (> 6 times the upper reference limit), 22 had hepatic copper concentrations < 300 µg/g, 7 had concentrations ranging from 400 to 600 µg/g, and only 3 had concentrations ranging from 700 to 1,250 µg/g.

In dogs with cirrhosis, copper accumulates in areas of inflammatory infiltrates or at the margins of regenerative nodules. In 116 dogs with histologically confirmed cirrhosis examined between 2015 and 2020 by one of the authors (SAC), hepatic copper concentrations ranged from < 400 µg/g to > 8,000 µg/g. Of these dogs, 23 (20%) had hepatic copper concentrations ≤ 400 µg/g, 8 (7%) had concentrations between 401 and 600 µg/g, 9 (8%) had concentrations between 601 and 1,000 µg/g, 30 (26%) had concentrations between 1,001 and 2,000 µg/g, and 46 (40%) had concentrations > 2,000 µg/g. All 76 dogs with hepatic copper concentrations > 1,001 µg/g had histologic evidence of copper-affiliated inflammation and injury, suggesting a causal association.

Determining Dietary Copper Requirements and Tolerability

According to World Health Organization standards, a nutrient requirement is the smallest amount (absorbed or consumed) needed to maintain optimal function and health.[50] Although requirements for copper intake can be estimated with metabolic balance studies, such studies are complicated by numerous variables, making them impractical, expensive, and unwieldly for assessment of long-term requirements. Copper uptake is self-regulated in response to dietary copper intake, which depends on a variety of factors including bioavailability of the specific copper formulation and interactions with multiple other nutrients. Thus, results derived from such studies[26,27,51,52] are specific for the particular diet formulation tested. Feeding trials can be used to investigate dietary copper requirements and can help define the minimum requirements (ie, the minimum amount needed to prevent disease manifestations associated with a deficiency) and the highest tolerable intake. However, feeding trials are also complicated by nutrient interactions that affect copper bioavailability and require long study durations (months to years) to establish safe intake levels. Such studies also are hampered by the lack of sensitive methods for determining intake sufficiency or insufficiency. In the case of copper intake in dogs, intolerable excessive intake manifests as hepatic copper accumulation with or without simultaneous increases in serum alanine transaminase activity. However, effects of intake insufficiency are not well defined.[53] A final approach for determining nutrient tolerability is to use epidemiological observations, combining details from experimental studies with findings in animals with spontaneous disease.[54] One or more of these methods can be used to establish a safe nutrient intake level (World Health Organization nomenclature) or a recommended dietary allowance (US National Academy of Sciences nomenclature). We propose using previously published data, epidemiological observations, and results of dietary interventions in dogs with copper-associated hepatopathy to inform revision of NRC and AAFCO dietary copper guidelines. This approach was recently used to determine tolerable and sufficient copper intakes for humans.[54]

An upper tolerability limit for dietary copper intake for dogs has not been established. Prior to 2007, the upper tolerability limit was based on data derived from swine, a species relatively resistant to copper toxicosis. The 2007 AAFCO Canine Nutrition Expert Subcommittee deleted the maximum copper concentration from the adult maintenance nutrient profile for commercial dog foods[55] and did not declare a new upper tolerability limit. Although defining a minimum requirement for adult dogs will be challenging, we believe that it is possible, on the basis of current information, to define an upper tolerability limit that could immediately benefit dogs at risk of developing copper-associated hepatopathy, even while specific tolerability studies are undertaken. Current copper intake clearly exceeds the limit of tolerance for a substantial number of dogs. A first step could be to change the recommendation for bioavailable copper content in dog food to what was recommended prior to 1997, when AFFCO guidelines were changed to require replacement of feed-grade copper oxide with bioavailable forms of copper such as copper sulfate. This could be done by estimating bioavailability of currently used copper moieties relative to the previously used food-grade copper oxide.

To determine a true upper tolerability limit for copper will be complicated because of physiologic

regulation of copper pools that avoid pro-oxidative states in times of relative deficiency or excess.[27] Increases in enteric copper uptake occur when hepatic stores are low, whereas increases in synthesis of metallothionein, a copper-binding protein that limits enteric uptake or distribution, and biliary excretion of copper occur when hepatic stores are high. Although these self-regulating adjustments ideally maintain hepatocyte copper content within safe metabolic limits, gene mutations influencing these mechanisms can modify or limit the appropriate physiologic response. This may be particularly evident when dietary intake is near the upper tolerability limit, which we believe is currently the case for dogs. The upper tolerability limit for copper in humans has also recently been questioned.[53,54] The current AAFCO recommendation for minimum daily copper intake for maintenance adult canine diets is 1.83 mg/1,000 kcal, which is equivalent to a copper intake of approximately 0.067 mg/kg/d (0.031 mg/lb/d) for a dog the size of a typical Labrador Retriever. Although it is not known how many diets exceed this minimum recommendation, investigation of some commercial dog foods demonstrated alarmingly high copper contents in some brands.[5]

Unfortunately, the true copper content of a pet food cannot be reliably ascertained simply by reading the food label. It appears that many manufacturers include premixes to ensure that their diets comply with AAFCO's minimum nutrient content recommendations; however, they may do so without taking into account native copper already in the baseline diet. Also, even if the copper content is referenced on a food label, the wide bioavailability of copper from natural ingredients complicates determining the true copper intake.

