

Type of Article- Review article

Title- The characteristic, occurrence of Aflatoxin and associated risk with human health

Abstract

Aflatoxins are toxins produced by the fungus *Aspergillus parasiticus* and *Aspergillus flavus*. They are colorless, cannot be detected under normal light, they are odorless and contaminated foods most often do not have any special or bad smell. Environmental factors such as the temperature, vectors causing grain damage have an important effect on favoring the colonization of fungus and production of aflatoxins. They contaminate agriculture products worldwide affecting their quality, safety & security. The effects on safety & security cause health threats among people and animals on their long term exposure through consumption because they are mutagenic, teratogenic, genotoxic, and carcinogenic. Humans and animals can develop the disease known as aflatoxicosis as a result of aflatoxins known as Acute and Chronic primary aflatoxicosis. Aflatoxins' long-term effects have been shown to decrease normal immune response also it can cause growth retardation in babies and effect nutritional deficiency. It can disrupt such enzymes who can affect hormones, endocrine glands, neurotransmitter which may influence a person's cognitive abilities, memory, and learning, restlessness, muscular tremors, seizures, absentmindedness, tremor, uncoordinated movement of muscle and aberrant agitation are caused by deficiencies in the neurotransmitters. Aflatoxin toxicity in humans can range from acute or chronic conditions to liver damage such as liver carcinoma, internal bleeding, edema, and instant deaths. Acute toxicosis can cause gastrointestinal dysfunctions in human and animal. Aflatoxins have been shown to have detrimental negative impacts on the vascular fragility and cardiovascular health, tissue bleeding, and teratogenic consequences. According to reports, aflatoxins have severe and detrimental impacts mostly on respiratory systems it can also cause lung cancer.

Key words: Aflatoxicosis, food security & safety, Fungi, One health.

Background

Aflatoxins are toxins biosynthesized by fungi *Aspergillus parasiticus* and *Aspergillus flavus*. Which are abundant in nature hence lying in the category of mycotoxins. The name aflatoxins were derived from a combination of Afla and toxins where 'A' in afla stand for **Aspergillus** & 'fla' stand for **flavus** [1]. Chemically, aflatoxins are derivatives of difurano coumarins possessing a pentanone ring joined to the coumarin nucleus by a bifuran group. [2]. Aflatoxins were first discovered in England during the 1960's when an estimate of 100,000 turkeys died after they had been fed with feeds contaminated with the fungi *Aspergillus flavus*. Environmental factors have a significant impact on aflatoxin contamination. [3]. An increase in temperature by every 2°C in **European nations proved to raise the risk of aflatoxin production in cereals and their probability of contamination of cereals such as maize is likely to keep increasing for the next thirty years due to ideal meteorological circumstances** [4,5]. Fungi colonization on the agriculture products the initial point through which aflatoxins enter the chain are favored by their nature (grain damage), moisture and the environment temperatures **figure 1**. Fungi grow in areas with temperature range of 12-48°C producing aflatoxins at a 25-37 °C temperature range, together with moisture content is of 80-85 percent [6, 7].

During this temperature range, the agriculture produces are experiencing a high rate of respiration. With one of the outcomes being water vapor, will lead to an increase in the moisture content providing the favorable environment for fungi colonization and synthesis of aflatoxins when it increases beyond 14%. The temperature range also favors the expression of genes by the fungi for the production of aflatoxins.

In countries, where agriculture production is very high, the environmental temperatures lay between 40°N and 40°S of the equator the range with which fungus development and aflatoxin formation is favored hence exposing the environment and its components to aflatoxins effects.

Types of aflatoxins

Aflatoxins are belongs to a difuranocoumarins group and categorized into difurocoumarocyclopentenone and difurocoumarolactone group as per their chemical structure summarized in table 1. Aflatoxins are of different types however, only four are major ones aflatoxins AFB₁, AFB₂, AFG₁ & AFG₂ **figure 2**. Aflatoxins B1 & B2 are hydroxylated when

consumed by animals to M1 {AFM₁} & M2{AFM₂} respectively [8]. AFB₁ and AFB₂ are found in crops and or their products whereas AFM₁ and AFM₂ are found in animals by-products. AFB₁ & AFB₂ are synthesized by the fungi *Aspergillus flavus* whereas AFG₁ & AFG₂ are synthesized by the fungi *Aspergillus parasiticus*.

