Aflatoxins – ~~A Faux Pas to GlobalHealth~~ A Faux Pas to Global Health

Abstract

Aflatoxinsare toxins produced mainly by the fungus *Aspergillus parasiticus* and *Aspergilus flavus*.~~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,vectorscausing grain damagehave an important effect on favoring the colonization of fungus and production of aflatoxins.They contaminateagriculture 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 poisoning known asAcute and Chronic primary aflatoxicosis. Aflatoxins' long-term effects have been shown to decrease normal immune response,~~also it can~~ causes stunting~~growth retardation~~ in children ~~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 conditionsto 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.

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Background

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]. 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 possessinga 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^{o}C in European nations proved to raise the risk of aflatoxinproduction in cerealsand their probability of contamination of cereals such as maize is likely tokeep 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 **figure1**. Fungi grow in areas with temperature range of 12-48^{O}C producing aflatoxins at a 25-37 ^{O}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^{o}N and 40^{o}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.

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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 aflatoxinsAFB_1, AFB_2, AFG_1&AFG_2**figure 2**. Aflatoxins B1& B2 are hydroxylated when consumed by animals to M1 {AFM_1}& M2{AFM_2}respectively [8]. AFB_1 and $AFB_2$are found in crops and or their products whereas AFM_1 and AFM_2 are found in animals by-products. AFB_1& AFB_2 are synthesized by the fungi *Aspergillus flavus* whereas AFG_1& AFG_2 are synthesized by the fungi*Aspergillus parasiticus*.

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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.

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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 andhave 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 237-306^{0}C 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 happenduring the pre-harvesting, harvesting and post-harvesting sessions leading to synthesis of aflatoxins.

According to FAO, more than 25percent 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].Aflatoxin contamination in theSub-Saharan Africa among 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

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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 of what? because of their nature of its carcinogenic, mutagenic, teratogenic, and genotoxic effects demonstrated 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 intoa decline inproductivity (of meat, eggs & milk), reduction in weight gain and an increase in disease incidences due to their immunosuppression abilities and the damage to vitalorgans. [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 expressedin 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 3moles of hydrogen and the formation of a tetra hydro deoxy derivative. When the hydrogenation process is interrupted after 1mole of hydrogen is taken up, aflatoxin B_2 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

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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.

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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 exposure. (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].

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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

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discovered that AFB1, 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, pulmonicembolism, 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].

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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].

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.

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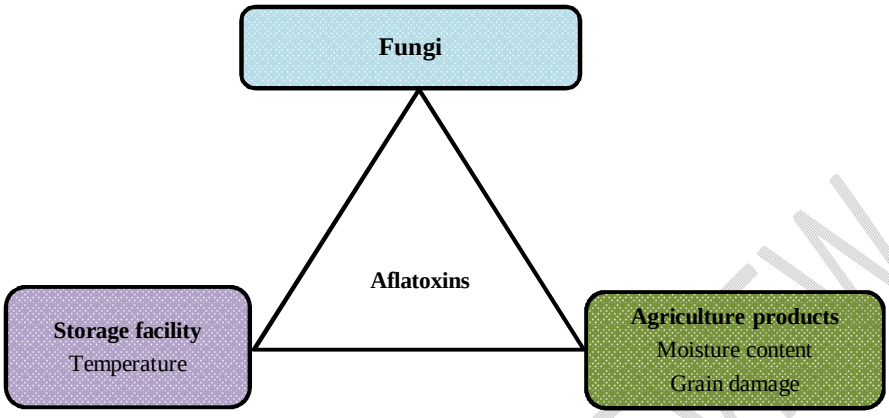

