

Narrative Review

A Comprehensive Review on Aflatoxin Contamination, Its Impact on Human Health and Management Strategies

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Conflict of Interest: None.

Sultan HM., et al. (2024). 4(2): DOI: <https://doi.org/10.61919/jhrr.v4i2.1087>

ABSTRACT

Background: Aflatoxins are secondary metabolites produced by *Aspergillus* species, significantly impact global economic and health sectors, and contaminating key agricultural products such as maize, cotton, and groundnuts. The mycotoxins, particularly types B1 and B2, pose severe risks to animal and human health, leading to diseases like hepatic cellular carcinoma and liver cancer.

Objective: This review aims to analyze the prevalent impacts of AF contamination on human health and to evaluate current management strategies to mitigate this issue.

Methods: We utilize a comprehensive array of techniques to detect AF in agricultural products, including culturing, chromatography, immunochemical methods, and molecular assays. Our review also explores preventive measures during the pre-harvest and post-harvest phases of crop development, focusing on the efficacy of biopesticides in reducing contamination levels.

Results: AF contamination levels vary widely, with some regions recording levels as high as 35 ppb in crops, surpassing the maximum residue limits (5-20 ppb) set by many countries. The application of biopesticides has shown a reduction in toxigenic strain prevalence by up to 40%, demonstrating a significant decrease in AF levels in treated crops compared to untreated ones.

Conclusion: Effective management of AF contamination involves early detection and the strategic use of biopesticides to control fungal growth. Adopting these strategies can substantially reduce the health risks associated with AF exposure.

Keywords: Aflatoxins, *Aspergillus*, Biocontrol, Contamination management, Human health.

INTRODUCTION

Aflatoxins, known as secondary metabolites, are produced by a variety of fungal species, primarily *Alternaria*, *Fusarium*, *Penicillium*, and *Aspergillus* (1). According to the Food and Agriculture Organization (FAO), mycotoxins are responsible for almost 25% of food contamination globally (2). A recent study revealed that mycotoxins infect about 80% of crops globally (3). The genus *Aspergillus* is the most common mycotoxins-producing genera that contain at least 339 species (4). The most common AF producing *Aspergillus* species are *A. flavus* and *A. parasiticus*, but there are also some other species reported to have produced AF (5). Different types of AF have been reported; their contamination of food and economically significant crops is a global health problem (6). Fungal toxicosis is a naturally carcinogenic and mutagenic cause of disease for both humans and animals (7). There have also been recent reports of fungal infections caused by *Aspergillus*, which increase the severity of the coronavirus infection in immunocompromised persons. There were a total of 480 cases of COVID-19-related pulmonary aspergillosis reported in 2022 (8) (9). Food and other products are contaminated by AF pollution, which affects approximately 5.5 billion people worldwide (10). Because of the adverse effects of AF contamination on humans and animals, the U.S. Food and Drug Administration (FDA) (11) set a maximum limit of 20 ppb parts per billion, and the European Union set a limit of 4 ppb (12).

The most prevalent and significant AF is B1, B2, G1, and G2 (13). They are more significant than the other categories because of their presence in food. AF B1 attaches to the DNA and modifies its structure resulting in mutations that lead to genetic change in

the liver cells, resulting in genotoxicity (14). The designations AF B1, B2, G1, and G2 refer to their ability to both absorb and release fluorescent colour. As a result, at 425 nm in the UV spectrum, B1 and B2 exhibit blue fluorescence, whereas G1 and G2 appear green AF B1 most frequently causes aflatoxicosis, chronic toxicity, genotoxicity, and immunotoxicity in humans as well as animals (15).

