Pet Food

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Pet Food

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INTRODUCTION

Dog and cat pet ownership is popular throughout the world and pets are increasingly treated as members of the family. The pet food industry started in England in 1860, when the first commercial dog biscuits were marketed. Today sales of pet food in the USA alone exceed 18 billon US dollars a year (APPA, 2012). There are three main types of commercial pet food products: dry and semi-moist shelf-stable extruded food; thermally processed low acid canned products; and a variety of product forms sold as treats. With the exception of some treats, most products are formulated to be nutritionally complete and balanced. Thus,

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the modern pet food industry provides an essential service to pet owners by making nutritious and palatable pet food convenient to acquire and feed.

The pet food industry utilizes the same ingredient streams as those of the human food supply making use of many of the by-products and co-products. Therefore, the food safety hazards potentially present in pet food ingredients are the same as the ones facing the food industry in general. There is, however, a difference in the severity of health effects of these hazards to cats, dogs and humans. Pets tend to be very resistant to the clinical effects of infection by human food pathogens. On the other hand, they may be very sensitive to certain natural toxins or food components (e.g. alkaloids, caffeine, etc.) as well as veterinary drugs and feed additives.

The most significant historical pet food safety incidents in terms of frequency of occurrence and severity are related to aflatoxins, veterinary drug contamination, *Salmonella* recontamination and, more recently, adulterated ingredients. Together, these hazards account for the vast majority of safety incidents where pets were severely affected. With the exception of the food pathogen *Salmonella*, most other food safety hazards are ingredients or formulations based and have no effective control measures in the manufacturing process itself (Table 15.1). Potential HACCP control strategies to address these food safety threats will be discussed in this chapter.

BIOLOGICAL HAZARDS

Salmonella Contamination of Dry Pet Foods and Treats

Salmonella is a Gram-negative, non-spore-forming, rod-shaped bacterium belonging to the Family Enterobacteriaceae. This genus includes about 2400 different serovars. Non-typhoid strains of salmonellae are a common cause of gastroenteritis and septicemia in humans and pets. Domestic and wild animals are often intestinal carriers of this pathogen. *Salmonella* is widespread in nature and has been found to survive for weeks in water and for several years in soil. In food ingredients, *Salmonella* can contaminate eggs, raw meats, poultry, fish and their by-products (Wareing and Fernandes, 2007). *Salmonella* is one of the leading causes of human gastroenteritis worldwide. In the USA there are an estimated 1.4 million cases a year and some 400 deaths (Voetsch et al., 2004). Salmonellosis remains the second most often reported zoonotic disease of humans in the European Union with 99,020 cases reported in 2010 (EFSA, 2012). Vulnerable populations include people with compromised immune systems, infants and the elderly. The enteric infection has an incubation time of 8–72 hours with symptoms that include nausea, vomiting, abdominal cramps, diarrhea, fever and headache. The symptoms can last from 2 to 5 days (Wareing and Fernandes, 2007).

Salmonella-contaminated feed may cause salmonellosis in animals. Generally, young animals are the most susceptible to an enteric-type infection but in more severe cases the infection may become systemic. In adult animals the infection is more likely to be asymptomatic. Prevalence of *Salmonella* carriage rates have been reported as high as 36% in healthy dogs, and 18% in healthy cats (Leonard et al., 2010; Sanchez et al., 2002). Dogs infected with *Salmonella* often carry multiple strains at a time. Most infections are asymptomatic or mild and are commonly not identified. Prolonged and sporadic fecal shedding of *Salmonella* is

TABLE 15.1 Most Common Hazards Associated with Pet Food Safety Incidents and their Control

Hazard	Type	Root Cause	Control
Salmonella	Biological	Post-CCP cross-contamination from contaminated factory surface, environment or ingredient. Potential sources of contamination include: birds (feces, feathers) entering via air currents or water leaks. Presence of raw materials past CCP due to poor dust tightness, zoning or traffic patterns. Pests	Good manufacturing practices (GMP): e.g. ingredient quality measures, hygiene practices, hygienic design and process validation and verification procedures (GMA, 2009)
Ionophore toxicity	Chemical	Cross-contamination of feed ingredient with antibiotics via shared production lines with medicated feed or labeling errors of medicated feeds or vitamin premixes	Procurement of ingredients from suppliers that do not manufacture medicated products on the same production line
Adulteration (e.g. melamine)	Chemical	Fraud	"Trust but verify" ingredient supplier quality assurance and traceability programs
Nutrient toxicity or deficiency	Chemical	Misformulation or mixing error at batching	Careful accounting of the ingredient usage rate during batching. Vendor assurance measures, including validated mixing processes. Premix monitoring
Mycotoxin toxicity (e.g. aflatoxins and DON)	Chemical	Contaminated cereals (contamination may occur in the field and/or storage at supplier)	A cereal sampling and testing operational prerequisite program is required. Depending on prevalence of aflatoxin and DON, potentially all cereal deliveries to a factory must be sampled and tested before use. Good silo storage practices are required if grain is to be stored at the factory for any length of time
Metal and other hard bodies	Physical	Metal contamination from ingredients or equipment	GMP-based foreign material control programs including inspection, line magnets and metal detection of packaged product (verification)

