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CASE REPORT

Copper toxicosis with hepatic cirrhosis in three dogs: report of a safety alert.

Carlos A. Flores Olivares[1*], Ignacio Oroquieta Fairlie[2], Constanza Cubillos Torres[3], Alejandra A. Covarrubias[1], Diana Leiva-Portilla[1]

[1] Laboratorio de Investigación de Ciencias Veterinarias, Facultad de Ciencias Agropecuarias, Universidad del Alba, La Serena, Chile.

[2] Facultad de Ciencias, Universidad Mayor, Santiago, Chile.

[3] Independent researcher.

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***Corresponding author**
carlos.flores@udalba.cl

ABSTRACT. In 2020, hundreds of thousands of dogs in Chile were exposed to toxic copper levels in commercial dog food, exceeding the legal copper limit tenfold. We report three fatal hepatic cirrhosis cases after at least three months of consumption of this product. All showed advanced stage liver injury, micro and macroscopic lesions, and high hepatic copper levels.

Keywords: Copper toxicity, food safety, pet food, regenerative nodules, toxicology, end-stage liver disease.

Copper (Cu) is an essential micronutrient in all eukaryotic species and plays a crucial role as a cofactor in hundreds of enzymatic reactions (Chen *et al*., 2020; Chen *et al*., 2022). Although cells have different mechanisms for maintaining copper homeostasis, its alteration hinders its excretion and promotes its intrahepatocellular accumulation (Center *et al*., 2021), subsequently leading to diseases such as chronic hepatitis (Fieten *et al*., 2014).

Copper-associated hepatopathy affects numerous dog breeds and mixed-breed dogs in the USA. Genetic variability undoubtedly influences the homeostatic copper balance and contributes to the heterogeneity of dietary copper tolerance among dogs. With the exception of the Bedlington Terrier, currently identified genetic markers have dubious value for diagnosis of copper-associated hepatopathy (Center *et al*., 2021; Langlois *et al*., 2013). Rather, it is suspected that excessive copper concentration in many commercial dog foods derives from the routine addition of over-formulated copper-containing premix supplements (Johnston *et al*., 2013; Strickland *et al*., 2018; Center *et al*., 2021; Center, 2025).

Recent trends in dog diets and supplements have led to questions about the proper tolerable limit values of copper concentrations, considering that liver Cu concentrations and their association with severe hepatic damage have increased over the last 25 years (Center *et al*., 2021), with substantial scientific evidence indicating that, in certain cases, dietary copper intake surpasses the physiological capacity of dogs to safely metabolize and excrete this element, thereby increasing the risk of copper accumulation and related hepatic pathology.

In June 2020, the state agency responsible for ensuring the protection of consumer rights reported a food safety alert (FSA) after confirming dog deaths caused by the consumption of a particular extruded dog feed (SERNAC, 2020). In response to this situation, the brand recalled 374.597 bags of extruded dog food, stating that there was a deviation in the functioning of a preservative, which generated rancidity and a foul odor in the product.

This report describes the association of this security alert with the diagnosis and cause of death of three canine patients with a dietary history of consuming this food exclusively for at least three months.

Quantitative analyses for Cu (measured by inductively coupled plasma mass spectrometry (ICP-MS) and expressed in ppm on a dry matter basis (DMB)) in the food samples reported here were conducted by Eurofins Testing Chile and the Subdepartment of Chemistry and Food Safety of the Agricultural and Livestock Service (SAG), Lo Aguirre, Chile. Cu quantification of fresh refrigerated liver tissue samples from the reported cases was performed by the Water and Food Unit of Dictuc and the Clinical and Veterinary Laboratory VetLab, Santiago, Chile, using atomic absorption spectrophotometry (EAA) following enzymatic digestion of the tissue samples. The results were expressed on a dry matter basis (DMB). Routine and histochemical histopathological analyses of these cases were performed at the Veterinary Histopathology Center, Chile (VeHiCe), and the Clinical and Veterinary Laboratory VetLab, Santiago, Chile.

