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Review Article

Aflatoxins and their Repercussions in Aquaculture: A Review

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Abstract

Fish consumption has been increasing globally, owing primarily to its availability, accessibility, and affordability in comparison to other types of meat consumption, such as beef, pork and poultry. The detection of mycotoxins in feeds and their constituents has gained popularity in aquaculture because of animal health losses caused mostly by the presence of aflatoxins in fish feed, consequently, various worries arise, particularly about the quality of fish available on the market due to the possibility of presence of aflatoxin in fish meat. Residues of aflatoxins could be found in any animal-derived product, posing a financial risk as well as a risk to human and animal health. Aflatoxins also represent a serious source of contamination in foods and feeds in many different parts of the world. The toxin has been reported to cause heavy mortality in aquaculture. Various physical, chemical and methods are employed to decontaminate the aflatoxins. In recent years, there has been a lot of talk about aflatoxins and their environmental effects in aquaculture.

Keywords: Aflatoxin, Aquaculture, toxicity, feed, ingredients

Introduction

One of the most serious issues confronting the aquaculture industry today is elimination of food-borne toxin exposure, such as aflatoxin B1 (AFB1). Aflatoxins (a type of Mycotoxins) are a group of approximately 20 related fungal metabolites and are of small molecular weight poisonous carcinogenic and mutagenic compounds produced mainly by two fungal species, *Aspergillus flavus* and *A. parasiticus*, which grow in soil, decaying vegetation, hay and grains in hot and humid regions of the world (Kumar, 2018). They are common in cereals, maize grains, cassava, chilli peppers, cottonseed, millet, wheat, peanuts, rice, sesame seeds, sorghum, sunflower seeds, sweetcorn, tree nuts, a variety of spices and poorly stored animal feeds. The other aflatoxin producing species include *A. bombycis, A. ochraceoroseus, A. pseudotamari, A. tamarii, Emericellaa stellata* and *Emericella venezuelensis*, which are scarce in nature and occasionally found in agriculture compared to *A. flavus* and *A. parasitica*. AFB1 is identified as the most powerful and lethal naturally occurring liver carcinogen. With rising demand for aquaculture comes increasing interest with regard to the definitive supply of raw materials needed to subsidize growth. Aqua feeds traditionally depend on fishmeal as a protein source, but with the latest trend in coming years it has moved towards replacing fish meal with less expensive sources of protein of plant origin. Aquaculture feeds are more likely to be infected by one or more forms of aflatoxins as a result of this pattern. *Aspergillus* species are widely distributed and are able to grow in a wide variety of substrates and under different environmental conditions (Dirican, 2015). Aflatoxins were first discovered in turkeys and in rainbow trout fed rations containing peanut and cottonseed meals (Blout, 1961). When temperatures are between 24 and 35°C, the toxins are generated as secondary metabolites by *aspergillus flavus* and *aspergillus parasiticus* fungi and they will develop within many commodities whenever the moisture content exceeds 7% (10% with ventilation) (Halver, 1965);

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Rucker et al. (2002); Park & Liang (1993). However, the meteorological conditions opportune for aflatoxin production are high moisture during harvest, dry weather near crop maturity and inadequate drying and storage of crops. Relative humidity, which can range from 88 to 95% in some cases and temperature, which can range from 36 to 38°C for mould growth and 25 to 27°C for maximum toxin production, are the most important factors influencing growth and aflatoxin production (Park & Liang, 1993). Aflatoxin production is influenced by post-harvesting conditions such as transportation, storage (excess heat and moisture, pest-related damage, long periods of storage) and food processing. Also, aflatoxins are toxic to human and animal health as they cause liver and kidney damage, cause immunosuppressive, carcinogenic and mutagenic effects (PACA, 2015).

