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Product Safety and Pet Food Recalls

Karyn Bischoff, DVM, DABVT
Cornell University
Department of Population Medicine and Diagnostic Sciences
Ithaca, NY
Email: klb72@cornell.edu

Abstract

Although pet foods are generally safe, incidents of contamination have led to recalls. Commercial pet food and animal feed recalls accounted for <10% of the total food recalls in 2011 and 2012. Slightly more than half of those recalls were due to chemical contamination, misformulation or foreign material. The rest were due to *Salmonella* spp contamination. Eleven commercial pet food recalls in the U.S. between 1996 and 2010 were caused by chemical contaminants and misformulations. As a result of these pet food recalls, there has been an increase in government oversight of commercial pet food manufacturers and human food manufacturers, greater manufacturuing vigilance, and increased awareness among veterinarians and pet owners.

Glossary of Abbreviations

CCP: Critical Control Point
COA: Certificate of Analysis
DON: Deoxynivalenol
ELISA: Enzyme-Linked Imunosorbent Assay
FDA: Food and Drug Administration
FDAA: FDA Amendments Act
HACCP: Hazard Analysis and Critical Control Point
HPLC: High-Performance Liquid Chromatography
IARC: International Agency for Research on Cancer
LD: Lethal Dose
MRI: Magnetic Resonance Imaging
NIR: Near-Infrared
PTH: Parathyroid Hormone

Introduction

Only 1.7% of reported poisonings in dogs and cats have been attributed to pet foods, thus the risk of illness due to pet food contamination is very small.[1] Incidents of chemical contamination occur through microbial action, mixing error or intentional adulteration. Although rare, the effects of pet food contamination can be physically devastating for companion animals and emotionally devastating and financially burdensome for their owners. Whereas most people consume a varied diet, diluting the effects of chemical contaminants, companion animals tend to consume a more uniform diet, often coming from a single large bag or cans from a single lot, for an extended time. Many animal owners consider their dog or cat to be a vulnerable family member that needs to be protected.[2] Based on the author's experience, some pet owners undergo seemingly disproportionate guilt when pets become sickened or die after being unknowingly fed contaminated pet foods.

The Food and Drug Administration (FDA) is charged with assuring the wholesomeness of pet foods. The U.S. Congress passed the 2007 FDA Amendments Act (FDAAA) to improve responsiveness to contamination of pet foods and other products after adulteration of pet food with melamine and related compounds was identified that year. The FDAAA requires manufacturers to report incidents of possible contamination to the FDA within 24 hours and to investigate the cause and report their findings. If contamination is confirmed, the pet food is recalled. Recall initiation is usually voluntary by the manufacturer at the request of the FDA. The FDA can secure a court order to issue a recall if the manufacturer is reluctant, but this is rare because of the potential for bad publicity and litigation should a manufacturer refuse to initiate a recall.[1] Consumer complaints can be reported to local FDA consumer complaint coordinators or online (http://www.fda.gov/cvm/petfoods.htm). Local government agriculture or food safety agencies also should be alerted when contamination of a commercial product is suspected.

Samples for laboratory analysis in a pet food investigation include the suspected food and its packaging (or, if unavailable, lot numbers, manufacturing codes and other identifying information) and samples from the pet, such as blood, serum, urine, vomitus or gastric lavage fluids, and feces. If the animal should unfortunately die, a full necropsy is necessary, and the postmortem sample collection for histopathology and analytical chemistry should include fresh urine, adipose tissue, heart blood, fresh and fixed brain, liver, kidney, as well as fixed lung, spleen and bone marrow for histology.

