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Costs and efficacy of public health interventions to reduce aflatoxin–induced human disease

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Abstract

This study reviews available information on the economics and efficacy of aflatoxin risk-reduction interventions, and provides an approach for analysis of the cost-effectiveness of public health interventions to reduce aflatoxin-induced human disease. Many strategies have been developed to reduce aflatoxin or its adverse effects in the body. However, a question that has been under-addressed is how likely these strategies will be adopted in the countries that need them most to improve public health. This study evaluates two aspects crucial to adoption of new technologies and methods: the costs and the efficacy of different strategies. First, we describe and categorize different aflatoxin risk-reduction strategies into preharvest, postharvest, dietary, and clinical settings. Then we compile and discuss relevant data on the costs and efficacy of each strategy, in reducing either aflatoxin in food or its metabolites in the body. In addition, we describe which crops are affected by each intervention, who is likely to pay for the control strategy, and who is likely to benefit. A framework is described for how to evaluate cost-effectiveness of strategies according to World Health Organization standards. Finally, we discuss which strategies are likely to be cost-effective and helpful under different conditions worldwide of regulations, local produce and soil ecology, and potential health emergencies.

Keywords

aflatoxin; public health interventions; cost-effectiveness; liver cancer; immunosuppression; economics; disability-adjusted life years (DALYs)

Introduction

Aflatoxins are secondary metabolites of the fungi *Aspergillus flavus* and *A. parasiticus*. These species are prevalent in food crops – particularly maize, groundnuts, oilseeds, and tree nuts – in tropical and subtropical regions worldwide. Factors that influence whether these fungi produce aflatoxin include drought stress and rainfall, adaptation of crop genotype for its climate, insect damage, and agricultural practices. These fungi can also produce aflatoxin in postharvest conditions: storage, transportation, and food processing. Maize and groundnuts are the major sources of human exposure (the number of exposed persons exceeding several billion) because of these foods' high consumption rates worldwide and their susceptibility to aflatoxin contamination (Strosnider et al. 2006).

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Aflatoxin B₁ (AFB₁), the most toxic aflatoxin, is the most potent naturally occurring chemical liver carcinogen known. For people who are chronically infected with hepatitis B virus (HBV; common in China and Africa), aflatoxin consumption raises by up to thirty-fold the risk of hepatocellular carcinoma (HCC; liver cancer) compared with either exposure alone (Groopman & Kensler 2005). Acute aflatoxicosis, characterized by hemorrhage, acute liver damage, edema, and death, can result from extremely high doses of aflatoxin. In recent years, hundreds of aflatoxicosis cases in Africa have been associated with consumption of contaminated home-grown maize (Azziz-Baumgartner et al. 2005). Aflatoxin exposure is also associated with immunotoxicity in humans (Turner et al. 2003, Williams et al. 2004, Jiang et al. 2005, 2008), and with stunted growth in children (Gong et al. 2002, 2004, Turner et al. 2007).

To limit aflatoxin exposure, over 100 nations worldwide have set maximum tolerated levels (MTLs) of aflatoxin in food (CAST 2003). These standards offer public health protection in industrialized nations, but arguably have little effect in less developed countries (LDCs), for several reasons. First, the food consumed from subsistence farms, which are widespread in LDCs, rarely enters any sort of regulatory inspection for aflatoxin (Williams et al. 2004, Strosnider et al. 2006). Second, even if this food did meet the MTLs for aflatoxin, many people in LDCs consume such high levels of maize and groundnut products that their daily aflatoxin exposure would still render them vulnerable to disease (Shephard 2008). Third, LDCs that attempt to export maize and nuts abroad may find their export markets severely jeopardized by strict aflatoxin standards, resulting in potential countervailing risks of exporting the best foods and keeping the worst domestically (Wu 2004).

Hence, it is estimated that about 5 billion people worldwide suffer from uncontrolled exposure to aflatoxin (Strosnider et al. 2006). Aflatoxin-associated health effects pervade sub-Saharan Africa and East Asia. These effects could be mitigated through effective use of current agricultural knowledge and public health practice. The discussion of this problem and its remedies must include the underlying question of food insufficiency and more general economic challenges in developing countries (Strosnider et al. 2006).

Several interventions to reduce and prevent aflatoxin toxicity have been developed. These range from aflatoxin control methods in agricultural practice through chemopreventive dietary constituents to vaccination against HBV. Agricultural interventions to reduce aflatoxin could be done either in preharvest (field) or postharvest (drying, storage, transportation, etc.) conditions. Meanwhile, there is growing research interest in using certain substances available in foods and natural products to reduce aflatoxin's adverse impacts in the body. By binding aflatoxin in the gastrointestinal tract, or inducing enzymes involved in aflatoxin metabolism pathways, several substances can reduce aflatoxin bioavailability in humans. The HBV vaccine neither reduces aflatoxin levels in food nor reduces aflatoxin's bioavailability in the body; however, it reduces aflatoxin-induced liver cancer by greatly reducing the risk of chronic HBV infection, thereby preventing the synergistic impact of HBV and aflatoxin in HCC pathogenesis.

Understanding the costs and efficacy of different aflatoxin control interventions can help decision makers – be they government policymakers or farmers or consumers – to optimally allocate resources, particularly in conditions of scarcity. Wu et al. (2008) presented three case studies for cost-effectiveness of aflatoxin control in the United States: two biocontrol agents (Afla-Guard™ in groundnuts and AF36 in cottonseed) and a transgenic crop (Bt maize). However, this assessment was limited to the US, and may not have equal applicability worldwide. This study reviews the available data on costs and effectiveness for interventions that could be used to control aflatoxin from a global perspective.

Table 1 shows the factors that we include in our analysis. First, we are interested in whether the intervention is agricultural (methods that take place in the field or postharvest settings), dietary (supplements or processing or natural constituents in food), or clinical (HBV vaccination). This gives us information about who needs to implement the intervention, and how often and in what context it needs to be done. Second, we are interested in whether the intervention in question reduces aflatoxin concentrations in food, or whether it reduces bioavailability of aflatoxin or its metabolites in the body. This provides useful information on the nature of the intervention and whether the intervention can potentially reduce health impacts, trade losses, or both. Third, we are interested in how much the intervention costs, and how effective it is. These are obviously the main factors in a cost-effectiveness assessment. Finally, we are interested in who pays for the intervention (e.g., growers, consumers, or local / national government) and who benefits from it.

Pre-harvest interventions

Because most aflatoxin problems begin and develop in the field, strategies are needed to prevent infection of growing plants by toxigenic fungi. Developing genetic resistance to *Aspergilli* in maize and groundnuts is a high priority (Cleveland et al. 2003, Munkvold 2003). Worldwide, the advantages of using resistant plant genotypes include direct health and economic benefits, the lack of impact on crops or the environment, and the ability to use these genotypes in combination with other aflatoxin control strategies (Menkir et al. 2006).

