afla control
Improving lives in Africa
FACILITATED BY IFPRI

THE HEALTH ECONOMICS OF AFLATOXIN: GLOBAL BURDEN OF DISEASE

WORKING PAPER 4 • FEBRUARY 2011

Felicia Wu, Clare Narrod, Marites Tiongco, and Yan Liu

CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

In 2004, several hundred Kenyans became severely ill, and 125 died, of acute aflatoxicosis: a disease of liver failure associated with consuming extremely high levels of aflatoxin in food (Lewis et al. 2005; Strosnider et al. 2006). Since then, over the last six years, greater global public attention has been drawn to aflatoxin and its associated health risk.

While this severe outbreak was devastating, far more individuals suffer from diseases associated with lower, chronic levels of aflatoxin consumption in maize and groundnuts. It has been estimated that more than 5 billion people in developing countries worldwide are at risk of chronic exposure to aflatoxins through contaminated foods (Shephard 2005; Strosnider et al. 2006). The primary disease associated with aflatoxin intake is hepatocellular carcinoma (HCC, or liver cancer). This disease is the third-leading cause of cancer death globally according to WHO (2008), with about 550,000–600,000 new cases each year. Eighty-three percent of these deaths occur in East Asia and sub-Saharan Africa (Parkin et al 2005; Strosnider et al. 2006; Kirk et al. 2006). Liver cancer has an increasing incidence that parallels the rise in chronic hepatitis B (HBV) and hepatitis C (HCV) infection (Liu and Wu 2010). Among the most potent hepatocarcinogenic agents known is aflatoxin, which belongs to a group of toxins called mycotoxins (toxins produced by fungi in food crops). Aflatoxins are produced by *Aspergillus flavus* and *A. parasiticus*, fungi that colonize maize and nuts (see Box 1). HBV infection and aflatoxin synergize to produce ~30-fold higher liver cancer risk in HBV-positive, aflatoxin-exposed persons, as compared to HBV-negative persons (Groopman et al. 2008; Wu and Khlangwiset 2010; Liu and Wu 2010). Unfortunately, HBV and HCV rates are high in sub-Saharan Africa as well as in Asia, which means that the risk of liver cancer from aflatoxin consumption is greatly magnified. As depicted in Figure 1, liver cancer is one of the most common liver diseases in sub-Saharan Africa and in the world. In addition to liver cancer, aflatoxin has also been linked to stunted growth in children and immune system disorders (Gong et al. 2002, 2003, 2004, Jolly et al. 2008, Khlangwiset et al. 2011).

Box 1: What are aflatoxins?

Aflatoxins are a group of approximately 20 related fungal metabolites produced primarily by the fungi *Aspergillus flavus* and *A. parasiticus*. The four major naturally produced aflatoxins are known as B_1, B_2, G_1, and G_2. "B" and "G" refer to the blue and green fluorescent colors produced under UV light on thin layer chromatography plates, while the subscript numbers 1 and 2 indicate major and minor compounds, respectively. Aflatoxin B_1, the most toxic of the aflatoxins, is the most potent naturally occurring chemical liver carcinogen known. Specific P450 enzymes in the liver metabolize aflatoxin into a reactive oxygen species (aflatoxin-8,9-epoxide), which may then bind to proteins and cause acute toxicity (aflatoxicosis) or to DNA and induce liver cancer (Wild and Gong 2010; Wu and Khlangwiset 2010). (Another form of liver cancer is cholangiocarcinoma, caused primarily by liver flukes; this type is relatively rarer.)