There are three types of recalls involving chemical contaminants:

- Class I — reasonable probability that the contaminated food will cause adverse health consequences or death
- Class II — the contaminated food can cause temporary or medically reversible adverse health consequences but is unlikely to cause serious adverse health effects
- Class III — the contaminated food is unlikely to cause adverse health consequences

There were 22 Class I and II pet food recalls in the U.S.

over a 12-year period (1996 to 2008). Six were due to chemical contaminants: Two were caused by aflatoxin, two from excess vitamin D_3, one from excess methionine, and one from adulteration of food ingredients with melamine and related compounds.[3] Since 2008, there have been three cat foods recalled due to inadequate thiamine, a dog food recalled due to excessive vitamin D_3, and one dog and one cat food recalled due to contamination with aflatoxin. There also have been two FDA warnings since 2007 concerning a Fanconi-like renal syndrome in dogs after ingesting large amounts of chicken jerky treat products manufactured in China and one local recall in New York due to low-level contamination of these products with sulfa antibiotics.[4] Pet food contamination incidents are only rarely due to adulteration, as occurred with melamine and cyanuric acid. The melamine contamination investigation in 2007 led to the discovery that other cases of melamine poisoning had happened in companion animals across Europe and Asia and in Africa.[5-7]

Natural Contaminants

The most commonly isolated natural contaminants in pet foods are mycotoxins. Aflatoxins are the most common mycotoxins associated with pet food recalls in the U.S. Other mycotoxin contaminants also have been reported, however. There was a recall of dog food due to contamination with the mycotoxin deoxynivalenol (DON) in 1995. DON is produced on grain by *Fusarium* spp. under temperate conditions. Pet food DON concentrations of >4.5 ppm and 7.7 ppm were associated with feed refusal in dogs and cats, respectively, and concentrations ≥8 ppm cause vomiting in both species.[8,9] Animals recover quickly once the food is replaced, though supportive care is needed if gastroenteritis is severe.[9]

Aflatoxins are a group of related compounds sometimes produced as metabolites of various fungi, *Aspergillus parasiticus, A flavus, A nomius*, some *Penicillium* spp., and others. High-energy foods, such as corn, peanuts and cottonseed, are most often affected. Rice, wheat, oats, sweet potatoes, potatoes, barley, millet, sesame, sorghum, cacao beans, almonds, soy, coconut, safflower, sunflower, palm kernel, cassava, cowpeas, peas, and various spices also can be affected.[10,11] Aflatoxin production can occur on field crops or in storage. Temperature, humidity, drought stress, insect damage, and handling techniques influence mycotoxin production.[10] Use of aflatoxin-contaminated food commodities in the manufacture of pet foods has caused aflatoxicosis in pets, but improper storage of dog food and ingestion of moldy garbage also have been implicated.[12]

Both dogs and cats are very sensitive to aflatoxin.[11] The oral median lethal dose (LD_{50}) for aflatoxin in dogs is between 0.5 and 1.5 mg/kg.[13] The experimental oral LD_{50} for cats is 0.55 mg/kg, though field cases of aflatoxicosis in cats are not well documented.[11] The period of exposure and amount ingested are difficult to determine in field cases, but aflatoxin concentrations of 60 ppb in dog food have been implicated in aflatoxicosis.[13] Factors associated with increased susceptibility to aflatoxicosis include genetic predisposition, concurrent disease, age, and sex, with young males and pregnant females considered particularly susceptible.[13,14] No carcinogenic effects have been reported in cats and dogs, though aflatoxins are known to be carcinogenic in some species, including rats, ferrets, ducks, trout, swine, sheep, and rats, and are classified by the International Agency for Research on Cancer (IARC) as Class I human carcinogens.[11,15]

The presentation of aflatoxicosis in small animals appears to be acute, but exposure to contaminated foods can occur for weeks or months before the onset of clinical signs. Indeed, the author was involved in one case in which known contaminated food was removed from the diet of a dog approximately three weeks before clinical aflatoxicosis became evident though the dog was closely monitored during that period by the owner and veterinarian. Many dogs die within a few days of initial clinical signs, but illness can be protracted for up to two weeks.[14] Early clinical signs of aflatoxicosis include feed refusal or anorexia, weakness and obtundation, vomiting, and diarrhea. Later, dogs become icteric, often with melena or frank blood in the feces, hematemesis, petechia, and epistaxis.[11,16]