Types of aflatoxins

Aflatoxins are poisonous chemicals generated by four species of fungi, all of which belong to the *Aspergillus* genus. Certain strains of *Aspergillus flavus* and *Aspergillus parasiticus*, as well as the related species *Aspergillus nomius* and *Aspergillus niger*, produce these toxins (Eaton & Groopman, 1994). Aflatoxin is composed of 20 distinct fungal metabolites. There are six forms of aflatoxinonly B1, B2, G1 and G2 are commonly found in plant-based foods, while M1 (metabolite of B1) and M2 are found in animal origin foods. *A. flavus* produces Aflatoxin B1 and B2 (Fig. 1). Aflatoxin G1 and G2 are produced by *A. parasiticus* (Wacoo et al., 2014); Wu et al., (2011); Bennett et al. (2007). B and G aflatoxins only glow when exposed to ultraviolet light on thin layer chromatography due to their heterocyclic chemical structure. The letters "B" and "G" stand for blue and yellow green fluorescent colours, respectively. The fluorescent hue that appears following exposure to ultraviolet light determines the B and G designations: blue for AFB1 and AFB2, and yellow-green for AFG1 and AFG2 (Sargeant et al., 1963; ROC, 1992).

Physical and chemical properties of aflatoxins

Aflatoxins are colourless to pale yellow crystals that fluoresce when exposed to ultraviolet light. They are slightly soluble in water (10-20 g ml^{-1}) and freely soluble in moderately polar solvents such as chloroform, methanol and dimethyl sulfoxide. They are unstable in UV light in the presence of oxygen, and they are unstable in extreme pH (3 or >10). The

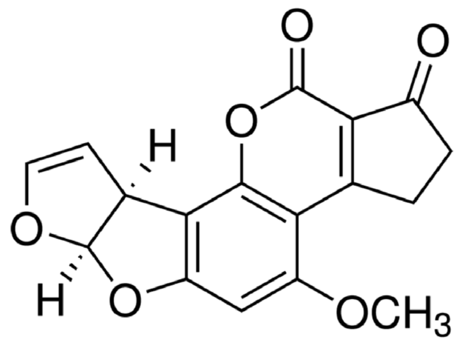

Fig. 1. Chemical structure of aflatoxin

lactone ring opens in alkaline conditions, destroying the aflatoxins (Fig. 2), but this reaction is reversible in acidic conditions. At high temperatures, ammonia causes the lactone ring to open, resulting in the decarboxylation of aflatoxins and this reaction is irreversible (Vankayalapati, 2018). Table 1 lists some of the important physical and chemical properties of major aflatoxins.

In addition, aflatoxin toxicity in fish varies depending on the type and amount of toxin used, as well as the length of time the fish was exposed to it (Table 2). It should be mentioned that there are several variances in fish species' susceptibility to various levels of aflatoxins. It's likely that various aflatoxin sensitivities are caused by a range of metabolic enzymes found in different fish species. In addition, the rate of activation of aflatoxins varies between individuals in several species. Furthermore, age and geographic location have an impact on aflatoxin

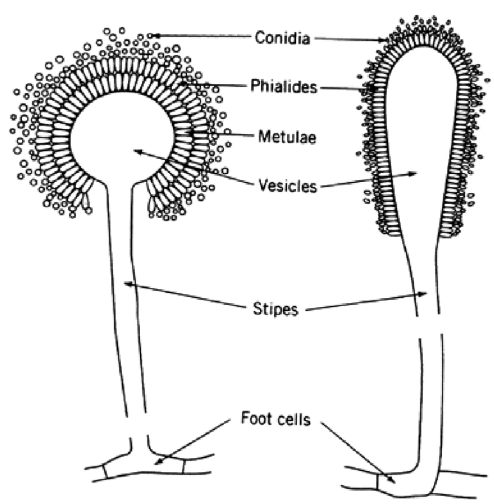

Fig. 2. Diagram of Aflatoxin (*Aspergillus flavus*)

Table 1. Physical and chemical properties of major aflatoxins

Aflatoxin Name	Molecular formula	Molecular weight	Melting point	UV absorption (e) Ämax (nm)	[(L. mol^{-1}. Cm^{-1}) x10^{-3}	Fluorescence Emission (nm)
B1	$C_{17}H_{12}O_6$	312	268-269	223	25.6	425
				265	13.4	
				362	21.8	
B2	$C_{17}H_{14}O_6$	314	286-289	265	11.7	425
				363	23.4	
G1	$C_{17}H_{12}O_7$	328	244-246	243	11.5	450
				257	9.9	
				264	10	
				362	16.1	
G2	$C_{17}H_{14}O_7$	330	237-240	265	9.7	450
				363	21	