Summary of Evidence for Reconsidering Dietary Copper Recommendations for Dogs

Several lines of evidence support our recommendation to reexamine dietary copper recommendations for dogs and reconsider current guidelines for copper content in commercial dog foods.

First, although the true incidence of copper-associated hepatopathy in dogs is not known, our collective clinical opinion is that the incidence of this disease began to increase after the 1997 development of new guidelines for copper content in dog foods. Although one could argue that the increased incidence also coincided with increased recognition of the disease and an increase in the number of hepatic biopsies being performed, studies[4,7] of tissue samples collected before and after the new guidelines for copper content suggest that these factors did not have a major role.

Second, the finding[b] that healthy feral dogs not fed commercial dog foods have significantly lower hepatic copper concentrations than do dogs fed foods compliant with current NRC and AAFCO recommendations for dietary copper supports that high copper intake may be associated with high hepatic copper concentrations.

Third, copper-associated hepatopathy can be successfully treated in Labrador Retrievers[56,57] and, anecdotally, dogs of other breeds through chelation with D-penicillamine followed by lifetime dietary copper restriction.

Fourth, studies[56,57] of Labrador Retrievers and the authors' clinical observations suggest that long-term feeding of copper-restricted diets (copper intake ranging from 0.04 to 0.07 mg/kg/d [0.018 to 0.032 mg/lb/d]) is safe in healthy dogs, dogs with unexplained fluctuations in serum hepatic enzyme activities, and dogs with various hepatic disorders, including congenital portosystemic shunts, acquired hepatic insufficiency, and copper-associated hepatopathy. In some instances, these diets have been fed to healthy dogs out of convenience because another dog in the household required a dietary adjustment, and to our knowledge, no dogs have developed clinical evidence of copper insufficiency (eg, anemia, neutropenia, neurologic signs, or changes in coat color or texture) while being fed these copper-restricted diets. Also, the authors have documented hepatic copper concentrations in dogs after chelation with D-penicillamine of 40 to 125 µg/g, well below the current reference range for dogs, but with no clinical evidence of copper insufficiency.

Fifth, the current AAFCO recommendation for minimum daily copper intake for maintenance adult canine diets of 1.83 mg/1,000 kcal is equivalent to a copper intake of approximately 0.067 mg/kg/d for a medium- or large-sized dog (the precise conversion is done on the basis of metabolic body weight). This represents approximately 1.7 to 1.8 times the copper intake associated with copper-restricted diets (0.9 to 1.1 mg/1,000 kcal, ranging from approx 0.04 to 0.07 mg/kg/d), which again, the authors have found to be safe for long-term feeding of healthy dogs and dogs with various hepatic diseases.

Sixth, widespread copper insufficiency was not recognized clinically prior to the development of new copper dietary guidelines in 1997. Although it is possible that deficiencies existed but were not recognized as important clinical problems, we consider this unlikely.

Finally, currently available copper-restricted diets were developed to meet perceived demands both for copper restriction in dogs with pathological hepatic copper accumulation and for protein restriction in dogs with hepatic encephalopathy secondary to advanced liver disease or portosystemic shunting.[58] However, most dogs with copper-associated hepatopathy do not have hepatic failure or hepatic encephalopathy, and protein restriction in patients with necroinflammatory hepatic disease is not ideal, because these patients can be expected to have heightened nitrogen turnover secondary to inflammatory cyto-

kines and catabolism. Therefore, we believe there is a need for maintenance adult canine diets that have a lower copper content but without protein restrictions. However, such diets should be tested for their ability to maintain a neutral copper balance when fed long-term and should be monitored so that alterations to the base formulation do not modify copper intake.

Conclusions

We understand that AAFCO recommendations are intended to broadly meet the needs of all dogs while allowing for the complex interactions that might influence bioavailability of certain ingredients and accounting for differences in energy needs and food intake. Nevertheless, we believe that the current recommendations for copper content in adult maintenance canine diets are too high and may exceed the upper tolerability limit for some dogs, resulting in hepatic disease. Therefore, we recommend that copper requirements for dogs be reconsidered and that the AAFCO consider establishing an upper tolerability limit. We believe that doing so would reduce the incidence of copper-associated hepatopathy in dogs and enhance canine welfare.

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Dr. Wakshlag is a consultant for Annamaet Petfoods, the Farmers Dog, and Petsmart. None of these companies are currently marketing or plan to market a copper-restricted diet.

Footnotes

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