World Mycotoxin Journal, 2015; 8 (2): 137-142
SPECIAL ISSUE*: Aflatoxins in maize and other crops*

Global impacts of aflatoxin in maize: trade and human health

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Received: 5 March 2014 / Accepted: 3 May 2014

REVIEW ARTICLE

Abstract

Maize is one of the most important agricultural commodities worldwide in terms of amounts produced, consumed, and traded. Hence, naturally occurring aflatoxin contamination in maize has important ramifications for both global trade and health. Aflatoxin is produced by certain species of the genus *Aspergillus* in a variety of food crops, including maize, peanuts, and tree nuts. Over 100 nations have aflatoxin regulations, which are intended to protect human and animal health, but also incur economic losses to nations that attempt to export maize and other aflatoxin-contaminated commodities. These economic effects must be balanced against the health protection afforded by the regulations. It is important to acknowledge that, even in nations that have aflatoxin regulations, many individuals consume maize that has undergone no regulatory inspection, especially in nations where subsistence farming is widespread. Hence, aflatoxin contamination, exposure, and lack of regulation can also contribute to adverse effects on trade and health worldwide. This review, part of a special issue on aflatoxin in maize, describes economic and health effects of aflatoxin in maize on a global level. It ends with a story of an intervention that reduced maize consumption in one population in China, which is likely the main determinant of the reduction in liver cancer mortality in that population over the last 30 years, from reduced aflatoxin exposure.

Keywords: *Aspergillus flavus*, aflatoxin, economic impact, epidemiological studies, health effects

1. Introduction

Aflatoxins, a group of chemically related toxins produced primarily by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, contaminate multiple staple foods, including maize, groundnuts and tree nuts. Aflatoxin is most prevalent in crops in tropical and subtropical regions of the world, and may occur in the field and post-harvest under suboptimal storage conditions. It has been estimated that 5 billion people worldwide are exposed to uncontrolled aflatoxin in the diet (Strosnider *et al.,* 2006).

Since the 1960s, it was known that aflatoxin exposure causes liver toxicity and cancer (hepatocellular carcinoma, or HCC) in multiple animal species. In 1993, the International Agency for Research on Cancer (IARC) classified 'naturally occurring mixes of aflatoxins' as a Group 1 carcinogen, meaning that sufficient evidence exists to link aflatoxin exposure to cancer in humans (IARC, 1993). In many parts of the world, particularly in Asia and sub-Saharan Africa, individuals are exposed both to high levels of aflatoxin and chronic hepatitis B virus (HBV) infection, which has been shown to greatly increase liver cancer risk (Qian *et al.,* 1994): a multiplicatively greater risk of developing HCC than those exposed to aflatoxin or HBV alone (Liu *et al.,* 2012). There is also suggestive evidence that aflatoxins modulate human immunity (summarised in Jolly *et al.,* 2008) and may contribute to growth impairment in children (Gong *et al.,* 2002, 2004; Khlangwiset *et al.,* 2011).

2. Impacts of aflatoxin on maize trade

To protect human and animal health, over 100 nations have established maximum tolerable levels for aflatoxin in food (Wu and Guclu, 2012). Some nations have set standards for the most toxic and carcinogenic of the aflatoxins, aflatoxin B_1 (AFB_1); others regulate 'total aflatoxins' (the sum of the concentrations of aflatoxin B_1, B_2, G_1, and G_2); and others have standards for both AFB_1 and total aflatoxins in foodstuffs. Additionally, several nations have set standards

for aflatoxin M_1 (AFM_1): the metabolite of aflatoxin B_1, which can be found in dairy products due to dairy animals' consumption of aflatoxin-contaminated feed. The most recent list of aflatoxin regulations on a nation-by-nation basis can be found in FAO (2004).

Both domestically and globally, aflatoxin can impose large burdens on maize trade. On the domestic level, estimates have been made in various studies on the cost of aflatoxin to food producers. Some studies segregate the costs of aflatoxin by crop (e.g. maize, peanuts), while others produce cost estimates across all crops, and include costs associated with livestock illness due to aflatoxin exposure.