resistance in different species (Dohnal et al., 2014). Animals and humans who ingest animal-derived products contaminated with aflatoxin residues are harmed by aflatoxin in feedstuff (Cardoso-Filho et al., 2013). AFB1 and its metabolites are rapidly disseminated but not entirely absorbed in the channel catfish (*Ictalurus punctatus*), a species thought to be resistant to aflatoxins, as evidenced by the considerable amount of AFB1 expelled in the faeces. AFB1 is readily converted to aflatoxicol in this species, allowing for rapid removal. In rainbow trout, an aflatoxin-sensitive species, however, all of the AFB1 appears to be epoxidized, resulting in the extremely carcinogenic AFB1-8,9-epoxide (AFBO) metabolite. When compared to trout, salmon resistance to aflatoxin can be related to the lesser efficiency of cytochrome P450-mediated AFB1 metabolism for AFBO production (Santacroce et al., 2008).

Toxicity and mode of action of aflatoxins

Aflatoxin-contaminated foods and feeds are linked to human and animal health risks. Aflatoxins have been shown to cause hepatotoxicity (Rotimi et al., 2017), mutagenesis (Kim et al., 2016), carcinogenesis (Sirma et al., 2019), immune suppression (Mohsenzadeh et al., 2016), neurotoxicity (Makhlouf, 2020), epigenetic effects (Ferreira et al., 2019), reproductive dysfunctions (Ferreira et al., 2019) and stunted growth (Chen et al., 2018). There have been many studies that explore the contraption of these health effects (Gong et al., 2016; Alsayyah et al., 2019; Wangia et al., 2019). As a result, non-identical and stringent regulations have been implemented globally to control aflatoxin contamination in foods and feeds with the goal of preserving human and animal health. Aflatoxin B1 is thought to be responsible for both toxicity and carcinogenicity. The International Agency for Research on Cancer classified it as a group I carcinogen (IARC). Chronic aflatoxicosis causes cancer, immune suppression, and other long-term pathological conditions, whereas acute aflatoxicosis kills. The liver is the primary target organ, and liver damage occurs when poultry, fish, rodents, and nonhuman primates are fed aflatoxin contaminated food (Wu, 2006).

Detoxification of aflatoxin contaminated foods

Detoxification of aflatoxin contaminated foods has long been a challenge for the food industry. High detoxification may occur as a result of the degradation of its structure by various gases or chemical agents that oxidise (e.g., hydrogen peroxide or ozone) or hydrolase (e.g., aldehydes, bases, or acids) or thermal treatment. A variety of methods for detoxifying aflatoxins are used (Fig. 3), including physical, chemical and biological methods (Nazhand et al., 2020). Physical, chemical, and microbiological methods must ensure that the degradation process preserves nutritive value of food, does not introduce new toxin or carcinogenic-mutagenic substances, and destroys Aspergillus spores and mycelia, preventing the proliferation and production of new toxins under favourable conditions. However, the