A number of resistant inbred maize lines have been indentified, including MI82 (Maupin et al. 2003), Mp420, Mp313E, and GT-MAS:sk (Brown et al. 1999). Sources of resistance to each of these pathogens have been identified and have been incorporated into public and private breeding programs, and have been extended to include germplasm lines from Africa (Brown et al. 2001, Menkir et al. 2006). Potential biochemical and genetic resistance markers have been identified in crops, particularly in maize, which are being utilized as selectable markers in breeding for resistance to aflatoxin contamination (Cleveland et al. 2003). Several proteins associated with resistance (RAPs) include, but are not limited to, globulin-2 proteins, late embryogenesis abundant proteins (LEA3 and LEA14), a stress-related peroxiredoxin antioxidant (PER1), heat-shock proteins (HSP17.2), a cold-regulated protein (COR), and an antifungal trypsin-inhibitor protein (TI) (Chen et al. 2007). Now that the sequencing of the *A. flavus* genome has been completed, and genes that potentially encode for enzymes involved in aflatoxin production have been identified, genomics as a tool for combating aflatoxin biosynthesis has gained much ground (Payne and Brown 1998, Bhatnagar et al. 2006, Yu et al. 2008).

The development of groundnut cultivars with resistance to preharvest aflatoxin contamination has also yielded promising results. Screening techniques have been developed that can measure genetic differences in susceptibility to aflatoxin contamination, and these techniques have been used to identify multiple accessions that have shown significant aflatoxin reduction in multiple environments. Groundnut genotypes with drought resistance have also shown aflatoxin reduction (Holbrook et al. 2006, Guo et al. 2008). Aflatoxin resistant genotypes have been developed in other parts of the world, and have shown success in aflatoxin reduction (ICRISAT 2006).

Transgenic (genetically modified) crops may also play a role in reduction of preharvest aflatoxin accumulation. Insect damage is one factor that predisposes maize to mycotoxin contamination, because insect herbivory creates kernel wounds that encourage fungal colonization, and insects themselves serve as vectors of fungal spores (Dowd 1998, Munkvold et al. 1999). Bt maize is one of the most commonly grown transgenic crops in the world today. It contains a gene from the soil bacterium *Bacillus thuringiensis* (hence the name Bt), which

encodes for crystalline proteins that are toxic to certain members of the insect order Lepidoptera (reviewed by Wu 2007). Earlier Bt events showed only mixed success in controlling aflatoxin (Wu 2007), as they provide insect protection primarily against European corn borer and Southwestern corn borer, as opposed to the insects that have been associated with aflatoxin contamination: fall armyworm and maize earworm. However, a new Bt event that has just become available commercially and provides enhanced protection against these insects has shown promise in significantly reducing aflatoxin in field trials (Odyssey and Chilcutt 2007). In addition to Bt maize, prototypes of genetically engineered crops have been developed that contain genes encoding fungal growth inhibitors for reducing fungal infection. Gene clusters housing the genes governing formation of aflatoxin have been elucidated and are being targeted in strategies to interrupt its biosynthesis (Cleveland et al. 2003).

Biocontrol of aflatoxin refers to the use of organisms to reduce the incidence of *Aspergilli* in susceptible crops, so as to reduce aflatoxin contamination. The most widely used biocontrol method employs atoxigenic strains of *Aspergilli* that can competitively exclude toxigenic strains from colonizing crops. These biocontrol methods have been used in maize, groundnuts, and cottonseed worldwide (Cotty and Bhatnagar 1994, Dorner et al. 1999, Bandyopadhyay et al. 2005, Pitt and Hocking 2006, Cotty et al. 2007, Atehnkeng et al. 2008). Importantly, atoxigenic *A. flavus* strains have been found in sub-Saharan Africa, which show promise for controlling aflatoxin in African maize (Bandyopadhyay et al. 2005, Atehnkeng et al. 2008). Biocontrol methods, though applied in the field, can result in reduced aflatoxin in crops for as long as six months postharvest (Dr. Ranajit Bandyopadhyay, personal communication).

Cultural practices, including crop rotation, tillage, planting date, and management of irrigation and fertilization, can also help to prevent *Aspergillus* infection and subsequent aflatoxin accumulation by reducing plant stress. These practices can have important effects on infection and subsequent mycotoxin accumulation (Munkvold 2003). Ultimately, a combination of preharvest strategies, as described above, may be needed to adequately prevent mycotoxin contamination in the field (Cleveland et al. 2003).

Post-harvest interventions

Current food storage and processing practices in industrial nations can prevent postharvest development of mycotoxins, but postharvest aflatoxin accumulation remains a threat in less developed countries (LDCs), especially in tropical areas. Hence, knowledge of the key critical control points during harvesting, drying and storage stages in the cereal production chain are essential in developing effective prevention strategies post-harvest (Magan and Aldred 2007). Possible intervention strategies include good agricultural and storage practices, such as early harvesting, proper drying, sanitation, proper storage, and insect management, among others (Wagacha and Muthomi 2008). This is true not just for maize and groundnuts (the major sources of aflatoxin exposure for humans), but also for tree nuts such as pistachios, where there have been dramatic improvements in aflatoxin reduction in Iran due to improved drying and storage conditions over the past decade (Wu 2008).

Removing existing aflatoxin contamination is possible by sorting aflatoxin-contaminated kernels from relatively cleaner ones. This can be done by either simple physical (e.g., handsorting) or flotation and density segregation methods. Sorting by these types of methods has been shown to significantly decrease aflatoxin levels in postharvest maize (Kabak et al. 2006).

After sorting, there are several methods to prevent the growth of *Aspergilli* and hence reduce aflatoxin contamination postharvest. These include control of moisture levels in stored crops, temperature, and insect pests and rodents (Kabak et al. 2006).

Combinations of these methods to reduce postharvest aflatoxin have been tested for efficacy in actual rural village conditions. Turner et al. (2005) describe a postharvest intervention package to reduce aflatoxin in groundnuts, tested in Guinea. The package consisted of six components: education on hand-sorting nuts, natural-fiber mats for drying the nuts, education on proper sun drying, natural-fiber bags for storage, wooden pallets on which to store bags, and insecticides applied on the floor of the storage facility under the wooden pallets.

In industrial nations, drying with forced air and supplemental heat is common to control moisture levels in crops. At 70°C, *A. flavus* infection in maize is significantly reduced compared to that in the maize dried at 40°C. But this method can potentially reduce seed germination and increase stress cracks (Hawkins et al. 2005).

Chemical methods can detoxify aflatoxins by reduction, destruction, or inactivation. These methods include ammoniation, acid treatment, oxidizing agents, and reducing agents; and are reviewed in-depth in Kabak et al. (2006). There are several issues and risks associated with these methods: it is difficult to detoxify the aflatoxin without reducing nutritive value and palatability; parameters such as reaction time, temperature, and moisture must be monitored; some necessary additional cleaning treatments can be expensive and time-consuming, and toxic byproducts may be produced.