Complete blood cell count, serum chemistry including bile acids, and urinalysis can be helpful to rule out other causes of liver failure. Total bilirubin is increased in aflatoxicosis, and hepatic enzyme concentrations, including AST, ALP and GGT, are variably elevated.[13,14] Liver function tests, though not specific for aflatoxin, are often more helpful in supporting the diagnosis. Prothrombin time is increased due to decreased synthesis of clotting factors, and serum albumin, protein C, antithrombin III, and cholesterol concentrations are decreased.[16] Post-mortem lesions can be highly suggestive, though not pathopneumonic for aflatoxis in dogs. Common gross necropsy findings include icterus, hepatomegaly with evidence of lipidosis, ascites, gastrointestinal hemorrhage, and multifocal petechia and ecchymosis.[12,15,16] Histologic lesions in acute aflatoxicosis include fatty degeneration of hepatocytes with one to numerous lipid vacuoles. Centrilobular necrosis and canalicular cholestasis with mild inflammation are commonly reported.[11,15] The presence of aflatoxin in dog food or other implicated material is extremely helpful toward confirming the diagnosis, but due to the extended time between exposure and onset of clinical signs, the contaminated food is often gone. However, if aflatoxicosis is strongly suspected, the FDA and pet food manufacturer should be alerted in case further investigation is warranted.

The prognosis for dogs with clinical aflatoxicosis is guarded. Early intervention improves the prognosis, but many cases fail to respond to treatment.[11,12,16] Intervention includes replacing the suspect diet, patient assessment and stabilization, and use of liver protectants, such as silymarin (a mix of silybin and other flavolignans from milk thistle), S-adenosylmethionine (SAMe), or *N*-acetylcysteine.

Commercial grain is routinely screened for aflatoxin, but

sampling error is possible due to the uneven distribution of mold within the grain and other commodities. Aflatoxin and other mycotoxins are produced under specific climatic conditions, and increased monitoring is warranted during those years when conditions are right for increased mycotoxin production. Current analytical techniques utilize enzyme-linked immunosorbent assays (ELISAs), high-performance liquid chromatography (HPLC) and LC/MS to detect aflatoxin in raw ingredients. Further analysis can be done on the finished product to assure that mycotoxins are not present.

Misformulation

Misformulation is another cause of adverse reactions to pet foods in cats and dogs. Hypervitaminosis D and thiamine deficiency have been reported recently. Other misformulations have involved excesses of methionine and vitamin A. Excessive methionine was associated with anorexia and vomiting.[3] Misformulation of a feline research diet in Thailand in 2009 resulted in evident hypervitaminosis A (per communication, Dr. Rosama Pusoonthornthum). Hypervitaminosis A in cats and dogs has been reported with homemade diets and caused osteopathy, commonly affecting the axial skeleton (lesions also noted in the Thai cats), and often presents as lameness, paresis or paralysis due to entrapment of spinal nerves.[17] Some animals with hypervitaminosis A, even those severely affected, recover in the long term after they are placed on a new diet.

Vitamin D is an essential vitamin, The two major active forms of vitamin D in mammals are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). There also is increasing use of 25-hydroxy vitamin D_3 in feeds for livestock. Oversupplementation and unintentional cross-contamination can cause vitamin D_3 excess in pet food.

Vitamin D poisoning occurred following prolonged ingestion of the contaminated food, usually after weeks of exposure. Cholecalciferol is rapidly absorbed from the gastrointestinal tract and transported to the liver, where it is rapidly broken down to 25-hydroxy vitamin D_3. This is further metabolized primarily to 1,25-dihydroxy vitamin D_3 (calcitriol) and 24,25-dihydroxy vitamin D_3 in renal proximal convoluted tubular epithelium. Calcitriol is the vitamin D metabolite that is most important in calcium-phosphorus metabolism.