Table 2. Toxic effects of aflatoxins on several fish species

Type of toxin	Species	Dose	Effects	References
Aflatoxin	Nile tilapia (*Oreochromis niloticus*)	100 mg kg^{-1}	Growth reduction	(El-Banna et al., 1992)
	Nile tilapia (*Oreochromis niloticus*)	200 ppb kg^{-1}	Reduced weight gain and survival, reduction in Hb, RBC &, WBCs	(Selim et al., 2014)
	Nile tilapia (*Oreochromis niloticus*)	5–38.62 mg kg^{-1}	Reduction in the rate of survival by up to 67%	(Cagauan et al., 2004)
	Nile tilapia (*Oreochromis niloticus*)	200 mg kg^{-1}	Mortality (16,7%)	(El-Banna et al., 1992)
	Nile tilapia (*Oreochromis niloticus*)	100 mg kg^{-1}	Severe hepatic necrosis with 60% mortality	(Tuan et al., 2002)
	Rohu (*Labeo rohita*)	12-13.3 mg kg^{-1} (i.p.)	Haemorrhages, lamellar hyperplasia, fusion accompanied by epithelial cell edema	(Sahoo et al., 2003)
	Catfish (*Ictalurus punctatus*)	12 mg kg^{-1}	Reduced growth rate and caused regurgitation of stomach content	(Jantrarotai et al., 1990b)
	Juvenile Rainbow trout (*Oncorhynchus mykiss*)	1190 μg kg^{-1}	Mortality	(Nomura et al., 2011)
	Rainbow trout (*Oncorhynchus mykiss*)	0.5 mg kg^{-1}	Caused tumour in liver	(Lovell, 1989)
	Rainbow trout (*Oncorhynchus mykiss*)	3.3 and 6.4 mg kg^{-1}	Reduction in feed intake and weight gain, Increase in respiratory burst	(Woodward et al., 1983)
	Mosquito fish (*Gambusia affinis*)	2150 μg kg^{-1}	Reduction of activity and loss of righting reflex with 100% fish mortality	(McKean et al., 2006)
	Rohu (*Labeo rohita*)	2.50 and 5.00 mg kg^{-1}	Reduction of production of oxygen radicals by neutrophils	(Sahoo & Mukherjee, 2001)
	Rohu (*Labeo rohita*)	10, 20 and 40 ppm	Total erythrocyte count, total leucocyte count, hemoglobin count and nitroblue tetrazolium decreased	(Mohapatra et al., 2011)
	Rohu (*Labeo rohita*)	1.25; 2.50 and 5.00 mg kg^{-1}	Reduction of total protein and globulin levels	(Sahoo & Mukherjee, 2001)
	Sea bass (*Dicentrarchus labrax* L.)	0.18 mg kg^{-1}	Loss of equilibrium, rapid opercular movement, hemorrhages of the dorsal skin surface	(El-Sayed & Khalil, 2009)
	Atlantic salmon (*Salmo salar*)	0.2-2.4 mg kg^{-1}	Increased mRNA expression of immune marker in the spleen	(Bernhoft et al., 2018)

biotransformation of aflatoxin mainly occurs in the liver and intestine (Sergent et al., 2008). Due to their liposolubility, the aflatoxins are absorbed in the gastrointestinal tract and distributed to muscle, kidneys, adipose tissue and mainly to liver (Batatinha et al., 2008). Intake may induce an inflammatory response, interrupt intestinal integrity, and eventually inhibit the growth of fish, (Souza et al., 2018; Ghafarifarsani et al., 2021).

WHO support in controlling aflatoxins

The World Health Organization (WHO) evaluates the science and develops risk assessments in collaboration with the Food and Agriculture Organization (FAO) to define safe exposure levels. Maximum levels of aflatoxins in various foods are recommended based on risk assessments. These serve as the foundation for national regulations aimed at limiting contamination. Since their discovery in the 1960s, aflatoxins have been subjected to toxicological testing and dietary exposure assessments by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2002). These evaluations are used by the Codex Alimentarius Commission, which has been working since 1963 to develop harmonised international food standards to protect consumer health and ensure fair trade practices. Codex standards establish maximum levels for contaminants and natural toxins such as aflatoxins in food and serve as the reference for international food trade, allowing consumers worldwide to be confident that the food they buy meets agreed-upon safety and quality standards, regardless of where it was produced. Aflatoxin levels in various grains, nuts, dried figs, and milk range from 0.5 to 15 ìg kg^{-1} (JECFA, 2002). Codex has also developed codes of practise that specify appropriate preventive measures to prevent and reduce the risk of aflatoxins in food and feed. The Food Contamination Monitoring and Assessment Programme of the WHO Global Environment Monitoring System, also known as GEMS/Food, collect food contamination data from nationally recognised institutions. The GEMS/Food contaminants database provides information on the levels and trends of contaminants in food to governments, the Codex Alimentarius Commission, and other relevant institutions, as well as the general public (JECFA, 2002).

Regulations to limit aflatoxin contamination by National authorities.

To protect the consumer, exposure to aflatoxins should be kept to a minimum. Many countries have regulations governing aflatoxins in food with prescribed acceptable limits, and the majority have maximum permissible or acceptable levels for various foodstuffs. The ingestion of aflatoxins from contaminated food and feed has led to serious health complications in humans and animals (Fung & Clark, 2004; Binder et al., 2007; Sherif et al., 2009). Therefore, different countries have implemented strict regulations for aflatoxins in food and feed to maintain the health of individuals (Juan et al., 2012). The tolerable daily intake of AFB1 stipulated in fish