a well-documented phenomenon (Morse et al., 1976). When symptomatic infections occur, clinical signs in young animals can include fever, anorexia, vomiting, intermittent diarrhea and bloody stools (Carter and Quinn, 2000). Infected dogs in the household pose a documented elevated risk of infection to their owners (Morse et al., 1976). Salmonellosis in cats is relatively rare, with subclinical infections and carriage rates among healthy cats reported to be very low. Nevertheless, cases of symptomatic infection, chronic carriage and transmission to humans have been documented (Van Immerseel et al., 2004).

TABLE 15.2 Recent North American Human Outbreaks of Salmonellosis Linked to Pet Food (FDA, 2012)

Country	Pathogen	Product	Date
Canada	*Salmonella* Infantis	Pig-ear dog treats	1999
USA	*Salmonella* Newport	Beefsteak-patty dog treats	2002
Canada/USA	*Salmonella* Thompson	Pet treats	2005
USA	*Salmonella* Schwarzengrund	Dry pet food	2006–2007

Pet food products contaminated with *Salmonella* pose a risk of infection to pet owners (Morse et al., 1976). Infection can occur via contaminated fomites or from ingestion of contaminated pet food (e.g. by children) (Behravesh et al., 2010; Morse et al., 1976). Numerous incidents in the USA have occurred where pet foods were found to be contaminated with *Salmonella* resulting in at least 13 recalls since 2006 (FDA, 2010a). Several human *Salmonella* infections and outbreaks have been linked to commercial pet food products (Table 15.2). One such outbreak of salmonellosis in the USA during 2007 was thoroughly investigated by the Centers for Disease Control and Prevention (CDC) and illustrates clearly the zoonotic potential of contaminated pet foods (CDC, 2008). Young children were found to be at a greater risk of infection than other family members. The specific family practices involved in the transmission of *Salmonella* to consumers included feeding the pet in the kitchen (Behravesh et al., 2010).

Dry pet foods are considered high fat, low moisture and low water activity (a_w) products. When formulated without humectants or preservatives, these products have an a_w of 0.65 or lower, corresponding to a moisture content of 12% or less. These are typically coated with fat (tallow, poultry fat) for enhanced palatability (Crane et al., 2000). At these low a_w levels, dry pet foods are shelf-stable because bacteria, molds and mites are unable to grow and spoil the food (FDA, 2012). Despite the inability of *Salmonella* to typically grow on low moisture foods, some cells have been shown to survive on pet foods and in pet food manufacturing environments for an extended period of time (GMA, 2009). The ability of some cells to survive on manufacturing surfaces can lead to the persistent contamination of processing areas, including air handling systems, floors and production equipment. The capacity to survive in a desiccated state is further enhanced by the presence of fat on product contact surfaces. Environmental moisture originating from cleaning and other sources can allow the multiplication of *Salmonella* in the factory (GMA, 2010a). Some factors that contribute to the possibility of cross-contamination include the existence of environmental conditions within the factory that generate microenvironments where *Salmonella* can grow in the proximity of the product stream. These include: condensation of moisture on production surfaces, poor hygienic practices (e.g. wet cleaning), poor equipment design, inadequate maintenance of equipment and inadequate zoning (e.g. incomplete segregation of pre- and post-extrusion environments and materials) (GMA, 2009). Important contributing factors for ineffective zoning include complex traffic patterns, poor dust control, uncontrolled ingress of external air and water, and the presence of pests and wild birds in and around the factory (GMA, 2010a). Contaminated ingredients used as post-extrusion flavor coatings can also be a source of *Salmonella* contamination.