Table 1. Aflatoxin-producing species and hosts affected by aflatoxin (12)

Aflatoxin	Aflatoxin-producing <i>Aspergillus spp.</i>	Host/Affected Entity
B (B1,B2)	<i>A. flavus</i> , <i>A. parasiticus</i> <i>A. parvisclerotigenus</i>	Fruit juices (apple, guava) Oilseed rape Peanuts
B3	<i>A. flavus</i> , <i>A. novoparasiticus</i> , <i>A. parasiticus</i>	Cereal grains legumes corn
G (G1,G2)	<i>A. nomius</i> <i>A. parasiticus</i> <i>A. terreus</i> <i>A. toxicarius</i>	Oilseed rape Peanuts Pea Pistachio Rice
GM1	Hydroxylated metabolite of aflatoxin G1, naturally produced by <i>A. flavus</i> , also produced by <i>A. parasiticus</i> <i>in vitro</i> .	Dairy products and Milk
GM2	Naturally produced by <i>A. flavus</i> and <i>A. parasiticus</i> and yeast, derived from aflatoxin G2	Dairy products and Milk
Aflatoxicol M1	Aflatoxin B1, aflatoxin R0, or aflatoxin M1 metabolite	Dairy products and Milk
Aflatoxicol H1	Aflatoxin B1 and aflatoxin Q1 metabolites	Dairy products and Milk
Aspertoxin	<i>A. flavus</i> and <i>A. parasiticus</i>	Crops and Plants

A. flavus is a highly widespread soil fungus that is particularly prevalent in tropical and subtropical regions, despite its global distribution (16). *A. flavus* can survive in soil as sclerotia or conidia, and in diseased plant tissues as mycelia (17). When the environmental condition is harsh, these sclerotia hibernate. Sclerotia germinates into mycelia in the presence of favorable environmental circumstances. These mycelia then create conidiophores, which spread through the air and infect a variety of crops (17).

There are numerous factors, such as temperature, humidity, environmental stress, wounds from insects or birds, and post-harvest practices, that can cause *A. flavus* to grow and colonization to produce toxins in the host (18). High temperatures in field conditions favour the production of AF (19). The infection of *A. flavus* in various crops can result in asymptomatic yellow mold growth as well as symptoms like boll or ear rot. *A. flavus* typically infects maize, groundnuts, chili, cottonseed, and tree nuts as pre-harvest hosts; however, wheat, sorghum, and rice are more susceptible after harvest (20). Improper crop handling and storage conditions greatly influence the post-harvest contamination of crops by *Aspergillus spp.* (20).

Abiotic factors influence AF biosynthesis

Abiotic factors that favour AF production include temperature, water activity, pH, carbon, and nitrogen (21) but in particular, temperature and water activity have a major impact on AF contamination. These two factors play a major role in stimulating the growth of fungi that make AF, mainly *A. flavus*, and activating the AF producing gene cluster. Higher water activity promotes fungal growth and toxin synthesis (22) (23). The optimal temperature that encourages the production of AF is 28–30 °C (19). Water activity and temperature play a significant role in the transcription of two important regulator genes, aflR, and aflS, in the AF biosynthesis pathways (24). Temperature is the main factor in the production of AF; temperatures below 25 °C and above 37 °C inhibit AF growth and production (25).

In 2023, the Rapid Alert System for Food and Feed database found that dry fruits like almonds, peanuts, and pistachios reported the majority of AF contamination (26). The recent COVID-19 pandemic and inadequate food management practices were the primary causes of food concentration (27). This will eventually lead to an increase in food that both humans and animals consume that contains AF. Consequently, we anticipate a surge in related health problems (27). Because of their favorable climates in the field and

storage conditions, the growth of aflatoxigenic strains is highest in Asia and Africa, which have the highest prevalence of AF contamination (28). China is also concerned about AF contamination in agricultural practices (29). Due to global climate change, AF is becoming more dangerous in areas that were previously free of this threat. Recently, there have been a few reports of AF in different parts of Europe (30)

Impact of Aflatoxin on Human Health

Aflatoxin is thought to be hazardous for humans as well as animals. Various diseases that are associated with AF are described here.