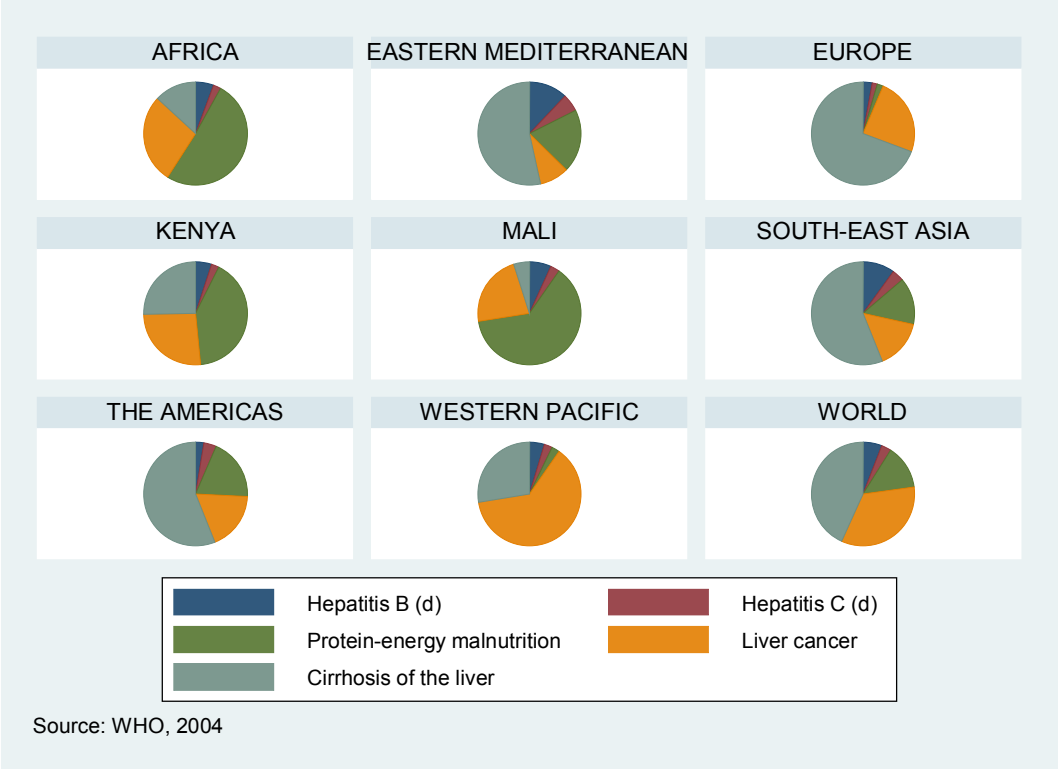

Figure 1 Liver diseases worldwide, by region, and in Kenya and Mali.

AFLATOXINS AND THEIR HEALTH CONSEQUENCES

Aspergillus flavus and A. parasiticus colonize a wide variety of food commodities including maize, oilseeds, spices, groundnuts, tree nuts, milk, and dried fruit (Strosnider et al. 2006). Whether these fungi produce aflatoxin depends on drought stress and rainfall, suitability of crop genotype for its climate, insect damage, and agricultural practices (Wu and Khlangwiset 2010). These fungi can also produce aflatoxin in "postharvest" conditions: storage, transportation, and food processing. Aflatoxin contamination is a particular problem in maize, oilseeds, spices, peanuts, tree nuts (almonds, pistachios, hazelnuts, pecans, Brazil nuts, and walnuts), milk (in the form of aflatoxin B1's metabolite aflatoxin M1), and dried fruit (Shephard, 2008). Maize and peanuts are the main sources of human exposure to aflatoxin because they are so highly consumed worldwide and unfortunately are also the most susceptible crops to aflatoxin contamination (Wu and Khlangwiset 2010). Figure 2 (Wu 2010) depicts the pathway by which aflatoxin accumulates in food crops and contributes to various adverse human health effects.