Many typical pet food ingredients are potentially contaminated with *Salmonella*; these include meat and poultry by-product meals, raw meats and even cereal grains. HACCP studies of typical pet food manufacturing processes identify extrusion cooking as the only effective critical control point (CCP) for the elimination of *Salmonella.* Given the temperature profiles of subsequent unit operations, it is unlikely that any of the post-extrusion processing unit operations (e.g. kibble drying, flavor coating, cooling, intermediate storage and packaging) are consistently effective in reducing or eliminating *Salmonella.* This indicates that the presence of *Salmonella* on pet foods is the result of a cross-contamination event caused by direct inoculation of the kibble by a contaminated material (Behravesh et al., 2010). To minimize the potential for post-extrusion product cross-contamination, the manufacturer must implement a comprehensive food safety system encompassing good manufacturing practices (GMPs) and HACCP principles. The Grocery Manufacturers Association (GMA) describes in detail seven GMPs and HACCP elements that must be emphasized for the control of *Salmonella* in low moisture foods when additional processing occurs after a heat inactivation control process, as is the case in pet food factories. The seven elements include ingredient quality measures, hygiene practices, hygienic design and process validation and verification procedures (GMA, 2009).

Other Potential Significant Biological Hazards

There have been near incidents and some speculation about the possible contamination risk of commercial pet foods with pathogens other than *Salmonella*. In September of 2007, the FDA issued a recall notice for a frozen chicken blend raw food product contaminated with *Listeria*. In 2001 and 2006 ProMED-mail posts (http://www.promedmail.org: accessed 25 April 2012) discussed the possible transmission of *Escherichia coli* O157 from a dog to a child in the UK and the carriage of this organism by healthy dogs. No clear link was made to commercial pet food. The recent trend towards innovation in the industry for less processed and "fresher" product concepts has led to the introduction of raw, chilled and frozen pet foods. Given the high incidence of microbial pathogens in raw meats, it seems unlikely that products with minimal or no heat treatments can succeed without significant attention to pathogen control strategies in their manufacture. Invariably the search for shelf-stable "fresh" product forms will lead the industry toward emerging processing technologies such as ultra-high hydrostatic pressure (UHP or HHP) pasteurization, among others.

During the mostly European epidemic of bovine spongiform encephalitis (BSE), some 100 cases of feline spongiform encephalitis (FSE) were reported from 1986 to 2001 among domestic cats and exotic zoo felines, mainly in Europe. Commercial cat food was clearly implicated in some instances and the sporadic cases in zoos were probably caused by infected bovine offal. The disease is characterized by progressive neurological signs, behavioral changes and death. The properties of FSE are identical to BSE and the variant Creutzfeldt–Jakob agent. Fortunately the measures taken across Europe to prevent the inclusion of BSE-suspect material in animal feeds, feed materials and pet foods were very successful in preventing new cases. No additional cases of FSE have been reported in cats since 2001 (http://archive.defra.gov.uk/foodfarm/farmanimal/diseases/atoz/bse/othertses, accessed on 25.02.2013). Even though the outbreak is now controlled and no new cases of TSE have appeared in domestic cats, it is important that control measures such as the strict

observance of the legally required controls on the disposal and feeding of specified risk materials be observed to prevent its re-emergence.

MYCOTOXICOSIS

Mycotoxins are toxic secondary metabolites produced by various molds (Richard, 2007). Mycotoxins are considered an important group of unavoidable chemical food safety hazards prevalent in many pet food ingredients. Mycotoxins commonly reported in pet food products include aflatoxins, ochratoxin A and the *Fusarium* mycotoxins such as fumonisins, deoxynivalenol (DON), T-2/HT-2 and zearalenone. Of these, only aflatoxins and DON have a significant history of pet food-related incidents. Fumonisins and zearelanone are frequently reported to contaminate pet foods in various concentrations but have not been directly implicated in commercial pet food safety incidents (Leung et al., 2006; Boermans and Leung, 2007). The toxicity of ochratoxin A (Szczech et al., 1973; Kitchen et al., 1977) and zearelanone (Gajecka et al., 2004) have been described for dogs. There is very little toxicological information with respect to cats.

Most mycotoxins are not reduced to an acceptable level or eliminated by typical pet food manufacturing processes. Thus, control of this hazard can only be realized through procurement of commodities with consistently low contamination rates. The sometimes poor track record of the pet food industry in managing this hazard is partly explained by the difficulty of routine and effective upstream supplier quality assurance strategies for agricultural commodities like cereal grains. For example, maize is generally harvested by a myriad of small to large producers and storage occurs in regional silos where the grain is comingled with that from an entire region. This situation combined with the seasonal variation and geographic incidence of various mycotoxins demands careful monitoring of each harvest and frequent verification of these levels in bulk deliveries to the factory. The factory monitoring programs must be based on statistically valid sampling plans and procedures (FAO, 2001). Care must be taken with local bulk storage of grains at the factory as unfavorable storage conditions may lead to molding and mycotoxin development in storage (Codex, 2003). Fortunately, rapid factory-friendly analytical methods, mainly ELISA-based assays, are available commercially to test most ingredients for many mycotoxins (GIPSA, 2013).