Dietary and food processing interventions

A variety of dietary interventions can reduce aflatoxin-related health risks. One simple dietary intervention, where feasible, is to consume less maize and groundnuts, in favor of other food crops that have significantly lower aflatoxin contamination, such as sorghum and pearl millet (Bandyopadhyay et al. 2007). Where it is not easy to make such a dietary shift, however (e.g., where maize and groundnuts have traditionally been staples), other dietary interventions may prove helpful.

One class of dietary interventions involves adsorption of aflatoxin. Adsorbent compounds can be included in food or feed or taken separately during mealtimes to bind aflatoxin in the gastrointestinal (GI) tract, resulting in reduced aflatoxin bioavailability. Several materials have varying degrees of this ability to bind aflatoxin, including bentonites, zeolites, diatomaceous earth, activated charcoal, and fibers from plant sources. One material that has proven effective in animal feed and is showing promise in human trials is calcium montmorillonite, marketed as NovaSil clay (NS). NS has been shown to prevent aflatoxicosis in many animal species when included in their diet, by binding aflatoxin with high affinity and high capacity in the GI tract (Phillips et al. 2008). NS has been shown to reduce aflatoxin toxicity on body and organ weights, feed intake, and hepatic vitamin A when tested in broiler chicks. No toxicity has been found in a dose as high as 0.5% w/w in the diet (Pimpukdee et al. 2004). Phase I (Wang et al. 2005) and Phase II (Afriyie-Gyawu et al. 2008) clinical trials confirm the safety of NS for use in human food, and provide assurance that NS does not bind with vitamin A and E, thereby does not result in elimination of these nutrients.

Green tea polyphenols (GTPs) have been shown to inhibit chemically-induced cancers in animal and epidemiological studies (Groopman et al. 2008, Phillips et al. 2008). GTPs inhibit initiation of aflatoxin-induced HCC in rats by modulating aflatoxin metabolism (Qin et al. 1997); and in humans, there are inverse associations between green tea consumption and cancer risk (Fujiki et al. 2002).

Chlorophyllin, a derivative of chlorophyll, is a natural constituent of green vegetables in the human diet that has shown anticarcinogenic effects in animals (Dashwood et al. 1998). Chlorophyllin appears to protect against aflatoxin by sequestering aflatoxin during the

digestive process and hence impeding aflatoxin's absorption. In addition, chlorophyllin may have enzyme-inducing properties that contribute to its mechanism of detoxification (Egner et al. 2001, Groopman et al. 2008). Aside from binding aflatoxin, chlorophyllin is capable of binding certain carcinogenic substances, such as polycyclic aromatic hydrocarbon (PAH), heterocyclic amines, and other hydrophobic molecules (Waladkhani and Clemens 2009). Moreover, other modes of action of chlorophyllin, such as scavenging free radicals (Kumar et al. 1999), inducing apoptosis in cancer cells (Diaz et al. 2003), inducing cell-cycle arrest, and altering markers of cell differentiation (Carter et al. 2004), have been proposed for its protective effects against DNA damage and colon cancer. Side effects of chlorophyllin are rare, but may include diarrhea and discoloration in urine and feces (Higdon 2007).

A variety of substances have the potential to reduce aflatoxin-induced HCC by inducing enzymes, such as glutathione-S-transferases (GSTs), that mediate conjugation of the reactive intermediate aflatoxin-8,9-epoxide. Genetic differences exist in the extent to which aflatoxin in the diet is biotransformed into this harmful epoxide; therefore, agents that induce GSTs have varying effectiveness among individuals. Dithiolethiones (oltipraz) and sulforaphane have this ability, and may also inhibit HBV transcription through elevation of p53 tumor suppressor genes (Chi et al. 1998). Oltipraz is an antischistosomal drug; while the precursors to sulforaphane, glucosinolates, can be found in cruciferous vegetables such as broccoli (Talalay and Fahey 2001, Kensler et al. 2005, Groopman et al. 2008).

There is increasing evidence that some lactic acid bacteria have the ability to bind aflatoxin B₁ (Haskard et al. 2000, Lahtinen et al. 2004, Hernandez-Mendoza et al. 2009). These bacteria are important in the fermentation of many foods, including vegetables, fruits, and dairy products. The main purpose of *Lactobacillus* inclusion in food has typically been fermentation, not the prevention of aflatoxin risk. Hence, inclusion of culturally appropriate fermented foods in the diet may be a feasible method of partially reducing aflatoxin risk. Other methods of food processing have moderate ability to reduce aflatoxin and other mycotoxins (Bullerman and Bianchini 2007), such as extrusion processing at temperatures greater than 150°C.

Hepatitis B vaccination

A regular practice now in the US and other developed nations, HBV vaccination in children is still rare in many parts of the world. Vaccinating children against HBV has been shown, over the last three decades, to significantly decrease HBV infection in several regions including Europe (Williams et al. 1996, Bonanni et al. 2003), Taiwan (Chen et al. 1996), and Thailand (Jutavijittum et al. 2005). This vaccine has already had, and will continue to have, significant impacts on liver cancer incidence, particularly in Africa and East Asia, considering that roughly 65 million out of 360 million individuals who are chronically infected live in Africa (Kramvis and Kew 2007). Though the vaccine itself has no impact on actual aflatoxin levels in diets, it reduces aflatoxin-induced HCC by lowering HBV risk, thereby preventing the synergistic impact of HBV and aflatoxin in inducing liver cancer. However, other health effects of aflatoxin such as retardation of growth and immunomodulation are not altered by HBV vaccination. Moreover, those who already have chronic HBV infection would not benefit from the vaccine, which is why it is very important for this vulnerable subpopulation to avoid aflatoxin exposure as much as possible.

Costs and efficacies of interventions to reduce aflatoxin risk

Tables 2 and 3 summarize the cost–effectiveness information for different interventions to reduce aflatoxin–induced adverse health effects. Table 2 contains information regarding agricultural interventions in preharvest and postharvest settings, while Table 3 contains information regarding dietary interventions and the hepatitis B vaccine. For agricultural

interventions, we label whether the cost and efficacy data for each method are relevant for maize, groundnuts, or cottonseed. For efficacy, we include data on the extent to which the intervention reduces aflatoxin levels in the food or feed, bioavailability of the aflatoxin (measured through reduction in key biomarkers), or HCC incidence. The cost data are given in terms of US dollars per relevant unit. In addition, we include columns for which stakeholder groups (e.g., growers, consumers) are likely to bear the cost for the intervention in the long run, and which groups are likely to benefit. All cost values have been converted to USD 2009.