Vitamin D has a major role in regulation of calcium and phosphorous. Clinical signs of vitamin D poisoning in pets include depression, weakness, anorexia, polyuria, and polydipsia. Diagnosis is based on clinical signs, decreased serum intact parathyroid hormone (PTH), increased total and ionized serum calcium, and serum 25-hydroxy vitamin D_3. Affected animals have gross and microscopic evidence of metastatic soft tissue mineralization on post-mortem examination and elevated concentrations of 25-hydroxy vitamin D_3 in kidneys.

Replacing the diet with uncontaminated food is often sufficient treatment for affected animals, but it can take weeks before clinical pathology changes resolve. More aggressive therapy to manage the imbalance of circulating calcium and phosphorus can include use of salmon calcitonin, pamidronate disodium and corticosteroids.[18]

There have been three recent cat food recalls in the U.S. due to inadequate thiamine supplementation. Thiamine is a required B vitamin (B_1). Monogastric animals like cats and dogs cannot synthesize thiamine, and because it is a water-soluble vitamin, there is no long-term storage in the body. Other factors, such as age and diet, affect the thiamine requirements for dogs and cats.[19] Pet foods should contain at least 5 mg/kg and 1 mg/kg thiamine on a dry matter basis for cats and dogs, respectively.[20] Thiamine deficiency in cats has been associated with a food containing 0.56 mg thiamine/kg, dry matter.[21]

Polioencephalomalacia describes the lesion associated with thiamine deficiency. Cats presenting during the 2009 recall exhibited anorexia, head tilting, dilated pupils, apparent blindness, circling, ataxia, seizures, positional ventroflexion of the head, and, in one case, marked extensor rigidity of the front limbs. All were responsive to thiamine treatment except the one with extensor rigidity. A study of puppies found that the first signs occurred after nearly two months on a thiamine-deficient diet and some individuals died before the abrupt onset of neurologic signs.[22]

Bilaterally symmetric changes in the central nervous system have been observed in affected dogs and cats using magnetic resonance imaging (MRI). Lesions were documented in the cerebellar nodulus, caudal colliculi and periaqueductal grey matter in dogs and in the red nuclei, vestibular nuclei, facial nuclei, and medial vestibular nuclei in cats.[23] MRI lesions correlated with those found on necropsy. The most common functional test for thiamine deficiency is erythrocyte transketolase activity, which has been used in humans and dogs, but no reference values are available for cats.[21] The reported thiamine pyrophosphate concentration is 32 μg/dL in healthy feline blood and 8.4 to 10.4 μg/dL in healthy canine blood.[22] Cats in the 2009 outbreak had blood thiamine pyrophosphate concentrations ranging from 2.1 to 3.9 μg/dL, but no samples from unaffected cats were analyzed.

Most affected animals respond to thiamine supplementation, as noted above. Thiamine hydrochloride is given parenterally at a dose of 100 to 250 mg/day for cats and 5 to 250 mg/day for dogs. After five days of parenteral dosing in cats, oral thiamine at 25 mg/day is continued for one month.[24] Improvement is usually rapid, with significant improvement observed within a few days and often complete recovery in one to 12 weeks.[21,23,25] However, persistent ataxia, hearing loss and positional nystagmus also are reported.[23]

Adulteration

Adulteration of pet foods is rare but was responsible for the largest pet food recall in U.S. history. Unknown to pet food manufacturers in the U.S. and other countries, melamine was

fraudulently added to some ingredients, which were produced by companies in China, in order to enhance the apparent protein content. Protein in pet foods is estimated based on the nitrogen content. Because melamine is 67% nitrogen by molecular weight, its addition increases the nitrogen content and thus the apparent protein content of the product. Melamine has numerous uses in industry and manufacturing, including pigment and polymer production but is not used as an ingredient in food production.