The sensitivity of cats and dogs to some prevalent mycotoxins, though not completely understood in all cases, is clearly a significant food safety hazard. In the following section, the specific cases of aflatoxins and DON contamination of pet food are discussed.

Aflatoxins

Aflatoxins are mycotoxins produced by the molds *Aspergillus flavus* and *A. parasiticus* as they grow on foodstuffs either under field conditions or during storage. The major types of aflatoxins are designated B1, B2, G1 and G2 with their main metabolites designated M1 and M2 (CAST, 2003). Aflatoxins are considered unavoidable natural contaminants of various pet food ingredients, especially maize (Table 15.3). The potential for significant aflatoxin contamination of susceptible ingredients varies due to seasonal and regional climatic conditions and local agricultural practices.

TABLE 15.3 Examples of Ingredients Known to be Potentially Contaminated with Aflatoxins

Cereals	Oilseeds/Nuts	Spices/Tubers
Maize (corn)	Peanut	Chili peppers
Corn gluten meal	Soybean	Black pepper
Corn gluten feed	Sunflower	Coriander
Dried distiller's grains (DDGS)	Cotton seed	Turmeric
Sorghum	Almond	Ginger
Millet	Pistachio	Tapioca (yuca, manioc)
Rice	Walnut	
Wheat	Brazil nuts	

Aflatoxins are rapidly and extensively absorbed from the gut and metabolized in the liver to toxic epoxides which bind to and damage essential cell components such as DNA, RNA and protein enzymes. In all animal species studied, the primary clinical effect of aflatoxin ingestion is related to liver damage. Different animal species will have different sensitivities to aflatoxin and young animals are more susceptible than adults (Bohm 2005). Dogs given a single dose of 100 µg/kgbw of aflatoxin B1 have been shown to excrete both the aflatoxin metabolites M1 and Q1 in their urine with 90% of a single dose excreted in 12 hours (Bingham et al., 2004).

Tragic incidents involving aflatoxin-contaminated commercial pet food have been reported in several areas of the world. Table 15.4 lists results of either market surveillance or reports following outbreaks of aflatoxicosis. The US dog food recall that occurred in 2005–2006 had reports of aflatoxin concentrations of 223–598 ppb (Newman et al., 2007; Stenske 2006). Affected animals showed the following progression of clinical signs: feed refusal, lethargy, vomiting, jaundice, diarrhea, peripheral edema with final onset of bleeding disorders and seizures leading to death (Dereszynski 2008). Experimental work has shown that aflatoxins given to dogs at 500 µg/kgbw can kill the dogs in as little as two doses and dogs fed for 10 weeks at 20 µg/kgbw/day (approx. 360 ppb in the diet) developed classic liver lesions (Armbrecht et al., 1971). Dogs fed 5 µg/kgbw/day for 10 weeks (approx. 90 ppb in the diet) did not have clinical changes but calculated projections indicated this level could result in serious problems, including sudden death if fed chronically. Dogs fed at 1 µg/kgbw/day and below for 10 weeks (approx. 20 ppb in the diet and below) showed no adverse effects and were expected to have no chronic adverse effects.

Aflatoxins are stable under conventional pet food manufacturing conditions including extrusion cooking, baking and retorting and are therefore not reduced during manufacturing of pet foods (IARC, 2002). Because there are no critical control points (CCP) for this hazard in the manufacturing process, it is imperative that ingredients used to manufacture pet foods have low levels of contamination within regulatory constraints. Regulatory limits for pet food are set at or below 20 ppb in most countries (Leung et al., 2006). The burden of sourcing low aflatoxin-containing ingredients is especially significant for maize and

TABLE 15.4 Examples of Reports of Aflatoxin-contaminated Commercial Dry Dog Food Products and Home Rations

Location	Year	AFLA (ppb)	Reference
United States	1986	250–450	Liggett et al. (1986)
South Africa	1987	100–300	Bastianello et al. (1987)
United Kingdom	1997	2.1 and 370	Scudamore et al. (1997)
United States	2001	150–300	Garland and Reagor (2001)
Mexico	2001	mean 5 and 8	Sharma and Marquez (2001)
Turkey	2002	1.75–20	Gunsen and Yaroglu (2002)
Portugal	2003	not detected	Martins et al. (2003)
Brazil	2004	mean 19 and 16	Maia and Pereira Bastos de Siqueira (2002)
United States	2006	579	Stenske et al. (2006)
United States	2007	223–579	Newman et al. (2007)
United States	2008	40–800	Dereszynski et al. (2008)
Argentina	2009	2–167	Juri et al. (2009)

its by-products (e.g. corn gluten feed and meal) given its high usage rate in the pet food industry.