At the domestic level, most economic impact analyses of aflatoxin have been conducted for the USA. Vardon *et al.* (2003) calculated the total costs of aflatoxin in the USA to be nearly $500 million annually, due to losses to maize, peanut, and other crop growers as well as through animal health effects (a small fraction of the cost). Wu (2006) made a more conservative estimate at an annual loss of $163 million on average to US maize growers from aflatoxin. The difference in results may have partially resulted from focusing on maize alone rather than all crops, and the assumption that a maize lot that is rejected for human food can be sold for animal feed or other purposes. Additionally, costs to manage aflatoxin in the USA range from $20-50 million per year (Robens and Cardwell, 2003). In other nations, Lubulwa and Davis (1994) estimated the annual cost of aflatoxin in three countries – the Philippines, Thailand, and Indonesia – to be nearly 1 billion USD per year, due to a combination of market losses and livestock and poultry health losses.

At the global level, the first study that caught significant policy attention was a World Bank estimate (Otsuki *et al.,* 2001) that the European Union (EU) regulations for aflatoxin at the time (2 ng/g AFB_1 and 4 ng/g total aflatoxins) were at a level of strictness that cost African food exporters $670 million annually. The economic model used to calculate this value was based on estimates of production and climate effects on aflatoxin contamination, and did not take into account actual aflatoxin levels in the foodstuffs nor actual volumes of trade of different foodstuffs between Africa and the EU. When a model includes actual volumes of maize trade between nations (Wu and Guclu, 2012, 2013), it emerges that very little maize trade occurs between Africa and the EU; hence, aflatoxin in African maize does not actually result in significant trade-related loss with the EU – although it has many other important consequences such as adverse health impacts in African populations. For aflatoxin in peanuts, it was estimated that the cost to African exporters to meet the EU standard would be less than $40 million annually (Wu, 2004). A later World Bank (2005) study corroborated these results, showing that the losses to African growers from EU aflatoxin standards were not as high as previously estimated.

More recently, social network models of maize trade have been developed (Wu and Guclu, 2012, 2013; Bui-Klimke *et al.,* 2014) to determine the relationship between nations' different aflatoxin regulations and trade patterns of aflatoxin-contaminated foods. For both maize and pistachios, it was found that nations that have identical or near-identical aflatoxin standards (not different by more than 5 ng/g) tend to conduct significantly more trade with each other, than nations with very different aflatoxin standards. Additionally, nations with no aflatoxin standards, or relatively relaxed aflatoxin standards, received the commodities with the highest aflatoxin contamination levels. From a trade standpoint, this implies that on a global scale, nations are aligning themselves in food trade, so as to minimise economic losses due to rejected consignments from aflatoxin (by trading with nations with identical or similar standards). From a health standpoint, this means that relaxed or non-existent aflatoxin standards have a direct impact on aflatoxin exposure, with potential human health impacts. These health impacts are discussed next.

3. Impacts of aflatoxin on global health

Two recent papers (Kensler *et al.,* 2011; Wu *et al.,* 2014) have summarised the adverse human health effects of aflatoxin exposure. The reader is directed to these papers for a more in-depth discussion of the toxicological mechanisms of aflatoxin in the body, and the epidemiology of aflatoxin-related illness. The state of knowledge of global impacts of aflatoxin in the human diet is summarised below.

Of all the human health effects associated with aflatoxin exposure, the weight of evidence is strongest for aflatoxin-related liver cancer, and secondarily of the synergism between aflatoxin exposure and chronic HBV infection in liver cancer risk. At least three analyses have been conducted to estimate the global burden of liver cancer attributable to aflatoxin; however, these were not limited to aflatoxin exposure through maize consumption, but include exposures through the consumption of other crops as well.

The Joint Expert Committee on Food Additives (JECFA, 1998) of the Food and Agriculture Organization and World Health Organization (WHO) posed hypothetical scenarios in which 1% vs. 25% of the human population was HBV-positive, and derived cancer potency factors for aflatoxin in HBV-positive vs. HBV-negative individuals by combining aflatoxin/HBV dose-response studies available at the time. JECFA estimated that in a population with only 1% HBV prevalence and consuming a 'European diet', changing an aflatoxin regulation (assuming it was enforced) from 20 ng/g to 10 ng would change liver cancer prevalence from 0.0041 cancers/yr/100,000 people to 0.0039 cancers/yr/100,000

people. The difference would amount to 2 fewer cancers/yr/billion persons, hardly detectable by epidemiological methods. On the other hand, where 25% of the population is HBV-positive and following a 'Far Eastern diet', changing an aflatoxin regulation from 20 ng/g to 10 ng would change liver cancer prevalence from 0.17 cancers/yr/100,000 people to 0.14 cancers/yr/100,000 people. The difference would amount to 300 fewer cancers/yr/billion: a more meaningful number when considering tightening standards to protect human health.