There are several caveats. This list is not by any means comprehensive. For example, many naturally occurring dietary chemopreventive agents may have some level of efficacy against aflatoxin-induced HCC, but we include only those that were tested in clinical trials. For some interventions, little if any cost information exists. For interventions for which cost information could be found, we did not include a direct cost-to-cost comparison of all of the interventions for which cost information was available, because the units are very different; e.g., the cost per acre of a preharvest intervention, compared with the cost per household of a postharvest intervention or the cost for a monthly supply of a dietary intervention. However, we discuss the economic significance of each of these measures in the Discussion.

Costs and efficacy of pre-harvest interventions

Breeding aflatoxin resistance into crops requires upfront research and development funds in and between various nations, depending on where the seed will be deployed. However, once the resistant strains of crops are bred, the seed need not be significantly more expensive to farmers than existing genotypes. Efficacy in reducing aflatoxin has been shown to be as high as 90–98% in resistant maize varieties developed and tested in the US (Guo et al. 1996). Groundnuts bred for aflatoxin resistance in the US achieved at least a 70% reduction in preharvest aflatoxin contamination in multiple environments (Holbrook et al. 2006). Similarly, naturally aflatoxin-resistant lines in India had significantly lower aflatoxin levels compared with susceptible lines and produced higher pod yield (ICRISAT 2006). These efficacies do not necessarily apply to maize- and groundnut-producing regions outside the US and India, but demonstrate what the breeding technologies have the potential to achieve. A caution with interpreting these differences in aflatoxin levels is that one should distinguish between naturally resistant vs. specifically bred lines in terms of aflatoxin reduction. Importantly, drought stress is a critical factor for preharvest aflatoxin contamination in groundnuts and maize. In years when drought stress is not critical, even susceptible lines of groundnuts are less likely to be contaminated by aflatoxin. Now breeding efforts are focused in releasing lines with the specific aflatoxin-resistant attribute rather than improving on serendipitous levels found in natural lines.

Transgenic maize varieties will likely incur a greater cost to growers; however, the cost of transgenic seed is lower in LDCs because biotechnology companies are providing free intellectual property there. In the US, Bt maize seed costs about \$21 per acre more than conventional maize seed (Wu et al. 2008); the cost would be significantly lower in LDCs. Field trials of new Bt maize events in the US, which are effective against the insect pests that predispose maize to *Aspergillus* infection, show a 47% reduction in aflatoxin compared with non-Bt isolines (Odvodny and Chilcutt 2007).

The costs of biocontrol vary depending on the product and the locale. In the United States, the per acre cost of applying AF36 to control aflatoxin in cottonseed ranges from \$6–\$16 per acre, and achieves 70–90% aflatoxin reduction compared with cottonseed from untreated fields (Cline 2005, Wu et al. 2008). Afla-Guard™ applied to groundnuts costs about \$17–\$32 per acre (Wu et al. 2008), with 70–91% aflatoxin reduction compared with untreated groundnuts (Dorner and Horn 2007). Because of the local strain-specific response and to avoid introducing

foreign Aspergilli, it is important to identify local atoxigenic strains that potentially competitively exclude toxigenic strains. Biocontrol studies in Nigerian maize using local atoxigenic strains of *A. flavus* have shown efficacy levels at as high as 90%, with a cost of about \$10–\$12 per hectare: \$4.04–\$4.86 per acre (Dr. Ranajit Bandyopadhyay, personal communication).

Though the cost per unit area provides useful information for policy makers and growers to determine total cost for applying biocontrol to a specific area, the cost of biocontrol per consumption unit helps policy makers and growers to roughly screen whether biocontrol is economic feasible. To convert the cost data to consumption unit, we obtained production yields per unit area (FAOSTAT 2009) and divided by the per unit area cost. In the U.S., predicted groundnuts production in 2009 (based on 2003–2007 FAOSTAT database) is about 3,300 kg per hectare, or 8,200 kg per acre, hence Afla-Guard™ costs 0.21–0.39 cents per kilogram of groundnuts. The cost of biocontrol per kilogram of maize in Nigeria ranges from 0.52 cents to 0.63 cents, based on the predicted maize yield in 2009 of 1,900 kg/ha.

A combination of irrigation systems and insecticide applications can reduce aflatoxin levels by 99% in maize, compared with non-irrigated, non-treated maize in the US (Smith and Riley 1992). However, this combined intervention might be costly in LDCs where irrigation systems have yet to be installed widely. The cost of insecticide varies widely, depending on the locale and the chemical.

Methods for irrigation vary greatly from a simple method using watering-cans or buckets to complicated methods that require complex equipment and maintenance. In the US, the initial cost of drip- and micro-irrigation systems ranges from US \$ 640 to \$4,000 per acre, depending on the type; e.g. surface, buried or sub-surface drip systems (Burt 2000). The capital cost per acre of sprinkler irrigation systems ranges from US \$740–\$940. The cost for ownership (depreciation, insurance, and interest) and operating per year is about US\$ 130–\$170 per acre (Scherer 2005).

Compared to sprinkler methods, surface irrigation systems, in general, need lower energy and capital requirements, but this method has disadvantages: higher labor requirements, lower water efficiency and potential soil erosion. The costs of four types of surface irrigation systems, including the siphon tube, the gated pipe, the surge flow, and the cablegation pipe have been estimated for 20 acres at \$220, \$170, \$250, and \$190, respectively (Smathers et al. 1995). The estimated cost for irrigation system installation is about \$1,100–\$1,300 per acre (Godsey et al. 2007), but if traditional crop-watering methods are used, the cost is much lower (and efficacy is perhaps also lower).

Costs and efficacy of post-harvest interventions

Aflatoxin control can also be achieved by sorting, proper drying of food, and suitable storage conditions. Mechanical blanching and sorting of groundnuts in the US has the ability to almost completely eliminate aflatoxin, and the blanching and sorting each cost about \$150–\$170 per ton (Dorner and Lamb 2006). In LDCs, it is far less common to have blanching and sorting machines, so most sorting of groundnuts is done by hand. The cost in terms of lost product varies enormously, depending on aflatoxin levels in any given harvest. Even the efficacy of sorting may vary, depending on how well farmers can identify aflatoxin-contaminated nuts – hence, the importance of education and outreach to farmers on aflatoxin contamination and its identification. However, time-related costs should also be taken into account. It is estimated that one farmer would require an entire day to hand-sort 40–50 kg groundnuts (Dr. Jonathan Williams, personal communication).

Turner et al.'s (2005) postharvest intervention package reduced aflatoxin levels in groundnuts by 69% compared with control groundnuts. Moreover, mean serum aflatoxin albumin adducts in villagers adopting this package was 57.2% lowered than that of the control villagers five months after harvest. While the initial cost of this package was about \$50 per household in 2005 to improve the storage condition of 25 groundnut bags, many components of the package last for several years (e.g., the wooden drying pallets, storage bags, and insecticide) (Turner et al. 2005).