B & G stand for the blue fluorescent and green bright colour created on the chromatographic plates when under UV light whereas the numbers 1 & 2 indicate major and minor compounds. B is produced by the flavus species and G by the parasiticus species.

Characteristics of aflatoxins

Aflatoxins are colorless and cannot be detected under normal light and can be made visible under UV light (basic detection method), they are odorless and contaminated food most often does not have any special or bad smell. Sometimes grains can smell moldy due to fungal contamination, when moisture content of the contaminated produce is still high.

They are insoluble in water, solubility in solvent polarity like chloroform and methane, they are unstable in extreme pH (<3 or >10).

Aspergillus flavus fungi are green and have the ability to multiply its population under stressing conditions. Penetration and colonization of fungi in crops is also supplemented by the injuries caused by vectors such as insects and nematode [9].

They decompose at temperatures of 237-306⁰C hence do not decompose quickly. [10]. Therefore, limiting the consequences of aflatoxin requires either stopping the development of the fungi or detoxifying contaminated feeds and meals. [11].

The prevalence of aflatoxin contamination in agricultural products

Contamination of food and feeds with aflatoxins worldwide presents major food and feed safety issues in areas of the world where humidity is high and temperatures are warm which encourage fungi growth **figure 3**. Fungi colonization and contamination usually happen during the pre-harvesting, harvesting and post-harvesting sessions leading to synthesis of aflatoxins.

According to FAO, more than 25 percent of total of the global agriculture commodities are contaminated by aflatoxins resulting into health issues when consumed. Aflatoxin contamination

also results in loss of market value[12].Mycotoxin contamination in theSub-Saharan Africaamong agriculture products is a great threat to health where more than250,000 deaths occurring annually are hepatocellular carcinoma-related resulting from aflatoxin contaminationalone. [13]

In country like Uganda more than 60% of the population carries out farming in which mycotoxins remain a scourge a previously unheard-of continue to decrease in the economic and dietary benefit of agriculture products [14]. The economic growth of many developing countries like Uganda greatly depend on trading of agriculture products and due to the poorly equipped pre-harvesting, during harvesting and post-harvesting handling by farmers and the favoring environment conditions leads to increase in aflatoxins contamination hence high levels beyond the acceptable quantities[15].

According to WHO, in Africa, the aflatoxins burden accounts for about 40% of daily disease. In 1974, there was an outbreak of Hepatitis in India due to aflatoxins which were found in their staple food maize. In Kenya, there are reported cases of disease outbreaks due to consumption of maize a staple food which also is a source of animal feeds contaminated with aflatoxins. In 2013, countries in Europe reported contamination of milk with aflatoxin, which was acquired by the animals through the feeds. Many countries cross check the level of aflatoxins levels in imported products to avoid till ill effect on their population.

Risk associated with Aflatoxins

Aflatoxins are toxins (poisonous substances) produced within cells of organisms. They are thus among the most toxic chemicals that have an impact on how plants, animals, and people are physiologic. This is referred to as aflatoxicosis hence a One Health concern.

Recognizing the connections between people, animals, plants, and their common environment, One Health is a coordinated, multisector, and transdisciplinary strategy working to achieve optimal health outcomes.Aflatoxins affectfood safety &security one of the issues One Health programfocuses on rectifying.

This causes health threats among people and animals on their long term exposure through consumption because of their nature of its carcinogenic, mutagenic, teratogenic, and genotoxic effectsdemonstrated in figure 4[16, 17].All vertebrate species are susceptible to aflatoxicosis with animals being more susceptible at a lower aflatoxin concentration as compared to People[6].The

aflatoxins in occurrence of feeds & foods of animals result into a decline in productivity (of meat, eggs & milk), reduction in weight gain and an increase in disease incidences due to their immunosuppression abilities and the damage to vital organs. [18]

On consumption of agriculture products contaminated with aflatoxins by both animals and humans, health issues arise. When animals feeding on agriculture produces are eaten or their products eaten by humans, these aflatoxins will be expressed in different tissues ending up in human bodies thus being hazardous.