Dog 1. Saint Bernard, female, 1 year and 6 months old. Hepatic Cu concentration: 397 ppm (DMB). Hematology revealed normal hematocrit (44.4%; RI: 37–55%), hypoproteinemia (4 g/dL; RI: 5.2–8.2 g/dL), and hypoalbuminemia (1.3 g/dL; RI: 2.3–4 g/dL). The patient had been exclusively fed food associated with the safety alert throughout its

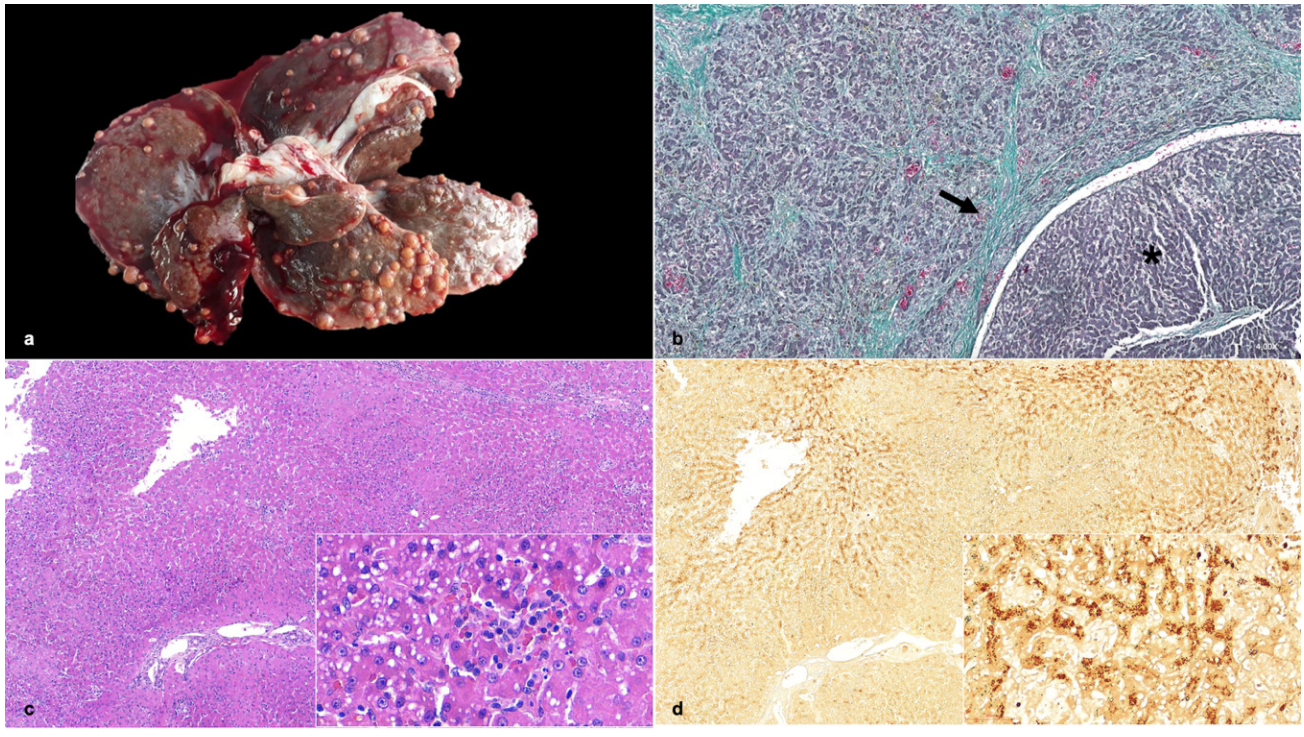
life and, at 1 year and 3 months of age, developed loss of appetite and abdominal fluid accumulation. The condition progressed to severe ascites, with more than 20 L of free translucent fluid in the abdominal cavity, accompanied by diarrhea and anorexia.

Supportive treatment, including furosemide, hepatoprotective agents, gastric protectors, and nutritional supplements, was administered; however, the dog was euthanized due to disease progression. Necropsy revealed that the liver exhibited dark red, retracted areas with multiple regenerative nodules and white, homogeneous proliferations measuring 0.1–1 cm in diameter (Figure 1a). Histopathological evaluation revealed panlobular regenerative nodules demarcated by fibrous connective tissue (Masson's trichrome staining; Figure 1b). Severe lymphohistiocytic necrosis and inflammation were observed, mainly in the centrilobular and mid-zonal regions, with associated hemorrhagic foci (Figure 1c). Hepatocytes and macrophages marginating regenerative nodules displayed numerous red/burnt-orange cytosolic granules (Rhodanine staining), consistent with copper-protein aggregates (Figure 1d). No clinically relevant histological alterations were identified in the non-hepatic organs.

Dog 2. German Shepherd, female, 1 year and 7 months old. Hepatic Cu concentration: 1034 ppm (DMB). Normal hematocrit, hypoalbuminemia (1.96 g/dL, RI: 2.3-4 g/dL), high ALT (138 U/L, RI: <85 U/L), high AST (118 U/L, RI: <90 U/L), high GGT (36, RI: <10 U/L), and high creatinine (142 µmol/L, RI: 35-115 µmol/L). The patient had consumed food associated with the safety alert for at least three months and developed progressive rejection of food, weakness, evident weight loss, severe ascites with multiple hepatic nodulations, and cholecystitis, which were diagnosed clinically and by ultrasound examination.