The cost of artificial drying to reduce aflatoxin depends on the costs of fuel and electricity, and the differences of moisture content (MC) in harvested crops and the required levels. Reducing one point of moisture from a bushel of maize (25.40 kg) costs about 4.5 cents (Roegge 2008). Whether they choose to dry their product using natural or artificial drying method, growers in developed countries, somehow, have to “pay” for excess moisture left in their grains. Increase in field loss due to stalk lodging, insect and spreading of ear molds often happens with field drying method. Grain storage operators charge growers about 11–12 cents per point (MC) per bushel (Roegge 2008) for drying grain delivered too wet.

One chemical treatment option, ozonation, costs only \$5 per ton (King and Prudente 2005). Although ozonation can completely degrade AFB₁ at high moisture and temperature for 2 hours, animals fed with the treated cottonseed and peanut meal had lower protein efficiency ratios than those fed the aflatoxin-contaminated meal, indicating that ozonation might degrade essential nutrients or produce new toxins (King and Prudente 2005).

Cost-effectiveness of dietary aflatoxin risk reduction strategies

Dietary interventions do not directly reduce aflatoxin in food, so aflatoxin biomarkers are the important intermediate endpoints to measure the efficacies of diet against aflatoxins' toxicities. Several metabolites of AFB₁ and aflatoxin macromolecular adducts are currently used as biomarkers of aflatoxin exposure. The most commonly used biomarkers for recent (short-term) aflatoxin exposure are urinary aflatoxin M₁ (AFM₁), and aflatoxin DNA adducts. AFM₁, secreted in urine and breastmilk, is an oxidative metabolite of AFB₁. Levels of AFM₁ reflect aflatoxin exposure in the past 24 to 48 hours. In humans, it is estimated that about 0.2% of AFB₁ is excreted as AFB₁-N⁷-Guanine. (Groopman et al. 1993). Twenty-four hour excretions of aflatoxin B₁-DNA adduct at N⁷ of guanine (AFB₁-N⁷-Gua) in urine following aflatoxin exposure in rats have shown to be linearly correlated with aflatoxin exposure. AFB₁-N⁷-Gua, aside from being a biomarker for aflatoxin exposure in more short-term time scales (over the last day), reflects DNA damage that can in the long term increase risk of developing HCC (Groopman et al. 2005). It is noteworthy that high variations of the short-term aflatoxin biomarkers, which may reflect the heterogeneity of contamination, have been reported (Wang et al. 2008, Tang et al. 2008). An increased excretion of urinary aflatoxin mercapturic acid (AFB₁-NAC), a phase 2 AFB₁ metabolite, is reported in a study of oltipraz, which is believed to induce phase 2 enzyme metabolism (Wang et al. 1999).

Unlike urinary AFM₁ and AFB₁-N⁷-Gua, albumin adducts of aflatoxin provide integrated levels of aflatoxin exposure over a period of months because of the relatively long turnover period of albumin (the half-life of albumin is approximately 20 days in healthy individuals). Though the longer period (e.g., years) of aflatoxin albumin adducts in body is also proposed (Wang et al. 2008). The level of aflatoxin albumin adducts in maternal blood has been associated with decreased height and weight gain during the first year of life (Turner et al. 2007).

Aside from the aforementioned biomarkers, radiolabeled aflatoxin B₁ has been used as markers in several *in vitro* and *in vivo* aflatoxin studies (Degen and Neumann 1978, Goto and Hsieh D

1985, Phillips et al. 1991). The results from a chicken study, in which carbon-14 (^{14}C) radiolabeled aflatoxin was used as a marker, showed that with NovaSil doses of 0.5%, bioavailability of aflatoxin in the blood and liver were 5.3% and 14.6%, respectively, compared to those in the control group (Phillips et al. 1991). Aflatoxin-albumin adducts in both low-dose and high-dose NovaSil intervention arms – when administered in capsules three times daily – were significantly lower than those in the control arm after 3 months, with a roughly 25% reduction: $0.89\text{--}0.90\text{ p mol mg}^{-1}$ vs. 1.20. A 58.7% reduction in AFM_1 was also observed in the high-dose arm three months into the study. (Wang et al. 2008). Adding 4.5 kg of calcium montmorillonite clay to a ton of animal feedstuffs costs \$2–\$6 (Paul et al. 1995). Texas Enterosorbent, Inc. has developed a new related product intended for future human use: calcium aluminosilicate/uniform particle size NovaSil (CAS/UPSN). This new product would cost about 18 cents per 3-gram daily dose (Dr. Robert Carpenter, personal communication). If NovaSil were blended into food, such as maize meal, the cost could be decreased and the efficacy might be increased, depending on dose. As such, the cost could be as low as \$0.73 per person per year (Dr. Timothy Phillips, personal communication).

Green tea polyphenols (GTPs) appeared to inhibit aflatoxin-induced initiation of HCC in rats, with 20–25% lower AFB_1 -DNA adducts compared with rats in a control group (Qin et al. 1997). In a human study in China, subjects in an intervention group receiving 500 mg daily GTP had 13% lower aflatoxin-albumin adduct levels after 3 months, compared with the placebo group; but there was no significant difference in albumin adduct levels between the placebo group and a group that received 1000 mg daily GTP. There was, however, about a 43% lower AFM_1 level in both GTP intervention groups compared with the control group (Tang et al. 2008). There were no significant differences between the groups after 1 month. The cost of GTPs ranges enormously depending on how it is administered: in the form of green tea, or in capsules. For tea that can be purchased in retail outlets, costs range from \$0.20–\$1.00 per day (LEF 2009, OrganicKingdom 2009, Vitaminalife 2009), providing a range of GTPs from 710–900 mg.

In a randomized, double-blind, placebo-controlled trial in China, subjects who consumed chlorophyllin in each meal for 4 months showed 55% lower aflatoxin- N^7 -guanine adducts compared with subjects in the control arm (Egner et al. 2001). The cost of chlorophyllin is comparable to that of NovaSil: about \$0.10 per daily dose (Dr. Thomas Kensler, personal communication).

Oltipraz administered in different schedules at different doses results in varied changes in aflatoxin biomarkers, indicating alterations in both Phase 1 and 2 metabolism of aflatoxin. In a human intervention group in China, one month of 500 mg oltipraz administered weekly resulted in 51% lower AFM_1 (phase 1 metabolite) levels compared with a placebo group, but no difference in aflatoxin-mercaptopuric acid (phase 2 metabolite) levels was found. Lower doses of oltipraz (125 mg) administered daily resulted in a 2.6-fold increase in aflatoxin-mercaptopuric acid excretion, but no difference in AFM_1 (Wang et al. 1999). In a study involving rats administered high aflatoxin doses for 5 weeks, those given oltipraz during each week achieved a 42% reduction in HCC risk (Kensler et al. 1997). No cost information is available on pharmaceutical-grade oltipraz; the cost for analytical-grade oltipraz is \$59 per 5-mg sample and \$236 per 25-mg sample (Sigma Aldrich 2009). Though oltipraz can reduce aflatoxin bioavailability via several mechanisms, its cost makes it an economically impractical intervention. Second- and third-generation dithiolethiones are less expensive and more potent than oltipraz (McBee 2005), but further studies on their potential side effects are needed.