Aflatoxins in humans affect the liver, kidneys, cause spleen enlargement, decrease protein & fats digestion as well as absorption, cause impaired carbohydrate breakdown, cause reduced sperm count & infertility, birth defects, higher incidence of cancer, decreased resistance & increased susceptibility to infections.

Chemical and biological effects of aflatoxins

Aside from work related to structure elucidation, little systematic research has been carried out to find out the behavior & reactivity of aflatoxins, and the agriculture products when treated with chemicals.

Aflatoxin B₁ undergoes catalytic hydrogenation, which results in the adoption of 3 moles of hydrogen and the formation of a tetra hydro deoxy derivative. When the hydrogenation process is interrupted after 1 mole of hydrogen is taken up, aflatoxin B₂ is produced in a quantifiable quantity. [19].

Aflatoxins can contaminate various agriculture products such as maize, g. nuts, barley, wheat, rice, sorghum, millet, soybeans, cassava, oilseeds, fruits, eggs, meat, animal feeds and milk. [20, 21]

Aflatoxins enter the food and any step in the feed chain, from pre-harvest through consumption [22, 23] causing many reactions within the cells. When the fungi colonize the plants in presence of favorable conditions, aflatoxins are produced which compromise the self-defense & growth of the plants, contaminate the crop seeds affecting the quality of the yield. [9].

Once produced within cells, aflatoxins cause programmed cell death (apoptosis), inhibits nucleic acid synthesis leading to a decrease in protein synthesis hence stunt growth; mutations hence, affects the cell membrane stability leading to cell damage.

Effect of Aflatoxins on health

A collection of naturally produced carcinogens known as aflatoxins is recognized to contaminate various foods used by both humans and animals, [24]. Food products that have aflatoxins are a prevalent issue in the tropics and subtropics regions all over the worldwide, particularly being developed nations with subpar sanitation systems and environments where fungi grow in environments with high humidity and warm temperatures. [25]. Humans and animals can develop the disease known as aflatoxicosis as a result of aflatoxins. (I) Acute primary aflatoxicosis, which is one of its two main manifestations, is caused when moderate to high quantities of aflatoxins are eaten demonstrated in figure 5. Hemorrhage, abrupt liver injury, edema, changes in digestion, food absorption, and metabolism are just a few of the symptoms of certain acute illness episodes that may occur [26]. (II) Consumption of Aflatoxin exposure in low to moderate amounts results in chronic primary aflatoxicosis. The impacts are typically subtle and difficult to spot. Some of the typical symptoms include poor food conversion and slower development rates, whether or not an overt aflatoxin illnesses has developed [27].

Aflatoxins' long-term effects have been shown to decrease normal immune responses by either lowering T cell or phagocytic activity quantity or functions, as seen in animal models of the disease. In a dosage response association between aflatoxins and growth rate in babies and children, aflatoxins have also been documented to affect nutrition [28]. In animal studies, aflatoxins also modify nutrients like vitamin A or D, rendering them inaccessible to the body's normal physiology and resulting in nutritional deficits [29]. Aflatoxins are harmful to prenatal exposure as well, as through breast milk; they are transferred from mother to child. It has been discovered that AFB, in particular, interferes with the enzymes and substrates required for the production of several hormones, causing the various endocrine glands to malfunction [30].

Aflatoxin toxicity in human can range from chronic or acute liver damage conditions as liver carcinoma, internal bleeding, edema, and instant deaths. [31]. AFB1, AFB2, and AFM were absorbed into the liver, bile duct, spleen, heart, muscle, and kidney. Mutation, cancer, immunodeficiency, lung damage, and birth abnormalities are all caused by these additional reactions [32]. Animals exposed to low dietary amounts of aflatoxins have immune suppression, reduced reproduction, liver damage, and decreased milk supply. In addition to fatty livers, and kidneys as well as cerebral edema and heart involvement, the symptom of aflatoxicosis in animal life may also be defined by nausea, stomach cramps, pulmonary embolism, coma, loss of

consciousness and death. [33]. Acute toxicosis can cause gastrointestinal dysfunctions like ascites, intense pain, stomach cramps, bleeding in diarrhea, reduced feed intake, visual loss, circling, ear trembling, , frothing at the lips, cumulative damage, and deaths in dairy and beef cattle, Other symptoms include tiredness, weight loss, depression, and sharp decreases in milk production weight loss, bleeding, [34].