Aflatoxicosis

Aflatoxicosis is a fungal toxicosis that can cause both acute and chronic aflatoxicosis in humans and animals, primarily through the consumption of *A. flavus* and *A. parasiticus* (31). Chronic aflatoxicosis can cause high fever, jaundice, liver disease, vomiting, edema of the feet, and human hepatic cell carcinoma (32). In addition, it also causes stunted growth and decreased immunity in children (33). Although the precise AF concentration that causes aflatoxicosis has not been confirmed, it is generally believed that 0.5 g/kg of AF concentration in food can cause AF toxicity in humans (34). For animals, the acceptable range is 50–300 g/kg (35). Kenya documented significant aflatoxicosis epidemics in 1981 and India in 1974, respectively. It is noteworthy to emphasize that, since 2004; there have been 500 cases of aflatoxicosis worldwide, with 200 fatalities (36). Mostly, aflatoxicosis occurs due to inhaling or taking contaminated spores or contaminated food. About 25% of instances of acute aflatoxicosis result in death, with children who are drunk having a higher mortality rate (15)

Cancer

Reports classify AF as a Group 1 carcinogen, and prolonged exposure to them can cause liver, lung, and colon cancer in both people and animals. AF B1 is directly linked with liver cancer, known as hepatocellular carcinoma (37) (38). Hepatocellular carcinoma is the 6th most prevalent disease among men and women (39). In Africa and Asia, about 4.6–28.2% of hepatocellular carcinoma cases are due to AF consumption (40) (41). Furthermore, researchers have determined that consuming a daily dose of 20–120 g/kg of AF B1, a group 1 carcinogen, for one to three weeks poses a risk. However, the host's immunity plays a major role in determining the level of AF toxicity (42). The incidence of hepatocellular carcinoma is increasing in Pakistan, with viral hepatitis being a major contributing factor. When AF exposure occurs in an individual who is HBV-infected, the risk of cancer increases twelve times (43).

Lung Infection

Aspergillus spp. can cause lung infections in immunocompromised people, known as aspergillosis (44). Twenty different *Aspergillus spp.* can cause aspergillosis, but *A. fumigatus* and *A. flavus* are the primary culprits in both humans and animals. Aspergillosis infection in humans worldwide is primarily caused by excessive inhalation of *Aspergillus* spores (45). Infections can also arise from spore transfer through infected wounds, contaminated tobacco smoke, or marijuana plant smoke. Aspergillosis also affects other species, including geese, mice, hens, and rabbits (46). Furthermore, *A. flavus* is the cause of honeybees' stone brood sickness (47). There are various clinical types of aspergillosis, such as extrapulmonary and invasive aspergillosis, as well as extrinsic asthma, saprophytic pulmonary, allergic alveolitis, and pulmonary colonizing (48). 2.5% of people with asthma and 1–15% of people worldwide who already have cystic fibrosis develop allergic bronchopulmonary aspergillosis (ABPA) (48). In addition to the 4.8 million people worldwide who suffer from ABPA, 400,000 more suffer from chronic pulmonary aspergillosis (CPA). However, 1.2 million individuals who have tuberculosis also have chronic pulmonary aspergillosis (CPA) (49). Aspergillosis is among the top four diseases globally that cause death in people with impaired immune systems (50). *A. flavus* rarely causes aspergillosis, but when it does, the infection can be extremely serious. *A. flavus* is responsible for around 65% of pediatric aspergillosis cases in North America. Furthermore, it primarily causes mycotic keratitis (51).