Sulforaphane administration did not result in significant reductions in aflatoxin- N^7 -guanine in two human intervention groups in China (high dose and very low dose), but interindividual

variation in bioavailability was high. An inverse association was found between urinary levels of dithiocarbamates (sulforaphane metabolites) and aflatoxin-DNA adducts (Kensler et al. 2005). Thirty sulforaphane capsules cost \$25 (0.21% sulforaphane in 250 mg) (amazon.com). If consuming broccoli sprouts or a tea from these sprouts, a dose of 385-gram sprouts containing over 400 μmol glucoraphanin (to be metabolized to sulforaphane) costs about \$0.31.

Costs and efficacy of hepatitis B vaccination

Because of the massive production of hepatitis B vaccines through improved biotechnologies, second-generation HBV vaccines' costs are much cheaper than the costs of the first generation vaccines. The vaccine's efficacies against HBV infection and chronic HBsAg carriage were 84–95% and 94–95%, respectively (Viviani et al. 1997, Whittle et al. 1995). It is estimated that 53% of global HCC cases are attributable to HBV (Perz et al. 2006); therefore, we assume in Table 3 that the corresponding reduction of HCC risk due to HBV vaccination ranges from 45–50%. Currently a dose of HBV vaccine costs less than US \$1 (Evans and Kaslow 1997). It is estimated that HBV vaccination costs \$910 for every death averted and \$23 for every disability-adjusted life year (DALY) averted (Griffiths et al. 2005).

Currently available vaccines for HBV are multivalent vaccines. One of them is a pentavalent vaccine, in which HBV vaccine is combined with vaccines for diphtheria, tetanus, pertussis, and Haemophilus influenzae b (Hib). The five-in-one vaccine is believed to provide economic advantages over multiple immunizations of each monovalent preparation (GAVI Alliance 2010a). The cost of the pentavalent vaccine is expected to drop to \$2.94 per dose in 2010, 50 cents less than its cost in 2009 (GAVI alliance 2010b). Moreover, one of the major benefits of pentavalent vaccine; particularly in less developed countries where there is often a scarcity of health care personnel, is that the pentavalent vaccine reduces the total amount of time healthcare personnel spend to immunize children (GAVI alliance 2010a).

How to analyze cost-effectiveness of interventions

The World Health Organization (WHO) Commission for Macroeconomics and Health (WHO 2001) provides the following guideline for thresholds of cost-effectiveness, as outlined in Wu and Khlangwiset (2010):

1. An intervention is considered very cost-effective, if the monetary amount spent on the intervention per DALY averted is less than the *per capita* gross domestic product (GDP) for the nation in which the intervention is applied. In other words, the total cost of the intervention should be less than the product of the GDP and total DALYs averted.
2. An intervention is considered moderately cost-effective, if the monetary amount spent on the intervention per DALY averted is less than three times the *per capita* GDP.
3. An intervention is not cost-effective if, per DALY averted, its cost is greater than three times the *per capita* GDP.

The disability-adjusted life year (DALY) is a measure of the burden of disease. It includes both potential years of life lost due to premature death and years of “healthy” life lost in states of less than full health, broadly termed *disability* (Havelaar 2007). The total number of DALYs associated with a disease is the sum of the years of life lost due to mortality from the disease (YLL) and the number of years lived with a disability multiplied by a weighting factor between 0 and 1, depending on the severity of the disability (YLD):

$$\text{DALY} = \text{YLL} + \text{YLD}$$

Equation (1)

Wu and Khangwiset (2010) estimate the cost-effectiveness of two aflatoxin control methods – biocontrol and postharvest drying and storage methods – in sub-Saharan Africa. By assuming a decrease in aflatoxin-induced HCC that is proportional to decreases in aflatoxin levels in maize preharvest and postharvest (for biocontrol) and aflatoxin-albumin adducts (for the postharvest intervention package), cost-effectiveness ratios (effectiveness in saving lives from cancer divided by cost of intervention) of 5.10–24.8 for biocontrol and 0.21–2.08 for the postharvest intervention package were estimated. Interventions whose cost-effectiveness ratios are greater than 1 can be deemed “very cost-effective” by WHO standards. These calculated ratios are actually underestimates of cost-effectiveness, because there are benefits to reducing aflatoxin other than decreasing liver cancer risk; there are benefits of improved immunity and reduced risk of stunting in children.

The cost information is usually presented in varying formats depending on the intervention in question; so cost-effectiveness analyses must be flexible, and care must be taken, to ensure that appropriate units are compared. For example, Wu and Khangwiset (2010) started with cost data on biocontrol and postharvest intervention packages in two different formats: Biocontrol cost was given as a monetary amount per hectare treated, while the postharvest intervention package cost was given as a monetary amount to store 500–1,250 kg of groundnuts. To convert this into usable cost-effectiveness information, it was necessary to convert the costs using other data (e.g., amount of maize produced per hectare, amount of maize consumed on average per individual per year, number of households in Republic of Guinea) to estimate how many individuals were affected by the intervention every year.

It is important to choose appropriate health endpoints (i.e., effects) by which to evaluate DALYs. Aflatoxin, as described in the Introduction, has multiple different adverse health effects. The relationship between aflatoxin and HCC is the most well-established (JECFA 1998). DALYs have been estimated for HCC, so this makes HCC prevention a convenient endpoint by which to evaluate the cost-effectiveness of aflatoxin risk reduction strategies. Stunted growth in children also has DALYs estimated for its societal impacts. Acute aflatoxicosis is a relatively less common effect associated with aflatoxin exposure. Immunosuppression is an extremely important effects associated with aflatoxin; however, the exact relationship is not as well characterized.

Table 4 lists the average annual GDP *per capita* in select nations across the world (The Economist 2007). These figures shed light on how feasible some of the aforementioned public health interventions would be in different parts of the world. In nations like Zimbabwe, where the average annual GDP per capita is \$280 (USD), it is impossible for most individuals to afford an intervention that would cost more than a few cents per day; as the average daily income is less than \$1. Even if the one-time cost of an intervention could improve health for years, it cannot be assumed that most families have saved enough money to be able to afford such an intervention. There are many competing demands for scarce resources, and often availability of food is more important than quality of that food. Moreover, a major challenge for any intervention in food-insecure countries is that there is little price differential for quality; hence, producers may have no incentive to invest in quality enhancement. It is likely that governments would need to pay for aflatoxin reduction interventions, at least in the foreseeable future.

Ironically, individuals in industrial nations such as the US, United Kingdom, Canada, and Australia rarely directly pay the price to reduce aflatoxin-induced illness, whether by agricultural or clinical means. These costs are usually borne by growers (agricultural interventions to reduce aflatoxin) or by health insurance institutions or the national government (HBV vaccination).