However, the JECFA (1998) analysis did not take into account actual aflatoxin exposures in different parts of the world, nor actual prevalence of HBV in different nations. Therefore, Liu and Wu (2010) conducted a quantitative cancer risk assessment based on calculated exposures and HBV prevalence in all nations for which data were available, using the JECFA cancer potency factors of aflatoxin in HBV-positive and HBV-negative individuals (JECFA, 1998; Henry *et al.,* 1999), and multiplying the corresponding cancer potency factors by the aflatoxin exposure data. The risk assessment resulted in an estimate of 25,200 to 155,000 global liver cancer cases per year attributable to aflatoxin exposure. This wide range in the calculation is due primarily to the large ranges in two factors: aflatoxin levels in foodstuffs measured in different countries, and estimated chronic HBV prevalence in different countries (Liu and Wu, 2010).

In a separate meta-analysis of 17 epidemiological studies that measured biomarkers of aflatoxin exposure, Liu *et al.* (2012) estimated global burden of aflatoxin-induced cancer by calculating population-attributable risk. It was estimated that about 23% (21-24%) of all global liver cancer cases could be attributable to aflatoxin exposure, including both HBV-positive and HBV-negative individuals, for a total of about 172,000 aflatoxin-related liver cancer cases per year.

Several studies have examined the link between aflatoxin exposure and markers of immune system modulation in humans. The reader is referred to Jolly *et al.* (2008) for a review of the evidence. In a Ghanaian study of HIV-positive and HIV-negative individuals, higher levels of the aflatoxin-albumin adduct, a biomarker of aflatoxin exposure and effect, were associated with lower levels of CD4+ T regulatory cells, naïve CD4+ T cells, and B-cells (Jiang *et al.,* 2008). In another study in West Africa, Turner *et al.* (2003) showed that Gambian children with higher levels of aflatoxin-albumin adduct (AF-alb), a biomarker of aflatoxin exposure and effect, had lower levels of secretory IgA in saliva. How these changes actually correlate to disease outcomes is less clear. Although the Jiang *et al.* (2008) study results imply that greater aflatoxin exposure correlates to poorer disease outcomes in HIV-positive individuals, more epidemiological studies are needed to corroborate these results for HIV and other infectious diseases.

Recently, interest has grown in the potential relationship between aflatoxin exposure and stunting in children. Stunting is defined as a condition in which the child's height for age is two standard deviations or more below a WHO growth reference (height-for-age z-score HAZ ≤-2). Although smaller height by itself may not pose a great health burden, environmentally-mediated stunting is associated with other conditions such as cognitive deficits and increased risk of infectious diseases, which can persist beyond early childhood (Ricci *et al.,* 2006).

One of the earliest epidemiological studies on the link between stunting and aflatoxin exposure (Gong *et al.,* 2002) showed that, in a cross-section of 479 children in Togo and Benin divided into quartiles by HAZ and weight-for-age z-score (WAZ), those in increasingly lower quartiles of both had increasingly higher AF-alb levels. Another study in this population (Gong *et al.,* 2004) showed that in a longitudinal (8 month) study, children who had the highest AF-alb grew the least in that time period. In The Gambia, Turner *et al.* (2003, 2007) found a correlation between AF-alb in maternal blood, cord blood, infant blood, and children's blood and poorer growth indicators for the infants and children. Likewise, in Ghana (Shuaib *et al.,* 2010), mothers' AF-alb levels have been associated with low weight babies at birth; and in Iran (Mahdavi *et al.,* 2010; Sadeghi *et al.,* 2009) AFM_1 in mothers' breastmilk was associated with lower length and weight of infants at birth. Examining food rather than biomarkers of aflatoxin exposure in Kenya, Okoth and Ohingo (2004) showed that aflatoxin levels in household maize flour correlated with wasting – lower weight for height – in children. The animal and human studies that describe associations between aflatoxin exposure and growth impairment are reviewed in Khlangwiset *et al.* (2011).

In addition to the chronic effects of aflatoxin exposure described above, aflatoxin at very high doses can also cause the eponymous acute aflatoxicosis, characterised by acute liver failure resulting from the AFB_1 dialdehyde forming adducts that have been theorised to be one cause of acute toxicity (Kensler *et al.*, 2011). While outbreaks of acute aflatoxicosis are relatively rare – several recorded outbreaks over the last four decades (Bhat and Krishnamachari, 1977; Krishnamachari *et al.,* 1975; Lye *et al.,* 1995; Strosnider *et al.,* 2006) – the case fatality rate is high, ranging from 20-40%. Most recently, aflatoxicosis outbreaks occurred in Kenya in 2004 and 2005, following consumption of mouldy maize that had been harvested early and stored improperly (Strosnider *et al.,* 2006). In the 2004 outbreak, the largest ever recorded, 317 people became ill and 125 died (Azziz-Baumgartner *et al.,* 2005).