After 1 month of treatment with diuretics, gastric protectors, hepatoprotectors, and appetite stimulants without clinical improvement, the dog was euthanized. At autopsy, the liver parenchyma showed multiple pale nodules measuring 0.2–0.6 cm in diameter, distributed throughout the entire liver. The parenchyma adjacent to the lesions appeared to be firm and pale brown. The gallbladder had slightly thickened walls with dense, granular contents. Histopathological features included diffusely and irregularly distributed regenerative nodules surrounded by fibrotic connective tissue, with bridging, extensive, and circumferential fibrosis. The hepatic parenchyma margi-

Figure 1.
(a) Gross overview of the liver from Dog 1 displays irregular randomly distributed micronodules (0.1-1.0 cm) consistent with diffuse regenerative nodule formation and advanced stage liver injury. Liver sections from Dog 1 display (b) severe fibrosis marginating regenerative nodules (arrows, Masson's trichrome green staining fibrous connective tissue, * regenerative nodule), (c) congestion in centrilobular and midzonal regions of parenchymal collapse and loss of hepatic cord structure (H&E staining), and (d) rhodanine positive staining (orange/red cytosolic granules) in centrilobular regions with inset illustrating copper-protein aggregates in hepatocytes and disorganized hepatic cords.



nating regenerative nodules displayed microvacuolated hepatocytes and disorganized hepatic cords. Occasional binucleated hepatocytes (consistent with an attempted regenerative response) and hepatocytes with abundant rhodamine-positive cytosolic aggregates were distributed in the centrilobular and midzonal regions.

Dog 3. Siberian Husky, male, 2 years old. Hepatic Cu concentration: 1370 ppm (DMB). The patient had a history of being exclusively fed a diet associated with a safety alert for at least six months and received treatment with diuretics and hepatoprotective agents but ultimately died naturally. At necropsy, advanced-stage liver disease with severe ascites was observed. Histological examination of the liver revealed diffuse regenerative nodules surrounded by fibrous connective tissue bridging between lobular elements. Centrilobular hepatocytes contained abundant cytoplasmic copper-protein aggregates that were positive for rubeanic acid staining. No clinically significant histopathological lesions were observed in the non-hepatic organs.

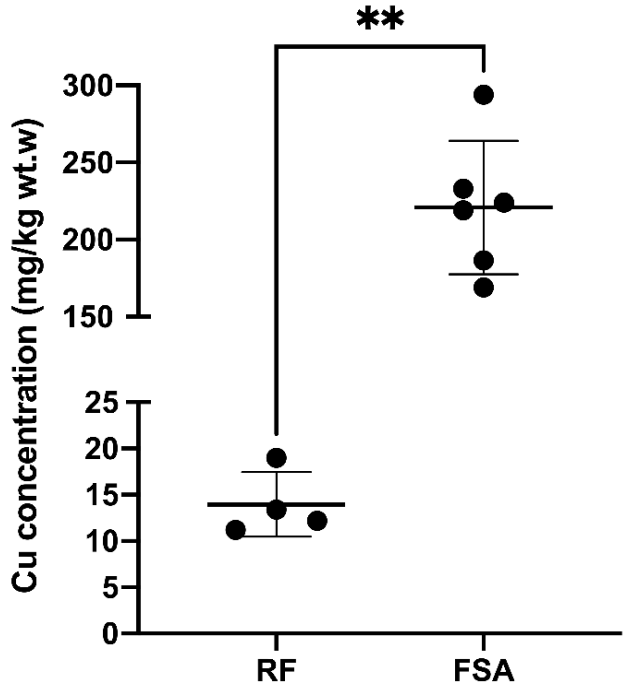
The copper concentration (derived from the labelling claim) of food recalled in the food safety alert (FSA, n = 6) was significantly ($P < 0.05$) greater (15.8-fold) than that of food not involved in the safety alert (RF, n = 4), as depicted in Figure 2. Notably, the copper content in the FSA recalled food (294 ppm DMB) exceeded the maximum copper limit for dog food declared by the European Union of 28 ppm (DMB) by 10-fold (FEDIAF, 2024).

Recent recommendations suggest that dietary copper concentration should be normalized (as Cu milligrams per 100 kilocalories) to ingested energy to allow for meaningful comparisons among products (Center SA, ACVIM Forum, 2025). Applying this approach to the recalled batches analyzed in our study, the mean copper concentration was calculated to be 9.95 mg/100 kcal (DMB). This value far exceeds the established threshold of 0.24 mg/100 kcal (DMB), above which there is an increased risk of hepatic copper accumulation.

