Abstract: This literature review focuses on the chemical compounds known as Aflatoxin. It contains an in-depth analysis about the many forms of the chemical and the effects they have on the health of both animals and humans. I plan to present my final project on the background of Aflatoxins and their role in the food humans consume daily. The final project will include graphs of our daily consumption of aflatoxins and approximately two additional case studies from human aflatoxin consumption in regards to hepatocellular carcinoma.

Disclaimer: The purpose of this writing is to fulfill course requirements for BBH 411W and to stand as a personal writing sample, but the findings should not be treated as generalizable research.
Analysis of Aflatoxins

Aflatoxins are a group of toxic chemical compounds derived from certain molds and food. They are of fungal origin including *Aspergillus flavus*, *A. parasiticus*, *A. nomius*, *A. pseudotamarii*, *A. bombycis*, *A. ochraceoroseus*, and *A. australias*. However, *A. flavus* and *A. parasiticus* are the cause for the majority of contaminated food stuff.\(^1\) There are six individual types of aflatoxins including Aflatoxin B\(_1\) (AfB\(_1\)), B\(_2\), G\(_1\), G\(_2\), M\(_1\), and M\(_2\). All six types have heterocyclic compounds that are highly oxygenated. Aflatoxin groups B and G are named from their exhibition of specific fluorescent colors under ultraviolet light and are the major types of aflatoxins. The B group exhibits blue fluorescence and the G group exhibits yellow-green fluorescence. The M group aflatoxins are found in the milk lactating animals that’ve been exposed to aflatoxins.\(^2\) While aflatoxins B\(_1\), G\(_1\), and M\(_1\) have been shown to cause cancers AfB\(_1\) is the only aflatoxin to be considered a true carcinogen as defined by the International Agency for Research on Cancer (IARC).

The occurrence of aflatoxins is common in both raw and processed foods. Corn, dairy products, cottonseed, peanuts and other nuts are often the foods with high risk for contamination. Corn appears to have the highest risk for aflatoxin contamination. Contamination to raw food can happen prior to crop harvest and postharvest. If drying of crops is delayed following harvest, a post-harvest infestation could occur that would allow fungus to contaminate the crops. In addition, mold growth during storage due to exceeding water limits could also result in an aflatoxin contamination.\(^3\) Humidity, temperature, and climate are major influences in aflatoxin

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contamination. Other routes of contamination may occur if aflatoxins contaminate animal feed. While most developed countries have developed regulations to monitor aflatoxin levels, the greatest risk for contamination is still present in developing countries especially those in tropical regions.4

In 1975 the aflatoxin B₁ was first recognized as a Group 1 carcinogenic by the IARC. Aflatoxin B₁ a naturally occurring potent chemical that is known to be statistically significant in causing liver hepatocellular carcinoma. Chronic exposure to low levels of aflatoxins, especially AfB₁, are highly associated with risks of developing hepatocellular carcinoma in both animals and humans.5 A study conducted by researchers Yan Liu and Felicia Wu collected data on a global level to determine the link between aflatoxin exposure and liver cancer in humans. It was discovered that aflatoxin may play a causative role in approximately 4.6-28.2% of liver cancer cases globally.6 The chemical mechanisms of the carcinogenic qualities of this fungus will be mentioned later in this paper.

Aflatoxin exposure tends to be very deadly for animals. Aflatoxicosis primarily leads to hepatic disease and causes severe liver damage. Before aflatoxin levels became government regulated a large amount of animals experienced death from aflatoxicosis. In 1960, more than 100,000 turkeys in England had died from Turkey “X” disease. As it turns out, the deaths were due to aflatoxicosis that occurred from contamination in feed from a brazilian peanut meal.7 During the 1960s in America fish also experienced high levels of aflatoxicosis due to

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contaminated feed. As many as 85% of fish hatchery Rainbow trout died from the development of liver tumors which can be observed in Figure 1. A plethora of studies have been conducted to illustrate the effects of aflatoxicosis on animals. A study by Tilton et. al in 2005 confirmed that aflatoxin B1 was a guaranteed liver carcinogen in trout. A study by Huang et al. in 2004 illustrated that aflatoxin contamination in mice led to an increased risk in lung adenocarcinomas. In 2009, Hao et al. confirmed that AfB1 caused hepatocellular carcinoma in Wistar rats. Figure 2 illustrates the livers of rats who were exposed to specific doses of aflatoxin.

Figure 1. Normal trout liver (left) Aflatoxicosis liver (right)

Figure 2. Control Liver (top left), Liver given highest dose of Aflatoxin (bottom right)

Aflatoxin is also positively associated with hepatocellular carcinoma in humans. While levels of aflatoxin are regulated to avoid contamination there are still low levels of the fungus allowed in the food supply. More than 55 billion people suffer from uncontrolled exposure to aflatoxin globally. Acute aflatoxicosis has been shown to cause vomiting, abdominal pain,
comas, pulmonary edema, and death due to fatty involvement with the kidneys, liver, and heart.

In 2010 a study by Yan Liu and Felicia Wu found that aflatoxin plays a causative role in approximately 4.6 to 28.2 percent of liver cancer cases globally. This study also discovered that individuals with both chronic Hepatitis B and chronic aflatoxin exposure were most likely to present with hepatocellular carcinoma.\textsuperscript{14} Several studies have suggested that being positive for Hepatitis B positively influences the complications from aflatoxicosis. One of the most severe and largest outbreaks of hepatocellular carcinoma occurred in 2004 and 2005 in Kenya following poor harvesting of corn. Between January and June of 2014 more than 300 people sought medical treatment for liver failure symptoms and 125 people faced death. This study conducted by Julia R. Barret was the first to quantify an association between Hepatitis B and the effects of aflatoxin poisoning.\textsuperscript{15}

The mechanism for aflatoxins carcinogenic qualities is incredibly complex. From a chemistry standpoint the chemical structure of aflatoxins include an epoxide. Epoxides are incredibly reactive. When specific enzymes known as P450 enzymes in the liver metabolize aflatoxin it becomes a reactive oxygen species and the highly reactive epoxide of aflatoxin tries to interact with proteins or DNA. At this point, aflatoxin can bind to proteins and cause toxicity or bind to DNA. When epoxides bind to DNA, the sequences for DNA replication are miscoded and mutations develop that usually progress to the development of tumors. Studies have been able to illustrate that when exposed to AfB\textsubscript{1} the AGG sequence is mutated to AGT which can cause mutations in codon 249 of the TP53 tumour suppressor gene.\textsuperscript{16} It has been illustrated that

\textsuperscript{14} Liu, Y., & Wu, F. (2010). Global Burden of Aflatoxin-Induced Hepatocellular Carcinoma: A Risk Assessment. Environ Health Perspect Environmental Health Perspectives, 118(6), 818-824. doi:10.1289/ehp.0901388


in cases of hepatocellular carcinoma due to aflatoxin exposure about fifty percent of tumors contain the point mutation in codon 249. This mutation provides a causal link between aflatoxin exposure and its role in hepatocellular carcinomas.