4. Interventions

As challenging as aflatoxin is from global economic and global health standpoints, it is possible to reduce the risk using a variety of interventions. A number of preharvest and postharvest interventions have been developed to counter both the economic losses and adverse health effects caused by aflatoxins in foods. At the preharvest level, these include interventions that can reduce fungal infection of crops in the field, such as good agricultural practices (Cleveland *et al.,* 2003; Munkvold, 2003); breeding resistance to the field conditions that favour *Aspergillus* infection and aflatoxin production (Brown *et al.,* 2013), including through knowledge of the genetics of aflatoxin production (Bhatnagar *et al.,* 2006); and biocontrol (Cotty *et al.,* 2007). Postharvest interventions include improved drying, transportation, and storage of food to reduce moisture and crop damage and prevent aflatoxin accumulation (Turner *et al.,* 2005), and dietary interventions to enhance aflatoxin detoxification and elimination once ingested (Wang *et al.,* 2008). These methods and their cost-effectiveness in reducing aflatoxin are summarised in Khlangwiset and Wu (2010). However, many of these strategies have not yet proven sustainable over extended periods of time, and many are not economically and logistically feasible in low-income communities worldwide that suffer the highest exposures to aflatoxin exposure.

Ultimately, increasing dietary diversity where possible, and/or moving away from the staple foods that are frequently contaminated with aflatoxin, may prove the most sustainable methods of reducing aflatoxin exposure in human populations. A recent study (Chen *et al.,* 2013) has shown that decreased intake of maize and increased consumption of rice and other foodstuffs has resulted in markedly lower aflatoxin exposures and, subsequently, dramatically declining liver cancer mortality rates in Qidong, China P.R. Prior to the 1980s, agricultural policies had restricted counties from trading food with one another, as food self-sufficiency was required of each county. Because the soil in Qidong was unsuitable for growing rice, maize was the primary staple grown, under environmental conditions that led to high aflatoxin contamination. As a result, Qidong became a 'liver cancer hot spot,' where 1 in 10 adult men died of liver cancer, often by age 45.

When market reforms were introduced in the 1980s, the Qidongese increased their dietary diversity, turning from maize to rice and other foodstuffs from neighbouring counties. As a result, aflatoxin exposure has plummeted in the last 30 years; correspondingly, the age-standardised rate of liver cancer mortality has decreased by 45% in the Qidong population since the 1980s (Chen *et al.,* 2013).

Introducing dietary diversity into populations where aflatoxin-contaminated maize is a dietary staple may not only reduce liver cancer risk, but may also reduce other adverse effects associated with aflatoxin exposure. If the weight of evidence increases that aflatoxin exposure is associated with growth impairment and immunotoxicity, then reducing aflatoxin exposure in at-risk populations could improve child growth outcomes.

5. Conclusions

The global cost of aflatoxin is large – both in terms of the market-related losses through selling aflatoxin-contaminated commodities, and of the human health losses due to adverse impacts of dietary aflatoxin exposure. In the USA alone, annual economic losses of aflatoxin range in the hundreds of millions USD; while, at the moment, there is no convincing evidence that aflatoxin exposure causes any human disease in the USA. In other parts of the world, both trade-related losses and human and animal health losses are huge. In the last decade, even more knowledge has been gained about diverse diseases and conditions associated with aflatoxin exposure, so its control in foodstuffs is critical.

Multiple interventions have been developed to combat aflatoxin biosynthesis and accumulation, ranging from preharvest to dietary interventions. Simply avoiding or reducing consumption of the foods that are frequently contaminated with aflatoxin has shown effectiveness in reducing liver cancer mortality in one population in China. Regardless of the type of intervention, there needs to be sufficient incentive for growers to adopt the interventions to reduce aflatoxin. There are three critical components: (1) providing economic incentives for adoption; (2) proving and/or improving the cost-effectiveness of aflatoxin control strategies; and (3) education and outreach across all relevant grower, industry, and consumer sectors (Wu *et al.,* 2008). These are the areas in which more research and extension are needed on a global scale, to combat the trade and health costs of aflatoxin.

Acknowledgments

The author gratefully acknowledges support from the US National Cancer Institute (5R01CA153073-02), National Institutes of Health.

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