

Aflatoxins, hepatocellular carcinoma and public health

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regulations and testing are not in place in many countries. The purpose of this editorial is to summarize the current knowledge on association of aflatoxin and HCC, encourage future research and draw attention to this global public health issue.

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Abstract

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths worldwide, primarily affecting populations in the developing countries. Aflatoxin, a food contaminant produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, is a known human carcinogen that has been shown to be a causative agent in the pathogenesis of HCC. Aflatoxin can affect a wide range of food commodities including corns, oilseeds, spices, and tree nuts as well as milk, meat, and dried fruit. Many factors affect the growth of *Aspergillus* fungi and the level of aflatoxin contamination in food. Drought stress is one of the factors that increase susceptibility of plants to *Aspergillus* and thus aflatoxin contamination. A recent drought is thought to be responsible for finding of trace amounts of aflatoxin in some of the corn harvested in the United States. Although it's too soon to know whether aflatoxin will be a significant problem, since United States is the world's largest corn producer and exporter, this has raised alarm bells. Strict regulations and testing of finished foods and feeds in the United States should prevent a major health scare, and prevent human exposure to deleterious levels of aflatoxin. Unfortunately, such

INTRODUCTION

On August 30, 2012, Reuters reported high alert in United States grain sector because of finding of trace amounts of aflatoxin in some of the corn harvested in the United States^[1]. Since strict regulations in the United States prohibit sale of aflatoxin contaminated crops, the alert was mainly because of potential economic consequences for United States farmers. Aflatoxins are one of the most important of the environmental toxins especially in the regions of the world where dietary foodstuffs are highly contaminated. Aflatoxins are primarily produced by fungal species *Aspergillus flavus*, *Aspergillus parasiticus*, and *Aspergillus nomius*, which colonize a wide variety of food commodities including maize, oilseeds, spices, groundnuts, tree nuts, milk and dried fruit^[2]. There are several different types of aflatoxins and nearly all of them can cause illness in human beings and animals. Aflatoxin B1 is the most abundant and toxic member of the family. It is also the most potent hepatocarcinogen known. Aflatoxin B1 has been classified by the World Health Organization as a "group A" carcinogen because of its proven contribution to the pathogenesis of hepatocellular carcinoma (HCC)^[3,4].

HCC is a leading cause of cancer related death and a major public health problem worldwide^[5,6]. Annual mortality associated with HCC is virtually identical to its incidence throughout the world, underscoring the high case fatality rate of this cancer type^[7].

The incidence of HCC varies greatly according to geographic region. The distribution of HCC also differs among different ethnic groups and regions within the same country. In parts of Asia and Africa, HCC accounts for nearly 70% of cancer deaths^[8]. In China, HCC is the third leading cause of cancer mortality accounting for at least 250 000 deaths per year and with an incidence rate in some counties approaching 100 cases per 100 000 individuals per year^[9].

The differences in distribution of HCC are thought to be because of different levels of exposure to HCC risk factors. In developing countries the major risk factors for HCC are chronic infection with hepatitis B virus and exposure to aflatoxins, while in developed countries the major risk factor is cirrhosis of the liver due to hepatitis C virus infection and alcohol abuse. In developed countries the majority of HCCs occur in older patients with long-standing chronic liver disease. In regions with high frequency of hepatitis B virus carriers and aflatoxin exposure, like sub-Saharan Africa, the mean age of presentation of HCC is decades earlier than in Western countries, often decreased to as low as 33 years^[10,11].

TOXICOLOGY

Aflatoxins are associated with both toxicity and carcinogenicity in human and animal populations^[12]. Acute aflatoxicosis results in death, whereas chronic aflatoxicosis results in more prolonged pathologic changes, including cancer and immunosuppression^[12]. The liver is the primary target organ, and liver damage has been documented in rodents, poultry, and nonhuman primates following ingestion of aflatoxin B1. Acute aflatoxicosis has been manifested in humans as an acute hepatitis^[12]. In India in 1974, an outbreak of hepatitis occurred in which 100 people died following consumption of maize that was heavily contaminated with aflatoxin. Aflatoxin B1 was detected in high concentration in the livers of those individuals who died^[13,14].

It has been hypothesized that kwashiorkor, a severe malnutrition disease, and Reye syndrome, marked by encephalopathy and fatty degeneration of the viscera, represent forms of pediatric aflatoxicosis. Although aflatoxins have been found in the livers of children with kwashiorkor and in Reye syndrome patients, a strong cause-and-effect relationship between aflatoxin exposure and these disease states has not been established^[12].

Chronic low-level exposure to aflatoxins in the diet is a risk factor for the development of HCC. Such exposure has been shown experimentally to produce cancer in many animal species and several epidemiologic investigations have shown that increased aflatoxin ingestion correlates with increased risk of HCC in humans^[12].