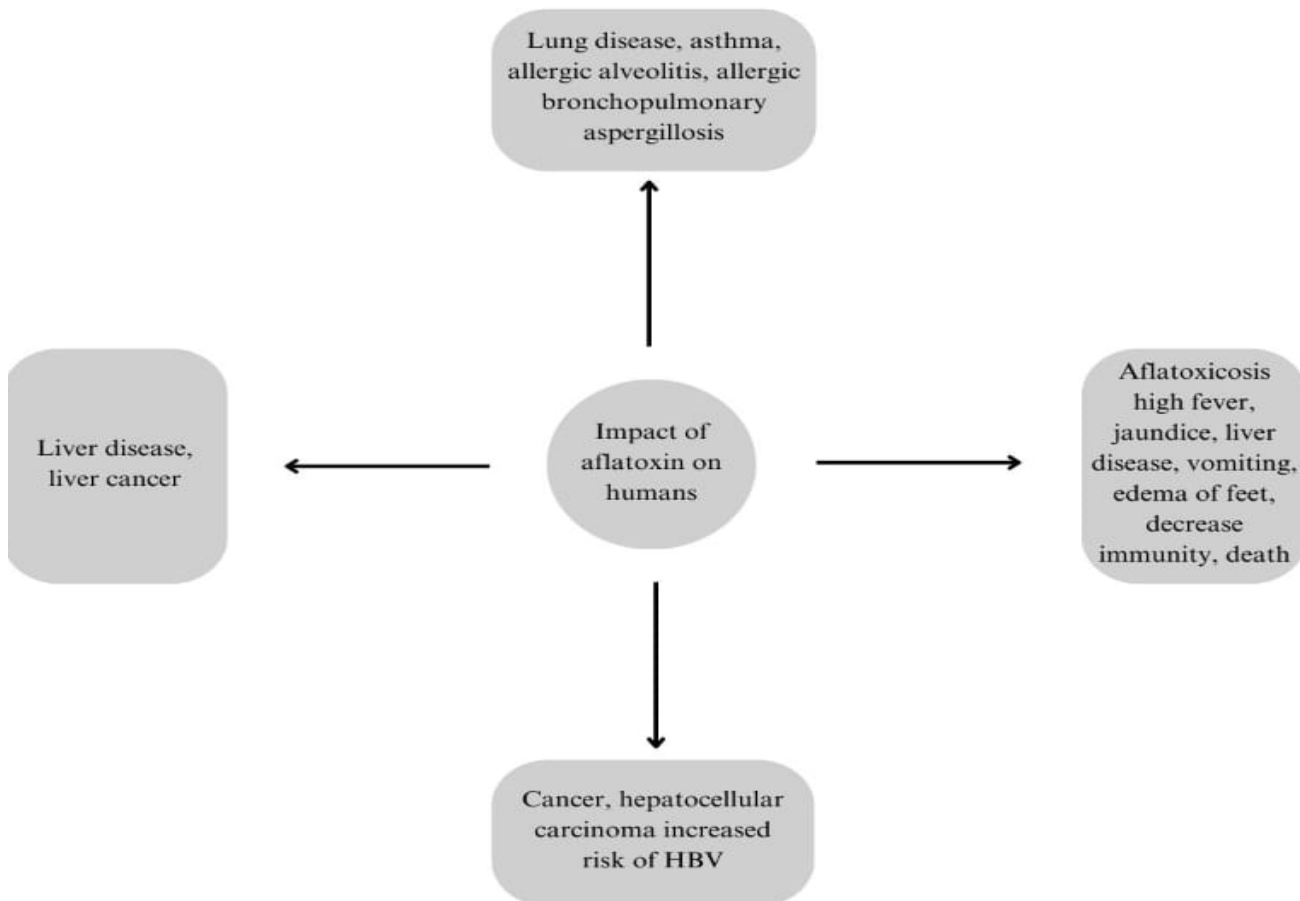


Figure 1. Schematic representation of health associated risk on humans upon the exposure of AF.

Controlling strategies for aflatoxin Contamination

Aflatoxin regulation is considered detrimental due to its effects on humans and animals worldwide. Various control strategies have been developed for the mitigation of AF. The strategies, which include chemical, physical, and biological management, are employed globally for the mitigation of AF and are discussed here.

Chemical Control

It has been demonstrated that certain chemicals and gases are used in the control of AF. These chemicals and gases, including citric acid, lactic acid, hydrochloric acid, and certain organic and inorganic acids, show a positive outcome in the chemical analysis of AF (52) (53). Chemicals such as calcium hydroxide, sodium bisulfate, and sodium borate were found to be effective in AF control (54). Sodium bisulfate has different AF control rates depending on the methods used to control the AF (54). For example, at 25 °C, the control rate is 28% and 65% when applying 0.2% H₂O₂ 10 minutes before sodium bisulfite. Citric acid was found to be effective in the detoxification of AF as compared to the other methods (55). During cooking under pressure with sodium chloride and citric acid, the amount of AF was considerably decreased than during frying. Additionally, using a variety of salts, acids, and alkaline materials during treatment can reduce AF contamination by up to 18–51% (52).