This finding makes the present case deeply concerning, and the authors have no record of another event with similar characteristics worldwide. The origin of the excessive copper content in the FSA recalled food remains unclear but implicates premix contamination as well as inadequate production quality oversight.

In this case, the affected families received financial compensation prior to signing a confidentiality agreement regarding the diagnosis of the animals. Following a thorough investigation prompted by numerous complaints, the Agricultural and Livestock Service (SAG) announced that the product was unfit for animal consumption due to excessive copper content, which exceeded the maximum limits established by international organizations (Servicio Agrícola y Ganadero (SAG), 2020). Strict regulation of copper levels in dog food and routine monitoring of patients are essential to prevent copper-associated hepatopathies. Education for animal owners and veterinarians is also necessary to promote early recognition and management of hepatic disease. Although liver biopsy remains the diagnostic gold standard, there is a pressing need to develop noninvasive diagnostic tools. Continued vigilance by manufacturers, veterinarians, and regulatory agencies is critical to ensure compliance and protect the health of canines.

Figure 2.
Individual value plots depicting copper (Cu) concentrations in food from labels not involved in the safety alert (RF) and extruded dry food associated with the safety alert (FSA). The horizontal line within each group represents the median; error bars indicate the 95% confidence interval of the median. Dots represent individual values. $P = 0.01^{**}$, determined by a nonparametric Mann-Whitney test. Copper concentrations are reported on a dry matter basis (DMB).



Excess copper can participate in Fenton-like reactions, generating reactive oxygen species that cause oxidative stress, hepatocellular injury, and ultimately tissue degeneration (Amundson *et al*., 2024). Chronic copper accumulation in dogs is particularly concerning because it is associated with progressive hepatotoxicity and, in severe cases, terminal liver failure (Nivy *et al*., 2024).

In dog 1, the hepatic copper value was 397 ppm (DMB), which is below the toxic level. We believe this finding is related to tissue selection, as a large proportion of the refrigerated fresh liver fragments submitted for analysis consisted of regenerative nodules. These nodules were negative for rhodanine staining, findings consistent with previous observations indicating that newly replicated hepatocytes typically exhibit low intracytoplasmic copper content. This may have led to an underestimation of the true copper concentration in these tissues (Center *et al*., 2021). Although

current guidelines recommend analyzing multiple samples from fresh, frozen, or formalin-fixed tissues to improve diagnostic accuracy, logistical and financial constraints in this case limited the analysis (Paßlack *et al*., 2015).

In general, the literature indicates that copper accumulation in the liver has three causes: increased copper uptake, primary defects in hepatic copper metabolism, or altered biliary copper excretion (Hoffman, 2009). In this study, although a primary defect in hepatic copper metabolism or impaired biliary excretion cannot be completely ruled out, the breed background and clinical histories of these dogs did not suggest a genetic predisposition or concurrent conditions typically associated with inherited copper storage disorders. Moreover, the pattern of copper accumulation and the temporal association with the consumption of copper-enriched recalled foods further reinforce dietary copper overload as the most plausible cause in these cases.

Clinical evidence and ultrasound examination showed that the animals presented with liver cirrhosis, which was confirmed by imaging testing, autopsy, and microscopic findings. In all cases, the lesions were progressive and showed remodeling, fibrosis, and multiple regenerative nodules. The clinical history, blood biochemical abnormalities, gross and histopathological findings, quantitative hepatic copper analysis, and supporting data from the food safety alert collectively support a diagnosis of hepatic cirrhosis induced by chronic dietary copper excess.

Despite the implementation of appropriate medical management, patients were diagnosed at an advanced stage of hepatic disease, with irreversible cirrhosis and marked ascites, which limited the likelihood of recovery (Thornburg, 2000). Taken together, these findings strongly suggest that exclusive consumption of a copper-rich diet led to progressive hepatic copper accumulation and severe, irreversible liver damage in these cases. While it is highly probable that chronic dietary copper exposure played a direct causal role in the outcome of these patients, we cannot discount the potential contribution of additional hepatotoxic substances present in the recalled diets. Therefore, it is not possible to conclude that dietary copper content was the sole cause of the severe liver injury observed. Nevertheless, the histological features and clinical scenarios documented in each case were entirely consistent with those described for severe copper-associated hepatopathy.