The mitochondrial DNA, composition and purpose of oxidative phosphorylation in brain cells are also abnormally affected by aflatoxins [35].

Acute treatment with AFB1 decreases regional brain acetyl cholinesterase enzymes, which may influence a person's cognitive abilities, memory, and learning. Dopamine, serotonin, and the precursor's tyrosine and tryptophan levels are all affected by aflatoxin.

Neurological symptoms such as neurocognitive deterioration, altered sleep patterns, and brain damage indicators including dullness and uneasiness, muscular tremors, seizures, memory loss, seizure disorders, loss of motor control, and abnormal feelings are caused by deficiencies in these neurotransmitters [36]. Aflatoxins have been shown to have detrimental negative impacts on the vascular fragility and cardiovascular health, tissue bleeding, and teratogenic consequences [37]. According to reports, aflatoxins have severe and detrimental impacts, mostly on respiratory systems. Also, one organ system with essential functioning components in continuous and direct interface with the environment is the respiratory system. Many people who work in the food industry are exposed to aflatoxins, particularly AFB1. These individuals have been linked to higher rates of the upper respiratory tract and lung cancer [38]. Higher levels of aflatoxins have reportedly been found in the sperm cells of infertile men in people who have regularly consumed meals infected with the toxin. [39].

Liver cancer (HCC)

AFB1 was classified as a Group 1 carcinogen in 2002 because it causes the creation of DNA adducts that aid in the development of liver cancer [40]. According to research, AFB1 is a significant cause of hepatocarcinoma, with 4.6–28.2% of hepatocellular carcinoma (HCC) cases worldwide being linked to AFB1 exposure [41]. In addition, those exposed to AFB1 have a 30-fold increased risk of developing HCC if they have Hepatitis B virus (HBV) [42]. Acute hepatitis is brought on by high exposure levels, and liver cancer is then brought on by long-term exposure [43]. The genotoxic effects of AFB1, on the other hand, are still unknown. Recently, some authors

treated the human HL7702 hepatic cells with Microcystin-LR (MC-LR) and AFB1 and showed that MC-LR and AFB1 co-exposure: (i) induced DNA damage; and (ii) increased the activity of Superoxide Dismutase and Catalase, the levels of glutathione, and the expression of APE. The link between AFB1 exposure and liver cancer is undeniable, so researchers are looking at how to create a diagnostic tool for early recognition of the consequences of AFB1 [44].

Moreover, liver tissues and blood from F344 rats exposed to AFB1 for 4 weeks were used to examine the impact of AFB1 on miRNA expression during the start phase of carcinogenesis. In both liver tissues and blood, these findings showed that AFB1 up-regulated miR-122-5p, 34a-5p, and 181c-3p more than controls, indicating that epigenetic modifications were brought about by AFB1 during the first stage of carcinogenesis [45]. Epigenetic processes are generally dysregulated in HCC patients following exposure to AFB1. Human hepatocytes actually exhibited six up-regulated and hypomethylated genes after AFB1 exposure, including Cyclin K (CCNK), Diaphanous Related Formin 3 (DIAPH3), Histone Cluster 1 H2B Family Member f (HIST1H2BF), RAS Oncogene 27A (RAB27A), Proliferating Cell Nuclear Antigen (PCNA), and Thioredoxin Reductase 1 (TXNRD1), which can be used as early markers [46].

Lung cancer

Workers who are exposed to pulmonary AFB1 exposure from grain dusts are at risk of developing lung cancer [47]. As a result, AFB1 is classified as a pulmonary carcinogen, and several epidemiological studies have concentrated on the link between AFB1 and lung malignancies. Some authors looked on the AFB1 detoxification in lobectomy patients' lung tissues in 1996. Their research proved that lung cytosols produced a DNA-binding metabolite as a result of being exposed to AFB1. Its cytosolic activation can increase human lung susceptibility to AFB1 and is strictly associated with the activities of PGH synthase (PHS) and lipoxygenase (LOX) [48].