Figure 1: Cycle for synthesis of aflatoxins

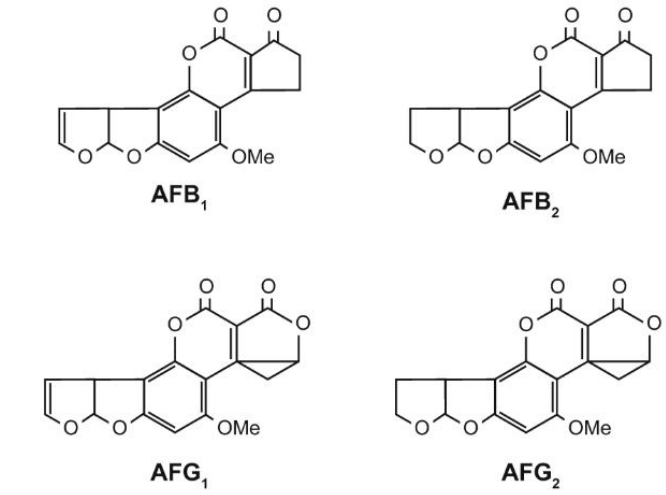

Figure 2: Structures for the types of aflatoxins

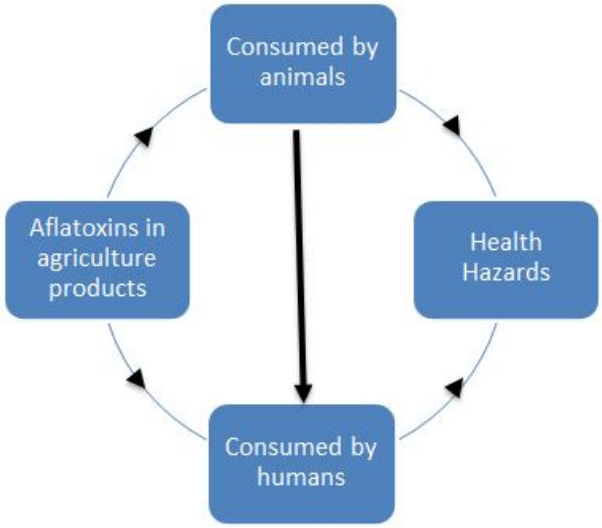

Figure 3: Aflatoxins flow along the feeding cycle leading to health

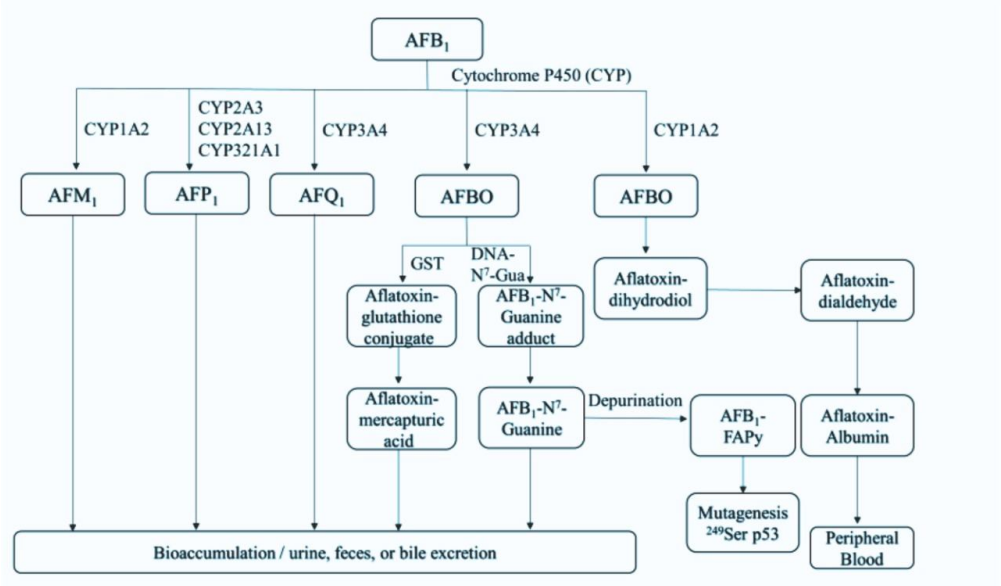

Figure 4: Overview of AFB1 metabolism and excretion in humans and animals.