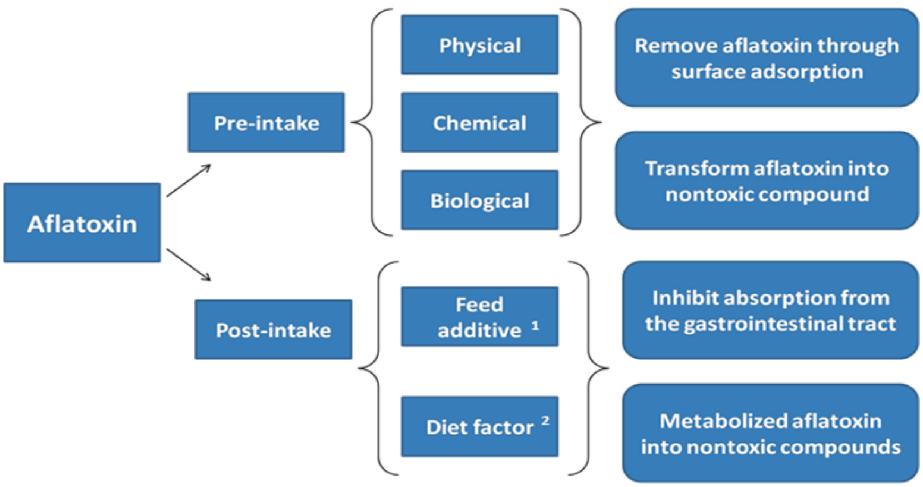

Fig. 3. Illustrative representation of aflatoxin reduction with different mode of action. Detoxification in animal body[1]; Detoxification in human body[2]

feed by the Food and Drug Administration (FDA) is 5 ìg kg^{-1} (FDA, 2015). Aflatoxin maximum allowable levels for human consumption range from 4 to 30 ìg kg^{-1}, depending on the food variety (Mahato et al., 2019). The maximum authorize levels of total aflatoxin by the EU is 2 μg kg^{-1} for AFB1 and 4 μg kg^{-1} for total aflatoxin (EC, 2007, 2010) but 20 μg kg^{-1} of aflatoxin in the United States (Wu, 2006; FAOSTAT, 2020). Moreover, In United States, Food and Drug Administration (FDA) has permitted a total amount of 20 ng g^{-1} in livestock feed and 0.5 g kg^{-1} or 50 ng^{-1} l in milk (Ellis et al., 1995). In European countries, permitted levels of aflatoxin M1 in milk, milk products and baby food are 0.005 mg kg^{-1} (Creppy, 2002). Also, different countries have set different regulations for permitted levels of aflatoxin in livestock feed. For instance, European Union (EU) has set permitted levels of aflatoxin from 0.05 to 0.5 μg kg^{-1}. Factors such as weather conditions are also effective in determining permitted levels of aflatoxin. Permitted levels of this toxin in tropical countries are higher compared to mild and cold countries (Egmond et al., 1989). Besides this, various innovative technologies and control strategies are applied for pre- and post-harvest management of aflatoxins to enhance sustainable overall productivity (Prietto et al., 2015). Though there are numerous publications are available on aflatoxins in food and feed. Furthermore, some countries have set permitted levels of aflatoxins in food in order to control and reduce detrimental effects of these toxins. These levels are variable and depend on economic and developing status of the countries (Galvano et al., 1996).

The effects of aflatoxin in aquaculture

There is a scarcity of data on the effects of aflatoxins in aquaculture (Han et al., 2008; Lovell, 1992; Pestka, 2007; Santacroce, 2011). Aflatoxin B1 is regarded as the most potent food-borne hepatotoxicant commonly found in animal feedstuffs and the causal agent in an unanticipated epidemic of fish mortality attributed to aflatoxicosis, which has been well documented in freshwater species (Dirican, 2015). The inclusion of more plant-based components in aquafeed formulations has intensified the potential onset for aflatoxicosis in fish farming systems because of the high loads of aflatoxin contamination carried over from vegetable sources (Santacroce, 2011). Aflatoxin can be produced directly in the field, during insiling, feed formula preparation, and also during improper feed storage in the farm by the most toxicogenic strains. Thermal treatments, which use high temperature pelleting procedures, on the other hand, destroy the mould but do not inactivate the heat-stable toxins found in spores and mycelium. Toxins accumulate in fish meal, posing a high risk to farmed species and ultimately, to customer health and safety. As a result, the issue of aflatoxin contamination in aquaculture has grown. Aflatoxin residues have been found in aquatic animal tissues, posing a potential public health concern after ingestion, according to several investigations (Han et al., 2010; Meissonnier et al., 2007; Puschner 2002; Tacon & Metian, 2008). Aflatoxin residues can be retained in aquatic animal tissues, posing potential public health risks after ingestion, (Han et al., 2010; Naylor et al., 2009). It reduces the nutritional value of administered feed in fish farms, affecting both fish and product quality (Naylor et al., 2009; Hassan et al., 2010). Exposure to highly contaminated feeds causes acute aflatoxicosis in fishes, poor growth rates and mortality (Agag, 2004). These lead to economic losses due to low output production, morbidity, mortality and poor quality of fish and fish products (Mahfouz & Sherif, 2015).