Ozone and chitosan nanoparticles have also been successfully used in several experiments to lower AF concentrations (55). However, the use of ozonation in reducing AF may be restricted due to its expensive cost (56). Adsorbents are another chemical control method for lowering AF. This technique can use a variety of adsorbents, such as zeolites, activated charcoal, complex carbohydrates like cellulose and polysaccharides, and active carbon (57). Consequently, the adsorbents adhere to the toxins, preventing them from combining with the blood and ultimately leading to their removal from the body (58).

Physical control

Preventative measures have been implemented to reduce AF contamination. Different physical techniques, including heat inactivation, thermal treatment, irradiation, and mechanical sorting, can be used to limit AF contamination in a variety of food items (52). Steam heat, dry roasting, washing, boiling, and cooking techniques are effective in minimizing AF contamination in various crops (59). For example, dry fruit decontaminated through heat has been successfully used to remove AF (60).

When a fungus is exposed to UV radiation and ionization, its cell walls break, causing a decrease in sprouting, which inhibits the growth of fungus, reduces the amount of AF in food, and increases the lifespan of the food (61). Depending on the product being treated and the type of heat treatment used (62), AF concentrations can be lowered by 9% to 100%. While autoclaving peanuts at 1.5 atm for 90 minutes can reduce AF content by up to 100%, autoclaving nuts at 120°C for 30 minutes reduce AF content by 9–39%. Gamma irradiation at 10 kGy reduced significant AF in soybean (63). Non-thermal treatments like cold plasma are used to break down AF up to 95%. The use of radiation in conjunction with a detoxifying enzyme has been reported to achieve up to 97% AF decontamination (64). Various other methods exist, like treating AF with an adsorbent that detoxifies them. Adsorbents can extend food shelf life by reducing the synthesis of AF (65). Using sorbents, clays, and activated carbons to treat food can help achieve the detoxification of AF like B and G.

Biological control of aflatoxin contamination

Biological control lowers AF by using biopesticides made up of atoxigenic strains that cannot make AF. Utilizing various fungal and bacterial isolates can also aid in the control of AF.

Comparison of Atoxigenic and toxigenic strains of *aspergillus*

Different biological techniques are implemented for controlling AF in pre- and post-harvest agricultural practices. By identifying a naturally atoxigenic strain of *Aspergillus* through single-spore isolation, we can control the toxigenic strains through competitive exclusion (16). In countries where maize is produced, atoxigenic strains of *A. flavus* have been used as a biological control to minimize the production of AF, depending on the competitive relationship between the toxigenic strains and atoxigenic strains (66). This method effectively decreased the AF in maize by about 50–85%. There is a lot of difference between the morphology of toxigenic strains and atoxigenic strains due to genetic variation (67). By using atoxigenic strains, we can effectively manage AF contamination in storage conditions. Cotty and Bayman initially applied atoxigenic *Aspergillus* strains against toxigenic strains a practice that has since spread globally to control AF (68) (69).

Table 2: Registered aflatoxin biopesticides along with countries where they are used

S. No	Product/Strain Name	Country	References
1.	AF36	U.S	(70)
2.	Afla-Guard(strain NRRL21882)	U.S	(71)
3.	AF-X1	Italy	(72)
4.	Aflasafe SN1	Senegal & the Gambia	(73)
5.	Aflasafe GH01	Ghana	(74)
6.	Aflasafe	Nigeria	(75)
7.	Aflasafe KE01	Kenya	(75)
8.	Aflasafe BF01	Burkina Faso	(76)
9.	Aflasafe TZ01	Tanzania	(77)
10.	Aflasafe ZM01	Zambia	(77)
11.	Aflasafe MW01	Malawi	(77)
12.	Aflasafe MZ01	Mozambique	(77)

For controlling the toxigenic strains, a high ratio of atoxigenic to toxigenic strains in the field is required (78). Furthermore, the use of atoxigenic biopesticides does not increase the quantity of *A. flavus* (79). Biopesticides (atoxigenic strains) delete a gene or genes involved in the AF production pathway, preventing them from producing AF. The AF36 strain stops manufacturing AF due to a single nucleotide polymorphism (SNP) that initiates a stop codon in the aflC (pksA) gene (80) (81). This stop codon is involved in the polyketide pathway of AF synthesis. The biopesticides also stop the growth of harmful fungi, which lowers AF by competing with harmful strains in the field (82).