Deoxynivalenol

Deoxynivalenol (DON), also known as vomitoxin, is a common and unavoidable mycotoxin contaminant of cereals in temperate climates, especially maize and wheat. DON contamination has been reported in commercial pet food (Table 15.5). In 1995 a product recall occurred in the USA after a commercial dog food containing wheat had been associated with feed refusal and vomiting, with other more severe clinical signs reported but not confirmed (Hughes et al., 1999).

DON is most commonly produced by molds in the genus *Fusarium*. DON-producing *Fusarium* strains are ubiquitous in temperate regions. Plant infections with *Fusarium* molds and DON production occurs mainly in the field during the flowering period which are favored by humid and cool weather. DON contamination affects predominantly maize, wheat and barley, and less often oats, rice, rye, sorghum and triticale. DON can be found in combination with other fusarial mycotoxins such as zearalenone, as well as the trichothecene mycotoxins nivalenol, T-2 and HT-2 toxins. Closely related metabolites of DON include 15-acetyl DON and 3-acetyl DON. Carry-over of DON to food products from animal origin does not appear to be of concern due to the rapid elimination of the compound from the body (meat) and the very low transfer rates to milk and eggs (EFSA, 2007).

TABLE 15.5 Case Reports of DON Levels in Commercial Pet Foods

Country	DON Concentration	Reference
US	7–23 ppm	Hughes et al. (1999)
Germany	22–1837 ppb	Songsermsakul et al. (2007)
Portugal	100–130 ppb	Martins et al. (2003)
Austria	0–1386 ppb	Bohm and Razzai-Fazeli (2005)

TABLE 15.6 Observed Effects of Dietary DON in Cats and Dogs (Data from Hughes et al., 1999)

	Feed Refusal	Vomiting	
	NOAEL[a] ppm diet	LOAEL[b] ppm diet	NOAEL ppm diet
Dog	4.5	8	6
Cat	7.7	10	8

[a]*NOAEL – no observed adverse effect level.*
[b]*LOAEL – lowest observed adverse effect level.*

Cats and dogs are sensitive to the toxic effects of DON, but the variability between individuals is high with low levels associated with feed refusal, vomiting and gastrointestinal upset. DON is rapidly and extensively absorbed from the gut. It is rapidly metabolized and excreted and does not accumulate in the body. It has been shown to inhibit the synthesis of DNA, RNA and protein. Acute DON toxicity appears as vomiting (hence the name vomitoxin) and diarrhea within 1 hour of ingestion. At levels below those leading to acute effects, anorexia (feed refusal) and the associated subsequent altered nutritional efficiency and reduced weight gain have been observed (Table 15.6). These effects are rapidly reversible with removal of DON from the diet. DON is also reported to be immunotoxic *in vitro*. Dogs previously exposed to DON-contaminated food preferentially select non-contaminated food if given the choice (Hughes et al., 1999).

Levels of DON contamination of cereals can exhibit wide annual variation due to regional or local growing conditions. DON is not reduced by milling, and is concentrated by dry milling in the grain by-products, such as wheat midds, fiber or hulls and dry distiller's grains (DDGs). DON is stable under conventional pet food processing conditions and will not be reduced by extrusion cooking, baking or retorting (EFSA, 2007). As with aflatoxin and all other mycotoxins, control of this hazard requires the procurement of consistently low contaminated grain. Routine factory verification of DON levels in the "at-risk" materials remains the core preventive strategy.