Discussion

The main purpose of this review is to bring together the scientific knowledge base (efficacies) and economic factors (costs, stakeholders) concerning aflatoxin risk-reduction strategies that could be deployed worldwide, and to highlight the importance of economic feasibility. Policy makers can use this information to decide: (1) whether the benefits (market and health) outweigh the costs of implementing the strategies, and (2) if so, then which stakeholders would pay the costs and which would benefit in the long run, to resolve potential mismatches in economic incentives (Wu et al. 2008).

This information can also be useful to researchers who are developing further aflatoxin control strategies, in that they can roughly position their interventions among various existing strategies in terms of economic feasibility. It can also be useful to decision makers who want to weigh the relative importance of two categories of cost: the cost of preventing aflatoxin-related risks (to both markets and human health), and the cost of *not* preventing aflatoxin-related risks.

In preharvest settings, conventional breeding of maize and groundnuts to resist aflatoxin has shown great promise in terms of achievable efficacies. While initial research and development funding is of course necessary, once the resistant varieties are developed and disseminated, significant reduction of aflatoxin contamination can be achieved at very low, if any, additional cost to farmers. Replacement of local maize cultivars with agriculturally-improved varieties has been well-accepted by African farmers in recent history. It is estimated that a large part of 40% of present African maize yield is the result of planting improved cultivars (Smale and Jayne 2004). Transgenic crops that demonstrate aflatoxin reduction, on the other hand, may encounter several problems regarding wide-scale adoption worldwide. One problem is cost. Though the actual cost per acre for transgenic seeds may not be high, farmers may be required to buy new seeds each season if the seeds were developed in the private sector. Such an expense for farmers who are used to saving seed from season to season might be considered unacceptable. Another problem is governmental regulations against commercialization and trade of transgenic organisms in many parts of the world. Hence, transgenic technologies in agriculture are at the moment best-suited to nations in which it is already customary to buy new seed each season, and where biosafety laws permit planting of transgenic seeds.

Biocontrol through atoxigenic strains of *Aspergilli* has shown significant promise in controlling aflatoxin in a variety of crops in both preharvest and postharvest settings. Depending on the product, costs vary widely; but low-cost options are available in LDCs that have naturally occurring atoxigenic strains in their native soils. Biocontrol can be extremely cost-effective in reducing aflatoxin-induced disease (Wu and Khlangwiset 2010) because of the protection against aflatoxin contamination that lasts for at least 6 months postharvest. As with transgenic crops, there may be regulatory issues to overcome in different nations, associated with the application of fungal strains to agricultural fields.

Good agricultural practices – those that can reduce various stresses on crop plants and hence reduce fungal infection – can reduce aflatoxin contamination. Irrigation systems combined with insecticides can achieve extremely high efficacy in aflatoxin reduction, but capital costs

to install the systems can be very high, as can operation and maintenance costs. These systems may not be affordable yet in many poorer LDCs.

In postharvest settings, physical methods to reduce aflatoxin accumulation are generally both less expensive and less risky than chemical methods. Physical sorting can remove the most contaminated food immediately postharvest. The postharvest intervention package described in Turner et al. (2005), which includes sorting as well as wooden drying pallets, natural-fiber storage bags, and insecticides, was estimated to be extremely cost-effective in reducing aflatoxin-induced HCC (Wu and Khangwiset 2010), without significant health or environmental risks. Chemical methods of destroying aflatoxin such as ammoniation and ozonation have extremely high efficacy levels at relatively low costs. However, handling ammonia can be dangerous if done improperly, and the process can cause reduced palatability and produce a byproduct which, though much less risky than AFB₁, may pose some health risks. Ozonation, because it appears to reduce protein efficiency in animals, may carry nutritional risks.

Dietary interventions to reduce aflatoxin risks can be considered forms of secondary prevention, as they do not actually reduce the amount of aflatoxin in the food, but can reduce its bioavailability in the body. NovaSil clay and chlorophyllin can both be produced at extremely low cost, and have shown significant reduction in biomarkers of aflatoxin-induced damage. Because both NS and chlorophyllin must be consumed at the same time as contaminated food in order to adsorb or sequester the aflatoxin, one potentially feasible mechanism is to blend these agents into a food item that is frequently used in local diets (e.g., maize meal). Green tea polyphenols would be an extremely cost-effective way to potentially reduce aflatoxin-induced health risks in cultures where green tea is already common in the diet. Otherwise, transportation costs and issues concerning the introduction of a relatively foreign drink (or pill) into the diet may render it impractical.

Chemoprevention through oltipraz and sulforaphane has shown some promise in reducing aflatoxin-induced HCC. Oltipraz is relatively expensive, however; and may not be practical as a long-term solution due to potential side-effects. With regard to obtaining sulforaphane from natural foods, at least two constraints exist: 1) the foods should ideally be locally produced, and 2) there is much variation in the concentration of the active compound in food. Therefore, it might be more reasonable to consider dietary chemoprevention as an additional intervention to other agricultural or clinical methods to reduce aflatoxin risks.

Hepatitis B vaccination has been employed in some degrees in Africa, initially with support from non-profit organizations such as the Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund (Zanetti et al. 2008). However, if support is withdrawn, each country has to determine the feasibility and costs of continuing this program within its own budget. As much of the infrastructure and basic materials needed for vaccination have been established during the initial phase, and inexpensive and effective vaccines are available, HBV vaccine programs are overall a useful, cost-effective, and feasible strategy to reduce aflatoxin-induced HCC (and indeed, HCC in general). However, the vaccine has no effect in those already infected with HBV. Hence, other aflatoxin-reduction methods are desirable, particularly in nations where HBV prevalence is high and HBV vaccination is still scarce.

Overall, efficacy tends to be higher for agricultural interventions (preharvest and postharvest) and for HBV vaccination than for dietary interventions, to reduce aflatoxin-related health risks. However, there are times in which only dietary interventions would be helpful, such as in the case of an emergency. For example, if an acute aflatoxicosis outbreak is occurring, it is too late to adopt agricultural interventions or to administer HBV vaccines to reduce aflatoxin's

health effects – at least, to counteract the current crisis. Adsorbent compounds in the diet would make the most sense in such an emergency, if it is suspected that available food sources still contain dangerously high aflatoxin levels, and if the food cannot be simply discarded (e.g., for reasons of scarcity).

A limitation with the cost estimates of several of these interventions is that many of the costs reflect estimates from pilot studies (field or clinical trials) or anecdotal data. Actual costs done on a large scale for some interventions cannot be estimated, because some of the interventions have never been implemented on a large scale. Because of economies of scale, this is more likely to result in cost overestimates in this study, rather than underestimates. This highlights the need for further research to more accurately establish costs and efficacy of aflatoxin-risk reduction interventions worldwide.