AFB1 can also cause oxidative DNA damage and lesions known as 8-oxo-7,8-dihydro-20-deoxyguanosine (8-oxodG) that can be fixed with the treatment of 8-oxoguanine glycosylase (OGG1). As a result, some researchers investigated the impact of OGG1 deficiency on cancer and oxidatively damaged DNA caused by AFB1. One dose of either DMSO or AFB1 was administered to OGG1 null mice. OGG1 null mice treated with AFB1 lost weight and died, even though the incidence of lung cancer did not rise. The K-ras mutation pattern in lung tumour DNA was not consistent with AFB1-initiation. As a result, OGG1 status had no discernible impact on the DNA damage or tumorigenesis caused by AFB1, however the deletion of OGG1 alleles led to

an increase in sensitivity to additional AFB1 toxicity-related effects [49]. The effects of AFB1 on Src kinase and insulin receptor substrate (IRS) in lung cancer cells have recently been assessed, and cell migration was observed. After AFB1 therapy, the lung cancer cell lines A549 and SPCA-1 underwent a Western blot examination to assess IRS expression and Src, Akt, and ERK phosphorylation. According to these research, AFB1: (i) up-regulates IRS1 and IRS2; (ii) increases Src, Akt, and ERK1/2 activation; and (iii) stimulates lung cancer cell migration, which is blocked by saracatinib [50].

Gastrointestinal cancer (GIC)

Numerous research have examined the relationship between aflatoxins and the digestive system because, after exposure through contaminated food, the digestive system typically serves as the first line of defence against carcinogens. Harrison et al. hypothesised in 1993 that even in affluent nations, exposure to human aflatoxin could pose a risk to organs other than the liver. The authors looked for an AFB1-DNA adduct by analysing normal and tumour samples from various organs (colon, rectum, breast, cervix, and liver) to support this claim. It's interesting to note that every sample tested positive, and colorectal tumour tissue in particular displayed a greater adduct concentration than normal tissues from the same patients [51].

The effects of AFB1 alone and in combination with other mycotoxins were assessed in Caco-2 cells. AFB1 was the third most cytotoxic mycotoxin that was evaluated, with a cytotoxic effect at a concentration of 19.28 M [52]. To confirm its impact on genotoxicity and DNA damage, AFB1 (3-5 M) was applied to HCT116 colorectal cancer cells in a different investigation. According to this study, AFB1 treatment: (i) slightly increased H2AX phosphorylation in HCT116 cells by inducing an ATM response; (ii) did not activate P53, CHK1 or CHK2, and (iii) did not block the G1 phase of the cell cycle [53]. Authors in 2016 confirmed that AFB1 exposure causes MDM2 up-expression, a p53 negative modulator, in murine intestinal cancer cells [54].

Conclusion

Information on the contamination and colonization of fungi and the negative impacts associated with it through production of aflatoxins in agriculture products and most of the developing countries are still lacking due to lack of public awareness on their effects on the quality of agriculture products and their potential hazardous effects on human and animals health. Therefore focusing on the increasing public awareness on what aflatoxins and their effects on agriculture, health and economic growth is required.

In addition, target genes altered by AFB1 and AFM1 in light of the paucity of evidence indicating whether genes, proteins, or miRNAs might be employed as damage markers owing to exposure. According to the network analysis, the thirteen proteins (CYP3A4, TP53, GSMT1, MDM2, CAT, OGG1, IRS1, IRS2, SRC, AKT1, MAPK1, MAPK3 and PDK1) that are regulated by AFM1/AFB1 are connected to one another both directly and indirectly through nodes like NR1H2 and GNMT. However, the research of miRNA prediction has shown that there are twelve miRNAs that can specifically target the genes that are known to be affected by AFM1.

