Aflatoxins in Dogs Fed

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Contributor: Arturo G. Valdivia-Flores

The Aflatoxins (AF) are difuranocoumarin compounds produced as secondary metabolites of fungi of the genus *Aspergillus* spp. following a polyketide path.

Keywords: Aspergillus flavus ; aflatoxicosis ; biomarkers

1. Aflatoxins and Their Biotransformation Products

A. flavus is the main species of fungus involved in AF production [1][2][3]. Four AF naturally present in agricultural products are described (AFB_1, AFB_2, AFG_1, AFG_2); other forms of AF are derived from the metabolic process of these primary forms within the human or animal body [4]. AF are not destroyed by boiling nor do they confer, color, aroma, or flavor to contaminated ingredients, so they usually go unnoticed by both the owner and the dog [5]. When dogs ingest CDF made with ingredients contaminated with AF, the mycotoxin are absorbed in the duodenum and bind to plasma albumin and proceed to be transported through the bloodstream [6].

In various tissues, especially in the liver and kidneys, AF are biotransformed and bioactivated by isoenzymes of the multiple function oxidase system or cytochromes (CyP_{450}), giving rise to highly active electrophilic forms called 8,9 endo-epoxide and 8, 9 exo-epoxide, which bind and exert an electrophilic attack on subcellular structures [7]. When AF are metabolized (hydrolysis, demethylation, or ketoreduction), they form less toxic intermediate compounds with greater solubility in water (AFM_1, AFM_2, AFQ_1, AFQ_2, AFP_1, AFP_2, and aflatoxicol); therefore, they are eliminated through feces, urine, milk, or egg [8][9]. The most common ways of elimination of metabolites in the urine of dogs is AFM_1, as well as traces of AFQ_1 [10][11]. When the epoxide binds to DNA, then an AF-DNA adduct (dihydro-8-(N^7-guanyl)-9hydroxy-1 AF-N^7–guanidine) is formed, which rearranges as AF-formaminopyrimidine (AF-FAPy), or it is excreted through urine as AF-N^7guanine, which is considered a biomarker of genotoxic damage from AF [8][9][10][11]. In general, all compounds derived from natural forms of AF, due to the activity of the enzymes that participate in the detoxification process, are considered biomarkers of exposure and damage [12].

An important detoxification mechanism in many animal species is the involvement of a group of enzymes called Glutathione S-transferases (GST) [13]. The function of GST is to bind the epoxide with the reduced glutathione tripeptide (GSH), which loses two amino acids (glycine and glutamate) to be eliminated as a cysteine residue linked to AF, called mercapturic acid or N-acetylcysteine-AF, which is eliminated through bile or urine [14]. Dogs have a reduced GST activity, which makes them especially susceptible to AF damage; in addition, a deficiency of GSH or its three precursor amino acids facilitates the occurrence of the most extensive oxidative injury [15][16][17].

2. Contamination of Feed Ingredients by Aflatoxins

Cereals are usually integrated into dog feeds, especially corn, sorghum, rice, wheat, oats, barley, and millet; they are a good source of carbohydrates, fiber, protein, fat, minerals, and vitamins [18][19]. However, cereals present an important risk for the health of dogs because they are vulnerable to contamination by *A. flavus* both in the field and in storage [20][21][22]. In some CDF formulations for dogs, pumpkin seeds, chia, quinoa, and even some legumes such as lentils are included among the ingredients due to their high protein and mineral content. However, these ingredients can also be contaminated by some forms of AF [23][24][25]. Furthermore, the incorporation of both potatoes and sweet potatoes in the manufacturing of premium types of dog feeds is used as a source of carbohydrates and fiber. It is reported that the presence of *A. flavus* and high concentrations of AF can be found in potato tubers [26][27].

Fruits in CDF are used as a natural source of fiber; papaya is one of the main fruits that are included, however, it may have *A. flavus* in the postharvest, which has effects on its nutritional value, and it may also have AF concentrations [28]. Blueberries are used as antioxidants, although there are reports of *A. flavus* contamination and concentrations of AFB_1,

AFB_2, y AFG_1 [29]. Orange and coconut are other ingredients that are included in some dog feeds, but they can also be contaminated by FA-producing fungal microflora [30][31][32].

Dairy and meat products as well as eggs are added to dog feed as an important source of proteins and fats. However, secondary AF metabolites such as AFM_1, AFM_2, AFP_1 may be found, which can also contaminate these feed ingredients [33]. The AF residues can be located in by-products of animal origin used in the manufacturing of CDF, such as liver, kidneys, muscle, meat, milk, and egg. The residual compounds in eggs, milk and meat are derived from the biotransformation of the original AF ingested in the feed of animals used for food and remain in the dog that ingests the CDF [34].