TABLE 15.7 Veterinary Drug Residues in Pet Food Ingredients

Ingredients	Origin	Veterinary Drug	Reference
Molasses yeast from ethanol fermentations Dry distiller's grains (DDGS)	Ethanol fermentations	Penicillin Virginamycin Erythromycin Tylosin Ionophores Others?	RG-6 Regulatory Guidance: Ethanol Distiller's Grains for Livestock Feed. Canadian Food Inspection Agency, 2013
Bovine, swine and poultry: Meat Lung Liver Kidney Viscera	Illegal use in farm animals	Clenbuterol Ractopamine	Chan (1998) Salleras et al. (1995) Sporano et al. (1998)
Fish Shrimp	Aquaculture	Chloramphenicol Malachite green Furazolidone	Ellis and Turner (2007)

TOXICITIES CAUSED BY MEDICATED FEED CARRY-OVER INTO PET FOOD RAW MATERIALS

Veterinary drugs added to feeds can be toxic to dogs and cats. Pets may be exposed to a variety of pharmacologically active compounds through ingredient residues resulting from farm or industrial practices, with some of these being illegal (Table 15.7). Nevertheless, the most devastating incidents of toxicities have been associated with cross-contamination of feed ingredients with medicated feeds during feed or premix processing, handling or delivery. The GMP requirements for medicated feed producers (European Union, EC No. 183/2005 and USA, 21 CFR 225.10) cannot completely eliminate the possibility of cross-contamination of medicated residues in subsequent batches. Significant carry-over can occur even after multiple sweeper batches of unmedicated product have passed through the system. The factors that can influence the degree of carry-over include: strength of feed/drug/carrier adhesion to line surfaces, particle size and density and electrostatic properties of the materials (EFSA, 2008). Polyether ionophore antibiotic cross-contamination of pet foods is an example of the potential magnitude of this veterinary drug hazard. In 1996 a very tragic incident involving paralysis and death of several hundred cats occurred in the Netherlands (Van der Linde-Sipman et al., 1999).

Ionophore antibiotics include salinomycin, lasalocid, monensin sodium and narasin, among others. These commercially available feed additives are administered to poultry for control of coccidiosis and to beef cattle and swine for improved feed efficiency and meat production. Ionophores form lipid-soluble complexes with monovalent cations (Na^+, K^+)

and facilitate specific ionic transport across biological membranes. These result in changes in transmembranous ion gradients and electrical potentials. Salinomycin also increases the release of catecholamines (adrenalin, noradrenalin). The primary target organs of ionophore toxicity are cardiac and skeletal muscles and peripheral nerves. Dietary no observed effect levels (NOELs) of 1–2.5 mg/kgbw/d of salinomycin, lasalocid, narasin and monensin have been reported for dogs. However, toxicity has been observed in dogs after ingestion of canned pet food containing 10–15 mg/kg (ppm) of lasalocid. Assuming a 10-kg dog and a food energy content of 1.2 kcal/g, this would correspond to 0.6–0.9 mg/kgbw/d of lasalocid (i.e. slightly below the reported NOEL) (Oehme and Pickrell, 1999; Van der Linde-Sipman et al., 1999). In cats toxicity has been observed after ingestion of dry pet food containing 16–21 ppm of salinomycin. Assuming a food consumption of 16 g/kgbw/d, this would correspond to an intake of 0.26–0.34 mg/kgbw/d of salinomycin. In cats and dogs clinical signs appear as skeletal muscle paresis (incomplete paralysis). Usually the hind limbs are affected first, with more severe cases progressing to complete paralysis, dysphonia (altered voice production), respiratory distress and even death (Espino et al., 2003; Van der Linde-Sipman et al., 1999).

Because a drug may not be destroyed during the pet food manufacturing process, as is the case for ionophores, the most effective preventive strategy for this hazard is eliminating it all together. Pet food ingredient suppliers must be completely drug free. When this is not possible, exacting manufacturing quality control procedures and customer-managed verification programs must be in place.

ADULTERATION FOR PROFIT, THE MELAMINE CASE

The FDA defines an adulterated food as that containing "any poisonous or deleterious substances, such as chemical contaminants, which may or ordinarily render it harmful to health" and includes in this definition unavoidable contaminants that are either naturally present in agricultural commodities (e.g. mycotoxins and heavy metals) or are the result of industrial processing (e.g. dioxins and acrylamide) (FDA, 2010b). Another category of adulteration encompasses the criminal and willful substitution of a higher value ingredient with an ingredient of lesser cost. This type of fraud is defined by the GMA as "the intentional fraudulent modification of an ingredient for economic gain through the following methods: unapproved enhancements; dilution with a lesser value ingredient; concealment of damage or contamination; mislabeling of product or ingredient; substitution of a lesser value ingredient; or failing to disclose required product information" (GMA, 2012b). Food adulteration for profit has existed from ancient times and with today's globalized trade in foodstuff, it can impact any country. The range of recent food adulterations reported by the press actually shocks and disappoints, some recently reported incidents include: fake baby milk formulas, soy sauce made from human hair, fish soaked in ink for color, and eels fed contraceptive pills for enhanced growth (Barbosa and Barrionuevo, 2007).