The mechanism of aflatoxin-induced carcinogenesis is thought to involve tumor promotion or progression. There is evidence that aflatoxin is involved in the activation of proto-oncogenes and mutations in the tumor suppressor gene p53. Aflatoxin exposure and p53 mutations have been tightly linked in epidemiologic studies in Africa and China. Specifically, aflatoxin has been linked to a p53 mutation whereby there occurs a G-to-T transversion at codon 249^[15,16]. This biomarker has been used in epidemiologic studies to establish the link between aflatoxins and hepatic cancer and also to show that co-factors such as infection with hepatitis B virus increase the risk of HCC substantially. It has also been suggested that aflatoxin induces various chromosomal aberrations, unscheduled DNA synthesis and chromosomal strand breaks in human cells. Another suggested mechanism for aflatoxin-mediated carcinogenesis is production of mutagenic substances as a result of metabolism of Aflatoxin by hepatic cytochrome p450.

ENVIRONMENTAL RISKS

Aflatoxins can affect a wide range of commodities including cereals, oilseeds, spices, and tree nuts as well as milk, meat, and dried fruit. The major sources of exposure are maize and groundnuts as these are the foods that are most susceptible to contamination and consumed in the greatest amounts. Developing countries located in the tropical regions, are at greatest risk given their reliance on these commodities as their staple food source^[2]. Food insufficiency and lack of food diversity substantially increases the risk of exposure to aflatoxins among individuals who live in these regions.

Many factors affect the growth of *Aspergillus fungi* and the level of aflatoxin contamination in food. Contamination can occur at any stage of food production from pre-harvest to storage^[2,17]. Factors that affect aflatoxin contamination include the climate of the region, the genotype of the crop planted, soil type, minimum and maximum daily temperatures, and daily net evaporation^[2]. Aflatoxin contamination is also promoted by stress or damage to the crop due to drought prior to harvest, insect activity, poor timing of harvest, heavy rains at harvest and post-harvest, and inadequate drying of the crop before storage. Humidity, temperature, and aeration during drying and storage are also important factors^[2].

VULNERABLE POPULATIONS

Children

Children differ from adults in many ways that have relevance to environmental health^[18,19]. Due to smaller body weights, doses that might not affect adults may induce illness in children. They have more immature neurologic and immune systems and so are more prone to develop complications. Children's developmental state may have a disproportionate impact on their reaction to different environmental toxins.

It is well established that dietary aflatoxins reduce the rate of growth and other measures of productivity in animals. To assess the effects of aflatoxin exposure on growth in humans, Gong *et al.*^[20,21] conducted two separate epidemiologic studies in West Africa. Those studies revealed a striking association between exposure to aflatoxin in children and both stunting (a reflection of chronic malnutrition) and being underweight (an indicator of acute malnutrition). Aflatoxin exposure has also been shown to be a factor in modulating the rate of recovery from kwashiorkor in children^[22,23]. The exact mechanisms underlying these effects of aflatoxins have not been elucidated.

Individuals with viral hepatitis infection

The risk of liver cancer in individuals exposed to chronic hepatitis B virus infection and aflatoxin is up to 30 times greater than the risk in individuals exposed to aflatoxin alone^[24,25]. These two HCC risk factors, aflatoxin and hepatitis B virus, are prevalent in poor nations worldwide. Within these nations, there is often a significant urban-rural difference in aflatoxin exposure and hepatitis B virus prevalence, with both these risk factors typically affecting rural populations more strongly^[25,26].

Aflatoxin also appears to have a synergistic effect on hepatitis C virus-induced liver cancer, although the quantitative relationship is not as well established as that for aflatoxin and hepatitis B virus in inducing HCC^[25,27-29]. Studies have also shown that the genetic characteristics of the virus, and the age and sex of the infected person may play a role in increasing the risk of aflatoxin induced HCC^[27].

PREVENTIVE MEASURES AND INTERVENTION STRATEGIES

Role of politics

The political will at a national level to address the issue of aflatoxin exposure is probably the most important factor in reducing the health hazards associated with aflatoxins in poor countries. As signatories to Codex Alimentarius (World Health Organization and Food and Agricultural Organization documents that deal with food quality) aflatoxin regulatory programs are already in place in most countries^[30]. On the export side these regulatory programs are strictly enforced to protect the export market of agricultural commodities, otherwise the importing countries would reject the commodities resulting in a loss of valuable foreign exchange earnings. On the other hand, domestic regulatory measures on aflatoxins have received very little attention and are rarely enforced, with no incentives given for the aflatoxin free produce and no heavy penalty on the violators of aflatoxin regulations.

Information dissemination

Considerable information has been gathered concerning the health hazards of aflatoxin exposure and conditions that lead to mold growth and aflatoxin contamination

during growing, harvesting and storage of crops. Steps that can be followed to avoid or minimize contamination have been developed. Information is also available on safe storage, handling and transportation practices of agricultural commodities. However, this information is rarely communicated to farmers, traders and all those who need to be informed. Much could be done if the value of different interventions is communicated and the information is disseminated in an appropriate and accessible manner^[31]. As an example, during an outbreak in Kenya in 2005, individuals who received information on maize drying and storage had lower serum aflatoxin levels than those who did not receive this information^[2].