REFERENCES

Amundson, L.A, Kirn, B.N, Swensson, E.J, Millican, A.A., & Fahey, G.C. (2024). Copper metabolism and its implications for canine nutrition. *Translational Animal Science*, *8*, txad147. https://doi.org/10.1093/tas/txad147

Center, S.A. (2025). *Uncovered Truths About Liver Copper Accumulation in Dogs: Additional 2023-24 Studies*. In: ACVIM Forum 2025, Louisville, Kentucky, June 19, 2025. [Unpublished abstract].

Center, S., Richter, K., Twedt, D., Wakshlag, J., Watson, P., & Webster, C. (2021). Is it time to reconsider current guidelines for copper content in commercial dog foods? *Journal of the American Veterinary Medical Association*, *258*(4), 357-364. https://doi.org/10.2460/javma.258.4.357

Chen, L., Min, J., & Wang, F. (2022) Copper homeostasis and cuproptosis in health and disease. *Signal Transduction and Targeted Therapy*, *7*, 378. https://doi.org/10.1038/s41392-022-01229-y

Chen, J., Jiang, Y., Shi, H., Peng, Y., Fan, X., & Li, C. (2020). The molecular mechanisms of copper metabolism and its roles in human diseases. *Pflügers Archive*, *472*, 1415-1429. https://doi.org/10.1007/s00424-020-02412-2

FEDIAF (2024). *Nutritional Guidelines for Complete and Complementary Pet Food for Cats and Dogs*. Retrieved from https://europeanpetfood.org/wp-content/uploads/2024/09/FEDIAF-Nutritional-Guidelines_2024.pdf

Fieten, H., Biourge, V., Watson, A., Laegwater, P., Van den Ingh, T., & Rothuizen, J. (2014). Nutritional management of inherited copper-associated hepatitis in the Labrador retriever. *The Veterinary Journal*, *199*(3), 429-433. https://doi.org/10.1016/j.tvjl.2013.12.017

Hoffman, W.E. (2009). Copper-Associated Liver Disorders. *Veterinary Clinics of North America: Small Animal Practice*, *39*(3), 489–511. https://doi.org/10.1016/j.cvsm.2009.02.001

Johnston, A.N., Center, S.A., McDonough, S.P., Wakshlag, J.J., & Warner, K.L. (2013). Hepatic copper concentrations in Labrador Retrievers with and without chronic hepatitis: 72 cases (1980–2010). *Journal of the American Veterinary Medical Association*, *242*(3), 372–380. https://doi.org/10.2460/javma.242.3.372

Langlois, D.K., Smedley, R.C., Schall, W.D., & Kruger, J.M. (2013). Acquired proximal renal tubular dysfunction in 9 Labrador Retrievers with copper-associated hepatitis (2006–2012). *Journal of Veterinary Internal Medicine*, *27*(3), 491–499. https://doi.org/10.1111/jvim.12065

Nivy, R., Kuzi, S., Swinburne, J., Constantine-Casas, F., Gajanayake, I., Bruchim, Y., Berkowitz, A., Watson, P. (2024). Copper-associated chronic hepatitis in Cavalier King Charles spaniels. *Veterinary Record*, *194*(3), e3561. https://doi.org/10.1002/vetr.3561

Paßlack, N., Mainzer, B., Lahrssen-Wiederholt, M., Schafft, H., Palavinskas, R., Breithaupt, A., Neumann, K., & Zentek, J. (2015). Concentrations of strontium, barium, cadmium, copper, zinc, manganese, chromium, antimony, selenium and lead in the equine liver and kidneys. *Journal of veterinary Science*, *16*(1), 57-66. https://doi.org/10.4142/jvs.2015.16.1.57

Servicio Nacional del Consumidor (SERNAC) (2020). Alerta de seguridad: Alimento para perros Cannes y Charly, años 2019-2020. https://www.sernac.cl/portal/619/w3-article-58617.html

Servicio Agrícola y Ganadero (SAG). SAG establece que alimentos para perros Cannes no son aptos para consumo animal; Alertas Informativas SAG [Internet]. 2020 Jul 10 [cited 2025 September 26]. Available from: https://www.sag.gob.cl/content/alertas-informativas-sag-470

Strickland, J.M., Buchweitz, J.P., Smedley, R.C., Olstad, K.J., Schulz, R.S., Oliver, N.B., & Langlois, D.K. (2018). Hepatic copper concentrations in 546 dogs (1982–2015). *Journal of Veterinary Internal Medicine*, *32*(6), 1943–1950. https://doi.org/10.1111/jvim.15308

Thornburg, L.P. (2000) A perspective on copper and liver disease in the dog. *Journal of Veterinary Diagnostic and Investigation*, *12*(2), 101–110. https://doi.org/10.1177/104063870001200201