A critical component to implementing any or all of these methods is community education (Phillips et al. 2008). Not only should educational efforts include *how* to use the intervention properly to achieve maximum benefit regarding aflatoxin risk reduction, it should also include *why* the interventions are important from health and market perspectives, so that users have incentive to continue with the interventions.

In summary, to reduce aflatoxin related problems in less developed countries, multiple types of interventions are potentially cost-effective; as they focus on different targets, offer different outcomes, and achieve those outcomes under different time constraints. Understanding the costs, efficacy, and affected stakeholders of different aflatoxin control interventions can help decision makers – be they government policymakers or farmers or consumers – to optimally allocate resources, with the ultimate aim of improving public health.

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Table 1

Factors included in cost–effectiveness analysis of public health interventions to reduce aflatoxin and its related illnesses.

Factor	Categories	Rationale
Stage at which intervention occurs	<ul style="list-style-type: none"> • Agricultural • Dietary • Clinical 	To understand how many people, and what group of people, must implement the intervention; and under what conditions
What the intervention reduces	<ul style="list-style-type: none"> • Aflatoxin levels in food • Bioavailability of aflatoxin and its metabolites in body 	To determine whether the intervention reduces adverse health effects, adverse market effects, or both
Cost–effectiveness of intervention	<ul style="list-style-type: none"> • Cost • % reduction of aflatoxin or bioavailability of aflatoxin / metabolites 	To determine the economic factors underlying each intervention: costs vs. potential benefits
Stakeholder involvement	<ul style="list-style-type: none"> • Who pays for the intervention • Who benefits from the intervention 	To understand if the appropriate economic and health incentives exist for people to adopt the intervention

Table 2
Costs and efficacy of agricultural interventions to reduce aflatoxin and its adverse health effects.

Intervention	Efficacy		Cost	Who pays	Who benefits
	Aflatoxin reduction ^a	Aflatoxin adduct reduction			
Agricultural (preharvest and postharvest)	Aflatoxin resistance breeding (conventional and transgenic)	Conventional: >70%; 82–93% [G] (Holbrook et al. 2006; ICRISAT 2006) Transgenic: 47% in Bt maize (Odvody & Chilcutt 2007)	Research & development costs; no expected additional cost to grower	Institutes funding research	Growers, Consumers
	Biocontrol using competitive fungi	60–87% [M] (Domer et al 1999) 70–91% [G] (Dorner and Horn 2007) 80% AF36 [C] (Cline 2005)	\$10–\$12/ha (\$4–\$5/acre; Dr. Ranajit Bandyopadhyay, personal communication) ¢0.52 –¢0.63/kg (Nigeria) \$17–\$32/acre [Afla-Guard™] (Wu et al. 2008) ¢0.21–¢0.39/kg (USA) \$6–\$16/acre [AF36] (Wu et al. 2008) ¢1.50–¢4.00/kg USA	Growers Growers Growers	Growers, Consumers Growers, Consumers Growers, Consumers
	Irrigation+ insecticide	99% [M] (Smith and Riley 1992)	\$1,100–\$1,300/acre to install irrigation (Godsey et al. 2007) <i>Drip-Micro Irrigation System</i> \$960–1,770 / acre for the drip on orchard (surface) irrigation system (CI) \$1,300–2,250/acre for the drip on orchard (buried) irrigation system (CI) \$640–1,600/acre (CI) + \$240–480 (AC for hose replacement cost) for the above ground row crop drip system \$ 1,440–4,010/acre for permanent installation cost of subsurface row crop drip (Burt 2000)	Government, growers	Growers, Consumers

Intervention	Efficacy		Cost	Who pays	Who benefits
	Aflatoxin reduction ^a	Aflatoxin adduct reduction			
			<i>Sprinkler Irrigation System</i> \$ 740–940/acre (CI)+ \$130 –170 (AC) (Scherer 2005)		
			<i>Surface Irrigation System</i> \$400–810/acre (CI) + \$220/acre (AC) for the siphon tube \$210–420/acre (CI) + \$170/acre (AC) for the gated pipe \$600–1,200/acre (CI) + \$250 (AC) for the surge flow \$340–680/acre (CI) + \$190 (AC) for the cablegation pipe (Smathers et al. 1995)		
Postharvest intervention package (natural fiber bags, wooden drying pallets, insecticide)	69% [G] (Turner et al. 2005)	57.2% lower aflatoxin albumin adducts in humans	\$61 per household for several years [bags and wooden pallets can be reused] (Turner et al. 2005)	Growers	Growers, Consumers
Artificial drying			4.5 cents per bushel (M) (Roegge 2008)	Growers	Consumers

^{**} **Note:** All cost data are converted to USD 2009 values.

^a C= cottonseed, M= Maize, G = Groundnut, NA = Not available
CI = Capital investment, AC = Annual cost

Table 3
Costs and efficacy of dietary and clinical interventions to reduce aflatoxin's adverse health effects.

Intervention	Efficacy		Cost	Who pays	Who benefits
	Aflatoxin adduct reduction	HCC reduction			
Dietary/Chemo-prevention	NovaSil™ clay	58.7% lower AFB ₁ ; ~25% lower Aflatoxin albumin adducts in humans (Wang et al. 2008)	–	Consumers, government	Consumers
	Green tea polyphenols (500–1000 mg)	~ 43% lower AFB ₁ in humans; > 15% lower aflatoxin albumin adducts at 500 mg dose (Tang et al. 2008); 20–30% lower AFB ₁ -DNA adduct in rats (Qin et al. 1997)	Up to 70% lower hepatic preneoplastic lesions in rats (Qin et al. 1997)	Consumers	
	Chlorophyllin	55% lower AFB ₁ -N ⁷ -Guanine in humans (Egner et al. 2001)	–	Consumers	
	Oltipraz	51% lower AFB ₁ [500 mg weekly], 2.6-fold increase in aflatoxin B ₁ mercapturic-acid excretion [125 mg daily] (Wang et al. 1999)	42% lower HCC incidence in F344 rats (Kensler et al. 1997)	Consumers	
	Sulforaphane (400 μmol ~ 70 mg)	No significant reduction in AFB ₁ -N ⁷ -Guanine, but inverse association for dithiocarbamate excretion and AFB ₁ -N ⁷ -Guanine (Kensler et al. 2005)	–	Consumers	
Vaccine	Hepatitis B vaccine	–	84–95% HBV reduction → 45–50% HCC reduction (Viviani et al. 1997, Whittle et al. 1995, Perz et al. 2006)	Government	HBV-uninfected individuals

** Note: All cost data are converted to USD 2009 values

Table 4

Average annual gross domestic product (GDP) per head in select countries across the world, in USD 2008. Source: The Economist (2007).

Nation	Annual GDP per capita, USD 2008
Australia	\$36,260
Canada	\$34,480
China	\$1,700
Cote d'Ivoire	\$900
Kenya	\$550
Nigeria	\$750
Thailand	\$2,750
United Kingdom	\$36,830
United States	\$41,640
Zimbabwe	\$260