The cases of acute intoxication by aflatoxin are almost rare and exceptional, while the chronic toxicity is the serious and most prevalent problem, because of aflatoxin carcinogenicity upon long term micro exposures. When moderate to high levels of aflatoxin are consumed, fish develop an acute intoxication known as acute aflatoxicosis, which is characterized by poor health and fertility, decreased productivity, decreased weight gain, and immunosuppression. Pathological symptoms appear as a result of prolonged dietary exposure, causing genotoxic, tumorigenic and teratogenic, hormonal or neurotoxic effects in fish as well as humans. Chronic aflatoxicosis is a major concern in aquaculture systems because it has been linked to both a gradual decline in reared fish health status and decreased stock quality (Santacroce, 2011; Santacroce et al., 2008).

In the 1960s, the first documented cases of aflatoxicosis affecting fish health occurred in trout hatcheries. Domesticated rainbow trout (*Oncorhynchus mykiss*) developed liver tumours after being fed a pelleted feed contaminated with aflatoxins. In these hatcheries, up to 85% of the fish died. Although cottonseed meal is no longer a major ingredient in feed formulations, poor storage of other feed ingredients and nutritionally complete feeds can result in aflatoxin contamination (Alsayyah et al., 2019);Wangia et al., 2019). Rainbow trout, for example, is extremely sensitive to aflatoxin, whereas channel catfish is much less so. Rainbow trout fed diets containing aflatoxin at 0.0004 mg kg^{-1} feed (0.4 ppb) for 15 months had a 14% risk of developing tumours. Feeding rainbow trout a diet containing aflatoxin at 0.02 mg kg^{-1} feed (20 ppb) for 8 months resulted in a 58% incidence of liver tumours, and continued feeding for 12 months resulted in an 83% incidence of tumours. For 10 weeks, channel catfish were fed a diet containing purified aflatoxin at 10 mg per kg feed (10,000 ppb) and showed decreased growth rates and moderate internal lesions (Jantrarotai & Lovell, 1990). Aflatoxicosis is now uncommon in the rainbow trout industry due to strict FDA regulations requiring aflatoxin screening in oilseeds, corn, and other feed ingredients. However, as diets for these species are being formulated to contain more plant and less animal ingredients, interest in the toxic effects on cultured warm-water fishes such as tilapia (*Oreochromis sp*.) and channel catfish (*Ictalurus punctatus*) have become more common. This increases the risk of aflatoxicosis in these species because, as previously stated, plant ingredients are more likely than animal ingredients to be contaminated with aflatoxins.

Conclusion

Aflatoxin contamination of foods and feeds causes economic losses as well as direct and indirect effects on human and animal health. Aquaculture will continue to play a significant role in the global fish supply in the future. The negative effects of aflatoxins waste on aquatic environments are becoming more widely recognized in aquaculture. To reduce the risk of aflatoxin exposure, close collaboration among the trade, the public, and the government is required. Chemical agents should be handled with considerable caution since they leave residues that can cause many other problems. Aflatoxin contamination in humans, livestock and fish can be avoided if foods are properly dried before storage and storage conditions are continuously monitored. Properly planned aquaculture waste use reduces water pollution while also conserving valuable water resources and utilizing the nutrients contained in effluent. Aquaculture's goal is to grow in a way that does not harm aquatic ecosystems. As a result, monitoring the environmental effects of aflatoxins in aquaculture is critical for the conservation of aquatic ecosystems. In general, everyone involved in the commodity value chain should think about aflatoxin control measures to improve food safety, raise public health and prevention awareness, increase economic benefits, and reduce costs.

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