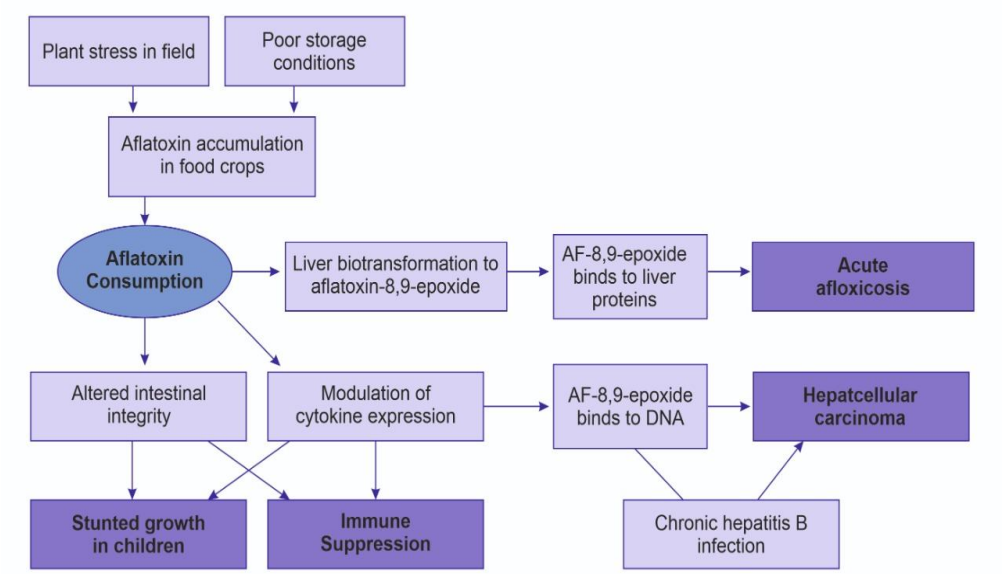

Figure 5: Aflatoxins disease pathway in humans

S. No.	Name of Toxin	Group	Species
1	Aflatoxin B1 (AFB1)	Difurocoumarocyclopentenone series	A. *flavus*
			A. *arachidicola*
			A. *bombycis*
			A. *minisclerotigenes*

			A. *nomius*
			A. *ochraceoroseus*
			A. *parasiticus*
			A. *pseudotamarii*
			A. *rambellii*
			Emericella *venezuelensis*
2	Aflatoxin B2 (AFB2)		A. *arachidicola*
			A. *flavus*
			A. *minisclerotigenes*
			A. *nomius*
			A. *parasiticus*
3	Aflatoxin B2a (AFB2a)		A. *flavus*
4	Aflatoxin M1 (AFM1)		A. *flavus*
			A. *parasiticus*
			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)		A. *flavus*
			Metabolite of AFB1
8	Aflatoxicol M1		Metabolite of AFM1
1	Aflatoxin G1 (AFG1)	Difurocoumarolactone	A. *arachidicola*

		series	A. *flavus*
			A. *minisclerotigenes*
			A. *nomius*
			A. *parasiticus*
2	Aflatoxin G2 (AFG2)		A. *arachidicola*
			A. *flavus*
			A. *minisclerotigenes*
			A. *nomius*
			A. *parasiticus*
3	Aflatoxin G2A (AFG2A)		Metabolite of AFG2
4	Aflatoxin GM1 (AFG1)		A. *flavus*
5	Aflatoxin GM2 (AFGM2)		Metabolite of AFG2
6	AFGM2A		Metabolite of AFGM2
7	Aflatoxin B3 (AFB3)		Transformation of AFG1
8	Parasiticol (P)		A. *flavus*
9	Aflatrem		A. *flavus*
			A. *minisclerotigenes*
10	Aspertoxin		A. *flavus*
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.