Early in 2007, there were several reports of renal failure in cats and dogs consuming commercial pet foods in the U.S. Clinical signs included inappetance, vomiting, polyuria, polydipsia, and lethargy. A large number of affected cats were on feeding trials at a laboratory.[26] A recall was initiated on March 15, and melamine was detected in the cat food two weeks later. Previous studies had proved melamine to have low oral toxicity, and it was not understood how or if melamine was producing morbidity and mortality, but this became clear later. Cyanuric acid, ammelide and ammeline, all structurally similar to melamine, also were detected in affected pet food products. The oral LD_{50} of melamine is 3200 mg/kg in male rats, 3800 mg/kg in female rats, 3300 mg/kg in male mice and 7000 mg/kg in female mice, but the combination of melamine and cyanuric acid is markedly more toxic to most animals than either compound alone. Cats fed diets containing 0.2% each of melamine and cyanuric acid had evidence of acute renal failure within 48 hours.[27]

The FDA investigation determined that wheat gluten and rice protein concentrates used in pet food production were intentionally mislabeled by Chinese exporters and actually contained wheat flour and poor-quality rice protein, respectively, mixed with melamine.[26] Samples of imported wheat gluten contained 8.4% melamine, 5.3% cyanuric acid, 2.3% ammelide, and 1.7% ammeline.[3] Eventually, >150 contaminated pet foods were identified, containing up to 3200 ppm melamine and 600 ppm cyanuric acid. Estimates of the number of pets affected range from hundreds to thousands. Many consider the 2007 pet food recall a sentinel event. A year later, melamine contamination of Chinese baby formula and other milk-based products was detected.

Clinical signs in cats ingesting contaminated food included inappetance, vomiting, polyuria, polydipsia, and lethargy. Urine specific gravities <1.035 and elevated serum urea nitrogen and creatinine concentrations were documented. Circular green-brown crystals were observed in urine sediment. Post-mortem examinations typically noted bilateral renomegaly and evidence of uremia. Microscopic lesions were primarily localized to the kidneys: renal tubular necrosis, tubular rupture and epithelial regeneration. The distal convoluted tubules contained large golden-brown birefringent crystals (15 to 80 micrometers in diameter) with centrally radiating striations, sometimes in concentric rings and smaller amorphous crystals.[26] Crystals from kidneys and urine contained 70% cyanuric acid and 30% melamine based on infrared spectra.[7] Melamine and cyanuric acid form crystals by binding to form a lattice structure. The optimal pH for this reaction is 5.8.[7]

Analysis of 451 cases matching the definition of melamine toxicosis found that 65.5% were cats and 34.4% were dogs. The case mortality rates were 73.3% and 61.5% for affected dogs and cats, respectively. Older animals and those with preexisting conditions were less likely to survive.[3] However, >80% of exposed cats during the original feeding trials survived with supportive care.[26]

Preventing Contamination

It is the manufacturer's responsibility to prevent contamination of pet foods.[28] This requires the use of safe ingredients from trustworthy sources, excellent sanitation, processing procedures that avoid contamination and destroy microbes, and excellent record keeping so that problems that occur can be traced. The Association of American Feed Control Officials (AAFCO) is composed of individuals responsible for enforcing laws related to animal feed and foods. The objective of the organization is to promote uniformity in the laws and enforcement of those laws. AAFCO publises a model of Good Manufacturing Practices (GMP) that can be used at the manufacturing or regulatory level to ensure food and feed quality. These include:

- Training of personnel
- Facilities and equipment maintenance
- Ingredient handling and tracking
- Packaging and labeling
- Storage and inventory of finished products
- Inspection and sampling of finished products
- Record keeping

A Hazard Analysis and Critical Control Point (HACCP) program, required by law, is used by manufacturers to identify points in the production process where contamination is most likely to occur. Steps to developing a HACCP program include:

- Consider all aspects of manufacturing, including ingredients, equipment, processes, storage, and distribution
- Analyze potential hazards based on probability and severity
- Control hazards at the critical control point (CCP)
- Document how CCPs will be monitored and problems handled

Obviously, the organization and cleanliness of the factory and personnel are of primary importance. Factories must be kept arthropod-free and rodent-free through insect- and rodent-proof construction, use of bait stations around the outdoor periphery, and, when needed, traps within the facilities. Surfaces within facilities should be routinely screened for contamination with *Enterobacteriacea* spp, many of which are human commensals. Personnel should wear clean uniforms and personal protective equipment with no visible long hair, buttons, jewelry, or other loose objects.