It is necessary to isolate the atoxigenic strains to evaluate their stability, adaptability, and effectiveness in various environmental conditions before using them as biocontrol agents. For this reason, we assess large deletions in the AF gene clusters found in potentially toxic strains. This AF gene cluster, which consists of 32 different genes, is located on chromosome III of the genome. These genes contribute to the production of AF (24). AF36 is the first biocontrol agent for AF contamination in cottonseed that was identified in the USA, and Arizona (83). This biocontrol agent demonstrated effectiveness against AF producing toxic strains of *A. flavus* in maize. Field tests have shown that atoxigenic strains reduce AF formation in cotton and peanuts by 70% to 90% (84).

Researchers have discovered that other strains like *A. flavus* strain NRRL21882 and *A. parasiticus* strain NRRL21369, when used in field settings, are highly efficient against AF contamination in peanuts during both the pre-harvest and post-harvest stages (85).

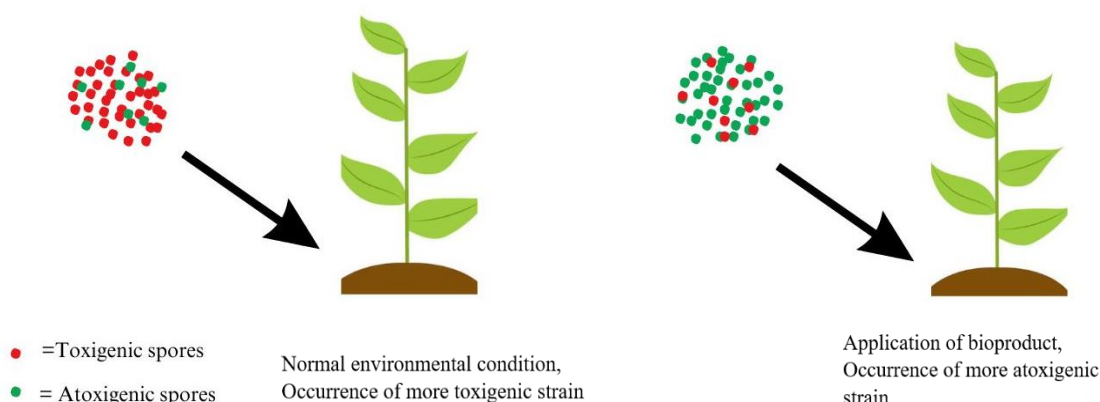


Figure 2. Schematic representation of the application of biocontrol. The ratio of toxicogenic strains is higher than the atoxicogenic strains (left side) Application of biopesticides decreases the toxicogenic strains (right side).

Many fungus species, such as *Trichoderma spp.* are useful biocontrol agents (86). It has been shown that the most effective *Trichoderma spp.* against AF are *T. harzianum* and *T. viridae*, with an inhibition rate of above 80% (87). Additionally, it was noted that *Trichoderma spp.* effectively decreased AF contamination in sweet corn and groundnuts by up to 65% and 57%, respectively (88). A protein produced by *Penicillium* species *P. chrysogenum* strain RP42C inhibits the development of harmful *Aspergillus* strains (89). *P. nalgiovense* is also thought to be a common biocontrol agent against a range of plants and dangerous fungus (90)

CONCLUSION

Fungi produce different types of AF. AF production by some *Aspergillus species*, such as *A. flavus* and *A. parasiticus*, results in secondary metabolites that are toxic and carcinogenic to both humans and animals. The contaminated crops cause serious problems when consumed by livestock and human beings. A hot and humid environment is a significant problem that produces AF, which cause cancer, asthma, liver failure, hepatic cell carcinoma, and even skin and liver cancer. One way to reduce AF in crops using biocontrol agents is through biological control products. Globally, researchers have also employed a variety of management techniques to control these AF. This review article provides an updated literature study about AF contamination and helps researchers devise a plan for mitigating strategies to control AF.

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