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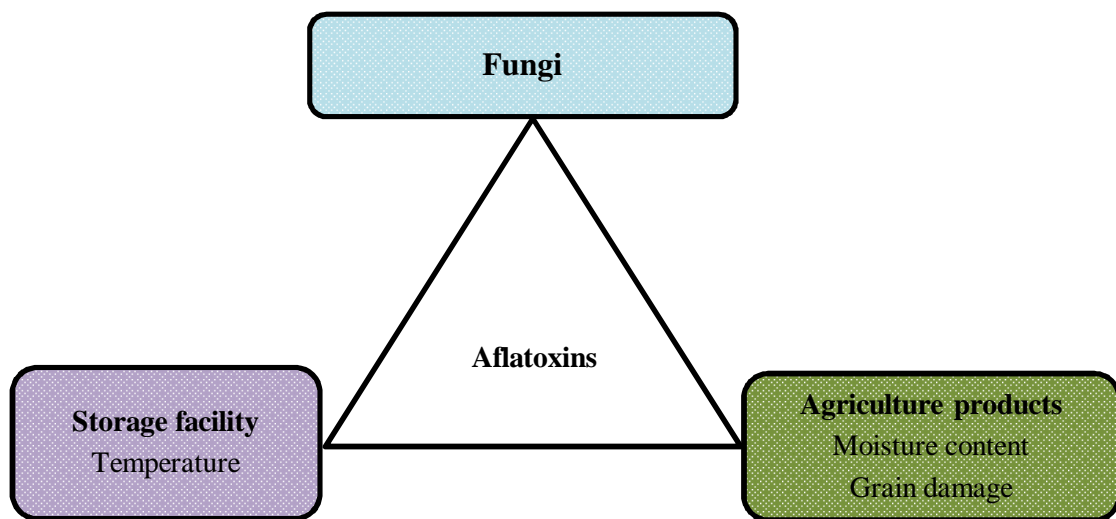


Figure 1: Cycle for synthesis of aflatoxins

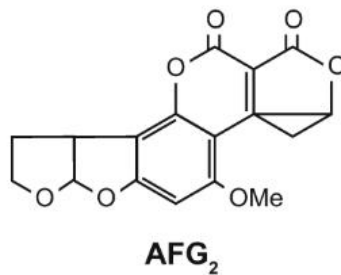
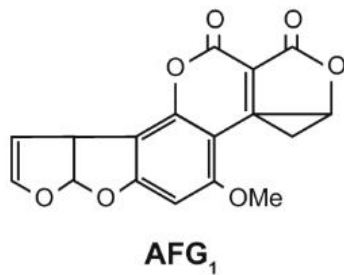
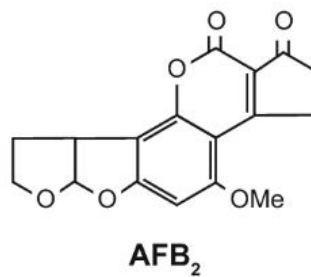
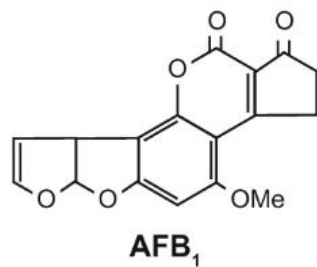