All ingredients received at the factory should be fit for purpose and within preset quality specifications. Certain ingredients come

with a certificate of analysis (COA) from the vendor. HACCP programs can require routine testing of ingredients, even those that come with a COA. Near-infrared (NIR) spectroscopy can be used as part of the routine testing program. A library of NIR spectra of all ingredients should be available. Matching the incoming ingredients' spectra to spectra in the library assures purity of the ingredients. The risk of misformulation is greatly minimized through rapid turnover of ingredients, highly automated production and constant maintenance of equipment.

Ingredients and food-grade chemicals should be kept in separate locations from nonfood-grade chemicals. Materials can be color coded. For example, those in white containers are finished product, yellow containers hold byproducts, gray containers hold waste, black contain nonfood material, etc.

Goals of HACCP in Pet Food Production

The goals of HACCP include consideration of all possible hazards associated with ingredients, manufacturing processes and storage. Three of the most important CCPs are the incoming raw ingredients, the thermal processing step (extrusion process for dry foods), and the external coating of kibble products.

Another goal of HACCP is to determine which hazards are of greatest importance due to probability and the severity of the problem. Mycotoxin contamination is a ubiquitous problem, and the mycotoxins of primary importance in the U.S. are aflatoxin, which can be lethal, and deoxynivalenol, which can cause significant morbidity and distress. The bacterial organisms of most concern based on pathogenicity, environmental persistence and likelihood of contamination are *Salmonella* spp and *Enterobacteriaceae*.

Mycotoxins can be produced in field and stored grain or in the stored final product, if fungal contamination is present. One CCP at the factory is the arrival of the grain. Mycotoxin contamination is prevented through thorough testing of multiple samples from all grain lots. Any grain containing 20 ppb or greater aflatoxin cannot be used due to FDA regulations. FDA also recommends that ingredients used in animal foods contain less than 5 ppm DON. Fungal contamination of the final product is prevented through factory cleanliness and pasteurization of the ingredients during manufacture.

The nature of certain raw ingredients makes it impossible to avoid bacterial contamination. A CCP for prevention of bacterial contamination, particularly *Salmonella*, is the extrusion process for kibble or the retorting process for canned pet foods. Prevention of bacterial contamination is achieved through pasteurization of the product. The extrusion process and retorting time and temperature are constantly monitored to be certain that adequate temperatures are reached to kill pathogenic bacteria.

Because it occurs after thermal processing, there is the risk for bacterial contamination during the coating process in dry foods. Therefore, all coatings must be certified as pathogen-free.

Some of the considerations for HACCP are mentioned here, but other aspects of manufacture, such as drying and bagging, also must be evaluated and routinely monitored. Monitoring of CCPs can be automated and all information stored in an accessible database that can be viewed at any time during or after production. HACCP data should be analyzed and confirmed to be within specification before a lot of product can be released. Product lots should be subsampled, and samples analyzed and warehoused for long-term stability determination and ease of retrieval.

Under this type of HACCP program, an error in any part of the manufacture, from formulation to final packaging or analysis of the final product for contaminants and nutritional value, warrants a stop in the production line. The problem is brought to the attention of the appropriate personnel, including on-site and off-site experts, for consultation. Production does not begin until a solution can be initiated.

Conclusion

With a myriad of possible contaminants, ranging from bacteria to fungal metabolites like aflatoxin and vomitoxin, to misformulations producing nutritional excesses and deficiencies, to adulteration with industrial chemical such as melamine and related compounds, it is impossible to predict the cause of the next pet food recall. Nevertheless, pet food recalls are quite rare compared to recalls for food products for human consumption, and compared to other causes, illnesses associated with pet food are rare. Pet food manufacturers have instituted HACCP and ingredient control practices that minimize the risk of contamination, mixing errors and adulteration, and assure product safety and quality. When rare contamination incidents occur, vigilance on the part of regulators, manufacturers and veterinarians is our major line of defense.

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