Agricultural strategies

Agricultural interventions are methods or technologies that can be applied either in the field (“pre-harvest”) or in drying, storage, and transportation (“post harvest”) to reduce aflatoxin levels in food^[32].

The presence and growth of *Aspergillus* on pre-harvested crops is dependent on the environment. Agricultural practices including proper irrigation and pest management can reduce aflatoxin contamination^[2]. Pre-harvest interventions include choosing crops with resistance to drought, disease, and pests and choosing strains of that crop which are genetically more resistant to the growth of the fungus and the production of aflatoxins^[2]. Elimination of inoculum sources such as infected debris from the previous harvest may prevent infection of the crop^[2].

Before storage, crops should be properly dried to prevent the development of aflatoxins. Sorting and disposing of visibly moldy or damaged kernels before storage has proven to be an effective method for reducing the development of aflatoxins^[2,33,34]. During storage, moisture, insect, and rodent control can prevent damage to the crop and reduce aflatoxin development. Aflatoxin contamination of maize is influenced by the facilities used for storage, storage time, and the form of maize stored^[2,35]. A community-based intervention study in Africa showed that simple and inexpensive measures such as thorough drying and proper storage of groundnuts can have a significant impact on aflatoxin levels^[34].

Vaccination against hepatitis B virus

Hepatitis B virus infection increases the risk of HCC in individuals exposed to aflatoxins exponentially. Vaccination against hepatitis B virus in infancy is an effective approach to prevent HCC, particularly in developing countries where both incidence of hepatitis B virus and exposure to aflatoxins are high^[26,36,37]. Although the vaccine itself has no impact on actual aflatoxin levels in diets, it reduces aflatoxin-induced HCC by lowering hepatitis B virus risk, thereby preventing the synergistic impact of hepatitis B virus and aflatoxin in inducing liver cancer^[38]. Those who already have chronic hepatitis B virus infection would not benefit from the vaccine, which is why vaccination should be offered in infancy^[38]. Hepatitis B vaccination in infancy has been shown to be safe and effective^[26,39].

RESEARCH PROBLEMS AND NEEDS

Better funding

Aflatoxin research programs need adequate resources in terms of qualified personnel, capital investment, and analytical and technical facilities. Improved funding for aflatoxin research is in dire need, especially in countries with high rate of aflatoxin food contamination. Currently, on a global basis, there is an imbalance between the extent of aflatoxin problem and the funds that have been allocated to its research.

Promotion of a multidisciplinary approach

Aflatoxin contamination of food and feed is a problem that affects multiple disciplines such as agriculture, toxicology, medicine, biology, microbiology, veterinary medicine and other related fields. Hence, a multidisciplinary research approach to the problem should be encouraged and promoted.

Better sampling methods

Determination of aflatoxin levels in food or feed is done via sampling. Sampling of lots of food or feed for aflatoxin analysis is an important step in exposure prevention. Current sampling methods for aflatoxin are not considered totally reliable. Furthermore, sampling techniques have not been standardized and various trade bodies have their own sampling procedure and technique^[40]. Research is needed to identify better and cheaper sampling methods which can in turn lead to standardization of sampling procedures.

Development of resistant cultivars

One of the possible ways to reduce aflatoxin contamination of food commodities is the use of cultivars resistant to seed invasion by aflatoxin-producing fungi^[41]. Breeding for resistance to aflatoxin producing *Aspergillus* species can play a significant role in preventing aflatoxin contamination of food.

Development of competitive and antagonistic microorganisms

Theoretically, competitive and antagonistic native microorganisms that can reduce the populations of aflatoxin producing fungal strains present in the soil have the potential to reduce infection of the plants^[42]. Research is needed to develop such microorganisms and also to make sure that they do not pose any dangers to humans, animals or environment by their own.

Identification of modulators of aflatoxin toxicity

Whereas it is highly desirable that food is not contaminated, the reality is that in parts of the world food contamination with aflatoxins is unavoidable. Identification of substances that can be incorporated into the human diet to reduce or prevent aflatoxin toxicity would have a great potential in reducing the incidence of aflatoxin induced HCC in endemic areas.

Determination of in utero and early childhood exposure effects

In endemic areas, pregnant women are often exposed to aflatoxin contaminated food. There is lack of knowledge about the effects of aflatoxin exposure in utero and early childhood. Research is needed to better understand these effects. This knowledge is fundamental in identification and design of preventive strategies.

CONCLUSION

The purpose of this editorial is to summarize the current knowledge on association of aflatoxin and HCC, encourage future research and draw attention to this global public health issue.

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