Figure 2: Structures for the types of aflatoxins

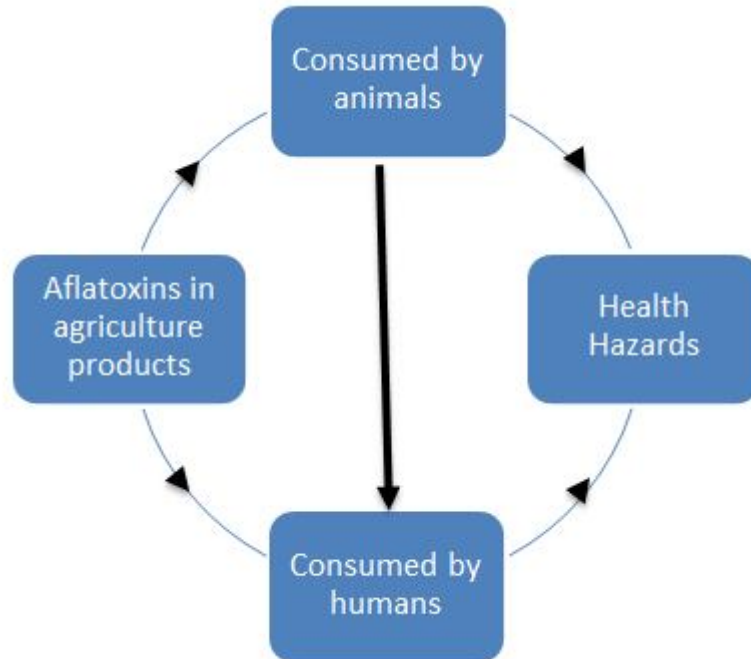


Figure 3: Aflatoxins flow along the feeding cycle leading to health

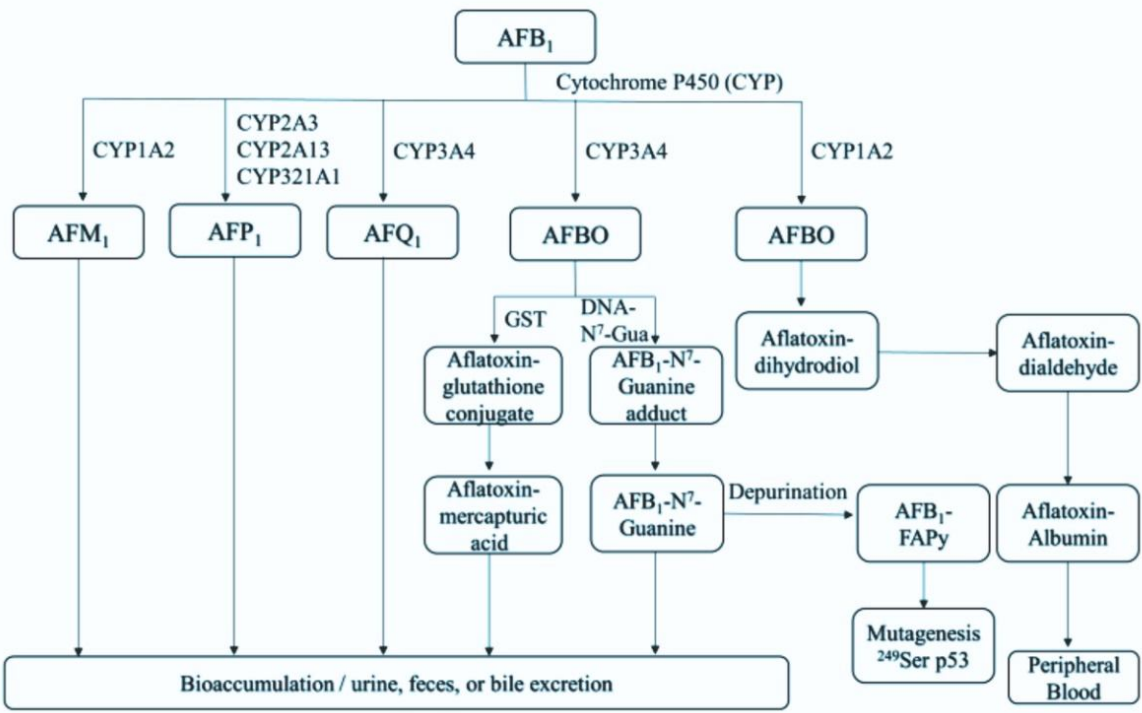


Figure 4: Overview of AFB1 metabolism and excretion in humans and animals.

