

Aflatoxins are a group of about 20 chemically related toxic chemicals produced primarily by the foodborne mold *Aspergillus flavus* and *A. parasiticus*. Aflatoxins contaminate a variety of staple foods including maize, peanuts, and tree nuts; they cause an array of acute and chronic human health disorders. Aflatoxin-contaminated maize was the most likely cause of the 1981 and 2004 acute aflatoxicosis outbreaks in Kenya, which resulted in 317 illnesses and 125 deaths, respectively (Strosnider et al. 2006). Aflatoxin B1, the most toxic of the aflatoxins, is a potent liver carcinogen, causing hepatocellular carcinoma (HCC) in humans and a variety of animal species. There is also an increasing body of evidence that aflatoxins modulate the immune system (Williams et al. 2004; Jiang et al. 2005) and may lead to stunted growth in children (Gong et al. 2002, 2004; Khlangwiset et al. 2011).

This brief summarizes information on the two chronic conditions for which the greatest body of evidence exists for a linkage with aflatoxin exposure: aflatoxin-induced liver cancer and aflatoxin-associated childhood stunting. A brief description is given of studies linking aflatoxins to immune system modulation.

### Aflatoxin-induced liver cancer

For decades, it has been known that aflatoxin exposure causes liver cancer in humans and a variety of animal species. The International Agency for Research on Cancer has classified “naturally occurring mixes of aflatoxins” as a Group 1 human carcinogen. Concomitant exposure to aflatoxins and the hepatitis B virus (HBV) is common in developing countries and greatly increases HCC risk (Wu et al. 2013). Individuals with both exposures have multiplicatively greater risk of developing HCC than those exposed to aflatoxins or HBV alone (Groopman et al. 2008). A recent systematic review and meta-analysis determined that the risk of developing liver cancer was over 6 times higher in individuals with detectable aflatoxin biomarkers than in those without, over 11 times higher in individuals with chronic HBV infection than in those without, and over 73 times higher in individuals with both detectable aflatoxin biomarkers and HBV positivity compared with those with neither risk factor—a nearly perfectly multiplicative relationship (Liu et al. 2012).

Two separate analyses have been conducted to estimate the global burden of liver cancer attributable to aflatoxins. Liu and Wu (2010) used a quantitative cancer risk assessment approach, using dose-response data for the relationship between aflatoxins and liver cancer risk in populations of HBV-negative and HBV-positive individuals (JECFA 1998; Henry et al. 1999) and multiplying the corresponding cancer potency factors by aflatoxin exposure data for multiple nations worldwide. In their analysis that included about 5 billion individuals around the world (summing populations across nations for which aflatoxin data were available), they estimated that 25,200–155,000 liver cancer cases annually could be attributed to aflatoxin exposure.

In a follow-up study, Liu et al. (2012) used a different approach to estimate global burden of cancer caused by aflatoxins: estimating population-attributable risk from a systematic review and meta-analysis of 17 epidemiological studies on aflatoxins, HBV, and liver cancer in Africa and Asia. It was estimated that about 23 percent (21–24 percent) of all HCC cases annually maybe attributable to aflatoxins, for a total of up to 172,000 cases per year. Since liver cancer is the third-leading cause of cancer deaths worldwide, and mortality rapidly follows diagnosis, the contribution of aflatoxins to this deadly cancer is significant.

### Aflatoxin-associated childhood stunting

Aflatoxin exposure has also been associated with childhood stunting: a condition in which the child's height for his or her age is two standard deviations or more below a World Health Organization (WHO) growth reference. Stunting is important from a public health perspective because it is associated with effects such as increased vulnerability to infectious diseases and cognitive impairments that last well beyond childhood (Ricci et al. 2006).

Khlangwiset et al. (2011) summarize the epidemiological studies that show an association between child growth impairment and aflatoxin exposure (the reader is referred to that study for an in-depth explanation of the available studies). They note that studies in Togo and Benin in West Africa (Gong et al. 2002, 2004) show that height and weight for children's ages are lower in a dose-dependent fashion for higher aflatoxin exposures, and children's growth over eight months was also compromised. Two studies of infants and children in The Gambia (Turner et al. 2003, 2007) show that aflatoxin-albumin adduct (AF-alb) levels in maternal blood, cord blood, infant blood, and children's blood are associated with poorer growth indicators. AF-alb is a biomarker of aflatoxin exposure and biological activation in humans. Aflatoxin levels in household flour in Kenya were associated with wasting in children (Okoth and Ohingo 2004). A Ghanaian study (Shuaib et al. 2010) linked mothers' AF-alb levels with low-weight babies at birth. In Iran, two studies (Sadeghi et al. 2009, Mahdavi et al. 2010) showed that aflatoxin M1 in mothers' breast milk was associated with reduced length and weight of infants at birth. Khlangwiset et al. (2011) also provide discussions of animal studies linking aflatoxin exposure with impaired growth outcomes, and of the importance of aflatoxin-free weaning foods.

At the moment, because of the relatively small number of epidemiological studies undertaken and the limited nature of dose-response relationships, it is not possible to conduct a quantitative risk assessment definitively linking an aflatoxin dose with a particular risk of stunting in a population. Further studies to explore the relationship between aflatoxins and childhood stunting are currently underway. However, while causality has not yet been confirmed, the body of evidence consistently shows an association between aflatoxin exposure and growth impairment in children.

## Aflatoxins and immune system modulation in humans

Several studies have examined the link between aflatoxin exposure and markers of immune system modulation in humans. Jiang et al. (2008) found that in HIV+ and HIV- study subjects in Ghana, higher levels of AF-alb were associated with lower levels of CD4+ T regulatory cells and naïve CD4+ T cells, as well as lower B-cells—all cells associated with immune responses. In an earlier Ghanaian study, other types of cells involved in immune response were found to be lower in individuals with higher AF-alb (Jiang et al. 2005). Another study showed that Gambian children with higher levels of AF-alb had lower levels of secretory IgA in their saliva, another immune parameter (Turner et al. 2003). Taken together, these few studies indicate that aflatoxin exposure is associated with changes in markers of human immune systems. How these changes actually correlate to disease outcomes, however, is less clear and was beyond the scope of the studies.

## Conclusions

Because aflatoxins are one of the most significant risk factors for liver cancer, one of the deadliest cancers worldwide, controlling

its presence in the food supply is critical. It is possibly responsible for up to 172,000 liver cancer cases per year, most of which would result in mortality within three months of diagnosis. Possibly even more critical from a global public health standpoint is the link between aflatoxin exposure and childhood stunting, which can lead to a variety of adverse health conditions that last well beyond childhood. However, at the moment there is insufficient evidence for a quantitative risk assessment to evaluate exact daily doses of aflatoxins that lead to particular levels of risk or adverse health outcomes in children. Additionally, while aflatoxins may lead to immunomodulation, not enough information is currently known about how this leads to particular adverse health outcomes in humans. However, the human health evidence points to aflatoxins' association with multiple adverse effects; hence, it is important to reduce human exposures to aflatoxins in the diet to the extent that feasible methods allow.

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