Ruminants can obtain protein from non-protein nitrogen (NPN) through fermentation by their rumen bacteria and NPN is often added to their diet to supplement protein.

Melamine and cyanuric acid have been used as an NPN in cattle, along with urea, ammonium nitrate and biuret. Nevertheless, melamine is not considered a good NPN because its hydrolysis in cattle is slow and less complete than other NPNs (Newton and Utley, 1978). Melamine is used in a wide range of industrial applications including the production of plastic by combining it with formaldehyde. It is a major component of countertops, fabrics, glues, flame retardants, colorants for plastics, fertilizers and derivatives of some drugs. Cyanuric acid is a structural analogue of melamine and is often found as an impurity of melamine.

Pets and other non-ruminant mammals cannot utilize inorganic nitrogen in the food. Adulteration of protein-rich feed ingredients and feeds has always been a problem in the industry and buyers have routinely screened for NPNs. The use of melamine to adulterate pet food ingredients was unexpected (Dobson et al., 2008). In 2007, fake wheat gluten (a thickening agent and protein supplement), made by blending wheat flour and scrap melamine contaminated with cyanuric acid, caused the deaths of several hundred animals and significant kidney disease in thousands more. The mixture was formulated to match the apparent protein content of wheat gluten as measured by the commonly used Kjeldahl method for total nitrogen content (Rovner, 2008). Smaller amounts of corn gluten and rice protein concentrate were also implicated in other cases. The adulterated materials were all imported from China via a number of middleman transactions that obscured completely the identity of the original manufacturers. A series of canned pet food product recalls followed encompassing over 5300 lots, affecting over 1100 products and brands in North America (Nestle 2008). Another important development in this saga came with publications that identified melamine in tissues of animals that had died in 2004/2005 of kidney disease associated with a pet food recall in Southeast Asia; therefore the industry had been victim of this fraud once before (Brown et al., 2007)! Incredibly, once the pet food feed ingredient stream was no longer available to the counterfeiters, they turned their attention to the human milk industry. In late 2008, melamine was found in China as a contaminant in milk, milk products, infant formula and eggs, resulting in the deaths of several children and causing kidney stones in thousands more (Barbosa, 2009).

Melamine and cyanuric acid alone proved to be remarkably non-toxic, even in large concentrations. Melamine alone when fed to dogs at 3% of diet for 1 year had no adverse effect on general health and produced no histopathological changes (Hodge et al., 1965; Lipschitz and Stokey, 1945). Cats fed melamine alone at up to 1% of wet diet for 11 days (181 mg/kgbw/d) showed no adverse health effects. On the other hand, the combination of melamine and cyanuric acid proved toxic. Cats with a single oral exposure to a mixture of melamine and cyanuric acid at 0.2% of diet (32 mg/kgbw of each) developed depression, vomiting and feed refusal approximately 12 hours after ingestion. The melamine and cyanuric acid were excreted in the kidney where they combined to form crystals which blocked the kidney tubules and resulted in kidney disease or failure. Kidney function was impaired by 36 hours and animals were euthanized at 48 hours because of acute renal failure. Histopathological changes, including crystal formation in the kidney, were similar if not identical to those found in clinical cases of animals ingesting tainted pet food (Puschner et al., 2007).

The HACCP implications of this tragic situation are clear and include: "a trust but verify approach" throughout the supply chain (Henry, 2009), including frequent audits of

suppliers. The implementation of routine product identity verification in addition to the standard quality control tests which can be fooled by an able counterfeiter. Reliance on early warning information is useful in allocating risk levels, for example a major fluctuation in ingredient prices can signal an attractive target for fraud. Most countries have now set regulatory limits on melamine and cyanuric acid. Although testing requirements and limits vary, the most common regulatory limit is 1.0 ppm melamine in infant formulas and 2.5 ppm melamine in other foods.

TOXICITIES CAUSED BY NUTRIENT MISFORMULATION

Essential nutrients such as vitamins, minerals and amino acids are many times added to commercial pet foods to assure that they are nutritionally complete and balanced as per trade or regulatory requirements (e.g. AAFCO 2012 Official Publication, http://www.aafco.org). Over- or under-supplementation of nutrients into the product can lead to regulatory non-compliance, risk of toxicity or risk of nutritional deficiencies. The risk of severe nutritional deficiencies exists because a given commercial diet may be the only food a pet animal consumes. A review of the product recall reports in the USA over the last decade shows an interesting pattern of multiple reports of excessive vitamin D_3 incidents involving dog foods and insufficient thiamine incidents involving cat products (Table 15.8). One report exists for excessive methionine in a dog product. Invariably, nutrient misformulation into diets can be traced to industrial accidents either at the pet food manufacturer or at the vitamin premix supplier, often due to formulation errors or improper mixing of the premix ingredients (Bischoff and Rumbeiha, 2012).