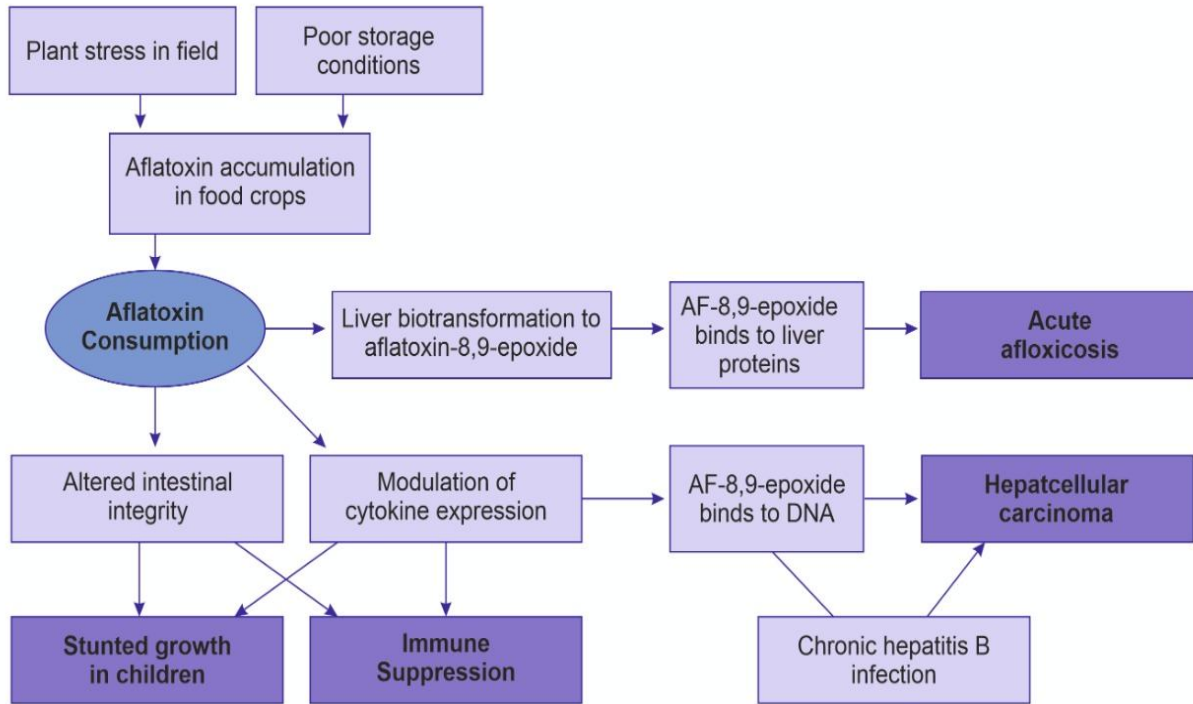


Figure 5: Aflatoxins disease pathway in humans

S. No.	Name of Toxin	Group	Species
1	Aflatoxin B1	Difurocoumarocyclopenten	<i>A. flavus</i>

	(AFB1)	one series	<i>A. arachidicola</i>
			<i>A. bombycis</i>
			<i>A. minisclerotigenes</i>
			<i>A. nomius</i>
			<i>A. ochraceoroseus</i>
			<i>A. parasiticus</i>
			<i>A. pseudotamarii</i>
			<i>A. rambellii</i>
			<i>Emericella venezuelensis</i>
			<i>A. arachidicola</i>
2	Aflatoxin B2 (AFB2)		<i>A. flavus</i>
			<i>A. minisclerotigenes</i>
			<i>A. nomius</i>
			<i>A. parasiticus</i>
3	Aflatoxin B2a (AFB2a)		<i>A. flavus</i>
			<i>A. flavus</i>
			<i>A. parasiticus</i>
4	Aflatoxin M1 (AFM1)		Metabolite of aflatoxin B1 in humans and animals and comes from a mother's milk
5	Aflatoxin M2 (AFM2)		Metabolite of aflatoxin B2 in milk of cattle fed on contaminated foods
6	Aflatoxin M2A (AFM2A)		Metabolite of AFM2
7	Aflatoxicol (AFL)		<i>A. flavus</i>
			Metabolite of AFB1

8	Aflatoxinol M1		Metabolite of AFM1
1	Aflatoxin G1 (AFG1)	Difurocoumarolactone series	<i>A. arachidicola</i>
			<i>A. flavus</i>
			<i>A. minisclerotigenes</i>
			<i>A. nomius</i>
2	Aflatoxin G2 (AFG2)		<i>A. parasiticus</i>
			<i>A. arachidicola</i>
			<i>A. flavus</i>
			<i>A. minisclerotigenes</i>
3	Aflatoxin G2A (AFG2A)		<i>A. nomius</i>
			<i>A. parasiticus</i>
4	Aflatoxin GM1 (AFG1)		Metabolite of AFG2
5	Aflatoxin GM2 (AFGM2)	<i>A. flavus</i>	
6	AFGM2A	Metabolite of AFG2	
7	Aflatoxin B3 (AFB3)	Metabolite of AFGM2	
8	Parasiticol (P)	Transformation of AFG1	
9	Aflatrem	<i>A. flavus</i>	
		<i>A. minisclerotigenes</i>	
10	Aspertoxin	<i>A. flavus</i>	
11	Aflatoxin Q1 (AFQ1)	Major metabolite of AFB1 in in vitro liver preparations of other higher vertebrates	

Table 1: List of the major aflatoxins produced by **Aspergillus** species.