3. Aflatoxin Contamination in Commercial Dry Feed for Dogs

Natural forms of AFs and its metabolites can be found in the ingredients used to make CDF for dogs (Table 2). Cereals used in the formulation of CDF may contain high levels of AF contamination (0.48–1.081 μg/kg), making them the most likely sources of aflatoxin contamination [35][36]. AFB_1 is the most abundant form in open sampling CDF trials, with values that vary widely (<0.5 and 4.946 μg/kg) [37][38]. CDF is classified into economic, premium, or super premium types of dog feeds according to the nutritional quality of the ingredients, but this classification does not guarantee that it is an AF-free product because they are found in all types of CDF [39][40][41]. Therefore, AF present in the CDF are a health risk, which is especially important because CDF is used as the sole or main component of the diet during most of a dog's life; in addition, all the feed contained on each bag is usually eaten until it is exhausted, suggesting that prolonged ingestion of feed contaminated with these mycotoxins, even at low doses, can have adverse health effects [42].

Table 2. Presence of aflatoxins in commercial dry feed for dogs.

Location	Number of Sample (*n*)	Test	Mean AF (μg/kg)	Positive Samples (%)
Brazil	45	TLC	AFB_1 (19.0)	AFB_1 (6.7)
Brazil	180	HPLC	AFB_1 (7.0)	AFB_1 (100)
Brazil	(AE) 49 (AP) 25 (ASP) 13	HPLC	(SF) AF (1.2) (PF) AF (0.4) (SPF) AF (0.5)	AF (95.4)
China	32	LC-MS/MS	AFB1 (47.7)	AFB_1 (87.5)
United States	9	ELISA, TLC, HPLC	AFB_1 (530) AFB_2 (19.0)	AFB_1 (88.8) AFB_2 (77.7)
Italy	(AE) 24 (AP) 24	LC-MS, PLC-MS/MS	AFB_1 y AFG_1 (<0.5) AFB_2 (5.7) AFG_2 (15.8)	AF (12.0)
Italy	55	UHPLC-Q-Orbitrap HRMS	AFB_1 (4.3)	AFB_1 (25.8)
Mexico	19	HPLC	AFB_1 (5.0), AFB_2(0.07), AFG_1 (0.05), AFG_2 (0.03), AFM_1 (2.0) AFM_2 (0.1) AFP_1 (1.1), AFL (0.3)	AFB_1 (79.0), AFB_2 (26.0), AFG_1 (63.0), AFG_2 (21.0), AFM_1 (63.0), AFM_2 (89.0), AFP_1 (58.0), AFL (47.0)
Mexico	29	HPLC-FL	AFB_1 (1.6), AFB_2(0.1), AFG_1 (28.2), AFG_2 (1.3), AFM_1 (1.8), AFM_2 (0.2), AFP_1 (1.7), AFL (28.6)	AFB_1 (76.0), AFB_2 (4.0), AFG_1 (86.0), AFG_2 (93.0), AFM_1 (48.0), AFM_2 (21.0), AFP_1 (100), AFL (100)
Nigeria	30	HPLC	AF (9.6)	AF (100)
Poland	25	HPLC-FLD	AF (0.2)	AF (4.0)
South Africa	(AE)10 (AP)10	TLC, HPLC-FLD	(SF) AFB_1 (44.1) (PF) AFB_1 (20.1)	AFB_1 (100)
Turkey	21	ELISA	AFB_1 (6.6)	AFB_1 (100)
Turkey	18	ELISA	AF 1.75 a 20	AF (16.7)
Brazil	Retrospective study	HPLC	AFB_1–AFG_1 (89.0–191)	-

Definitions: AF: Total aflatoxins; AFB_1: Aflatoxin B_1; AFB2: Aflatoxin B_2; AFG_1: Aflatoxin G_1; AFG_2: Aflatoxin G_2; AFL: Aflatoxicol; AFM_1: Aflatoxin M_1; AFM_2: Aflatoxin M_2; AFP_1: Aflatoxin P_1; ELISA: Enzyme Linked Immunosorbent Assay; HPLC: High Performance Liquid Chromatography; LC-MS/MS: Liquid Chromatography-Tandem Mass Spectrometry; LC-MS: Liquid chromatography coupled to mass spectrometry; PLC-MS/MS: Ultra performance liquid chromatography coupled to tandem mass spectrometry; UHPLC-Q-Orbitrap HRMS: ultra-high performance liquid chromatography coupled to high resolution mass spectrometry; HPLC-FL: Fluorescence High Performance Liquid Chromatography; HPLC-FLD with fluorescence detection (FLD); SF: standard feed; PF: premium feed; SPF: super premium feed.

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