Control of this hazard is linked to GMPs at both the vendor of the ingredients and at the pet food manufacturer. Critical GMPs include mixing validation and process capability studies, careful reconciliation of ingredient use to assure proper formulation and ingredient monitoring. Interestingly, the case of vitamin D toxicosis reported in 2010 which involved the carry-over of a vitamin D supplement (25-hydroxy vitamin D) used in other feed products into a correctly formulated pet food premix points to the risks of additive carry-over into products manufactured on the same manufacturing lines as other feed products. This type of sequence error on shared manufacturing lines has also resulted in the carry-over of antibiotics with disastrous consequences (see "Toxicities Caused by Medicated Feed Carry-over into Pet Food Raw Materials," above).

CONCLUSION

Complete and balanced pet food products are formulated to be the single source of nutrition for a pet. Most pets are sustained mainly through feeding of a reduced range of commercial products and a limited number of production batches for a prolonged amount of time. The impact of the diet and therefore food safety hazards on the health of the pet is more like that of a human infant than an older person eating a varied diet. A careful review

TABLE 15.8 Nutritional Toxicities and Deficiencies

Year	Nutrient	Exposure	Root Cause	Number Affected	Reference
1999	Excessive vitamin D_3	14.65 mg/kg BW	Feed-mixing error	Toxicity or death reported in at least 25 dogs	Rumbeiha and Morrison (2011)
2000	Excessive methionine	1.60–2.75%		Anorexia or vomiting was reported in 21 dogs	
2006	Excessive vitamin D_3	Up to 2664 IU/1000 kcal (ME)	Misformulated vitamin premix containing up to 284,700 IU vitamin D_3/kg	Toxicity or death reported in six dogs and five cats	Rumbeiha and Morrison (2011)
2009	Insufficient thiamin	Canned cat food. 1.5 ppm in the product	Misformulated vitamin premix	13 to 20 cats with reversible neurological symptoms including limb ataxia, rigid paralysis, flaccid neck, blindness, circling behavior, seizures, nystagmus and vomiting	Pet Food Recall 2009 – presentation by Karyn Bischoff Assistant Professor Animal Health Diagnostic Center College of Veterinary Medicine Cornell University Ithaca, New York 14853
2009	Excessive vitamin A	Feline research diet	Misformulation	Hypervitaminosis in cats	Bischoff and Rumbeiha (2012)
2010	Insufficient thiamin	Canned cat food			https://www.avma.org/News/Issues/recalls-alerts/Pages/pet-food-safety-recalls-alerts.aspx
2010	Excessive Vitamin D_3	Dry dog food	Scheduling error by Vitamin D supplier allowed for carry-over of vitamin D supplement (25-hydroxy vitamin D) into pet ingredient	16 dogs in eight states hypercalcemia, increased thirst and urination, weight loss, anorexia or azotemia	Hypervitaminosis D in Dogs Associated with Diet – Kent R. Refsal, DVM, PhD Diagnostic Center for Population & Animal Health | 4125 Beaumont Road, Lansing, MI 48910-8104 | PH: 517.353.1683 FX: 517.353.5096 | www.animalhealth.msu.edu WEBCD.GEN.REF.026.01 Issue Date: 10/8/2010
2011	Insufficient thiamin	Canned cat food "less than adequate levels of thiamine"		One consumer complaint received by the FDA	https://www.avma.org/News/Issues/recalls-alerts/Pages/pet-food-safety-recalls-alerts.aspx

of the industry record with regards to pet food safety reveals issues with the control of a small number of food hazards that account for the vast majority of incidents, these are:

- Aflatoxin.
- *Salmonella.*
- Sporadic adulteration of ingredients with veterinary drugs, inorganic nitrogen sources, specific risk materials (BSE) and heavy meals.
- Nutritional misformulation.

Most of these hazards originate in the raw material supply and have no effective control points in the process. Thus their control relies on food safety management practices by the raw material suppliers and a "trust but verify" vendor management program. All raw materials must be risk assessed via a comprehensive HACCP program and all potential hazards defined and controlled. Factories making low moisture pet foods need specific programs aimed at *Salmonella* control in the environment.

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FOOD SAFETY MANAGEMENT

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