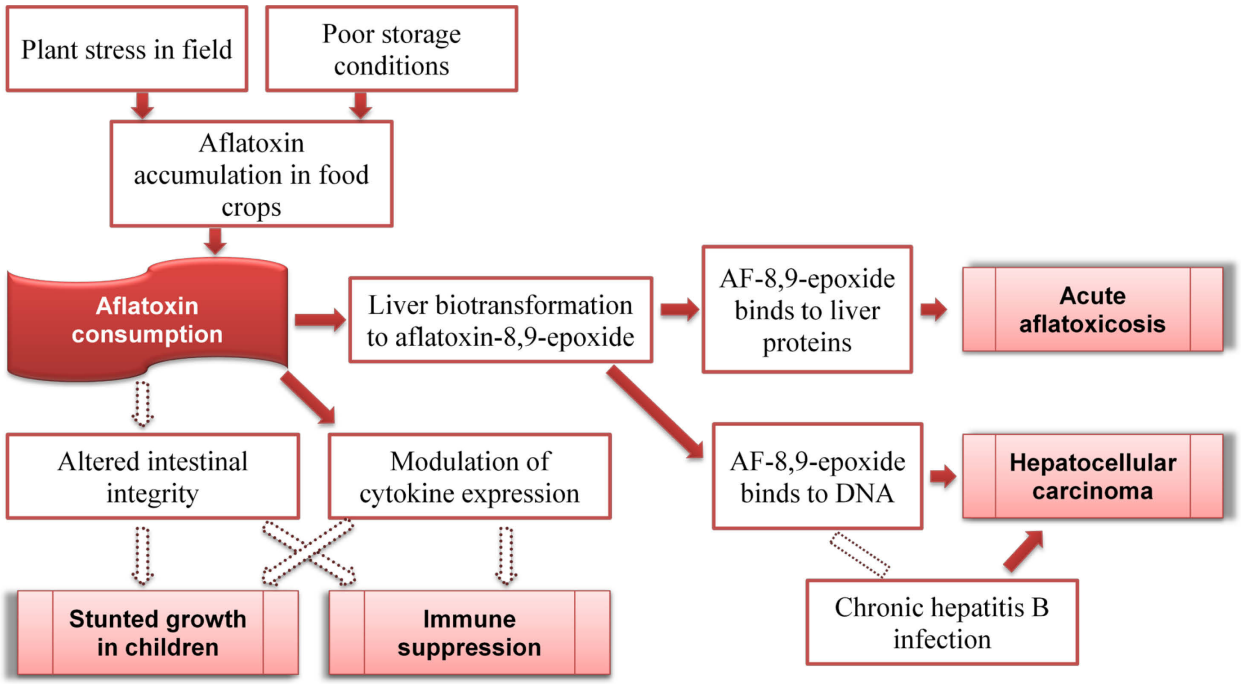

Figure 2 Aflatoxin and disease pathways in humans. Source: Wu (2010).

The darker arrows in Figure 2 denote linkages that have been well-established in agricultural and toxicological research, while the white arrows denote linkages that have been relatively less well-established (Wu 2010).

As the top portion of Figure 2 shows, the main predisposing factor in pre-harvest aflatoxin contamination is stress of the host plant (such as maize or peanuts). Stress can be caused by multiple factors, including use of a hybrid type that is unsuitable for the local geography, drought stress, high temperatures, and/or insect damage. All these factors increase the risk of the crop plant being infected by A. flavus or A. parasiticus. The main predisposing factor in postharvest aflatoxin accumulation in food is poor storage conditions; namely, excessive heat and moisture, pest-related crop damage, and extensive periods of time spent in storage (exceeding several months).

When aflatoxin is consumed, it can exert toxicity in several ways. It may alter intestinal integrity (Gong et al. 2008) or modulate the expression of cytokines, proteins that "signal" to each other and to immune system components. Both of these effects may result in stunted growth in children and/or immune suppression (Wu 2010).

In the liver, aflatoxin may be transformed by certain P450 enzymes (CYP1A2, 3A4, 3A5, 3A7) to its DNA-reactive form aflatoxin-8,9-epoxide. This molecule may bind to liver proteins and lead to their failure, potentially resulting in acute aflatoxicosis. Alternatively, it may bind to DNA, a step that is a precursor for aflatoxin-induced hepatocellular carcinoma (liver cancer). As mentioned earlier, there may be a synergistic effect between aflatoxin and chronic infection with hepatitis B virus (HBV) that results in significantly higher liver cancer risk (Wu 2010).

Acute exposure to aflatoxins

Acute aflatoxicosis, associated with extremely high doses of aflatoxin, is characterized by hemorrhage, acute liver damage, edema, and death in humans. Conditions increasing the likelihood of acute aflatoxicosis in humans include limited availability of food, environmental conditions that favor fungal development in crops and commodities, and lack of regulatory systems for aflatoxin monitoring and control. There have been several reported cases of acute aflatoxicosis in Africa associated with consumption of contaminated home-grown maize, including the outbreaks in Kenya in 1982, in which 12 people died, and in 2004, in which 317 people became ill and 125 people died in the central provinces (Nyikal et al. 2004; Azziz-Baumgartner et al. 2005; Probst et al 2007; Lewis et al. 2005; Stosnider et al. 2006; Siame and Nawa 2008).

Acute aflatoxicosis can also occur in animals. In 1960, more than 100,000 turkeys died on in the United Kingdom over the course of a few months, prompting the name “Turkey X disease” (Asao et al 1963). Later investigation revealed that the source of the disease was toxic peanut meal. In 1981, several hundred calves that had been fed on peanut hay died in Australia (McKenize et al 1981), and in 2007, several hundred animal deaths occurred on a chinchilla farm in Argentina; both these occurrences were linked to aflatoxin (González Pereyra et al, 2008).

Chronic exposure to aflatoxins

HCC as a result of chronic aflatoxin exposure has been well documented, presenting most often in persons with chronic hepatitis B virus (HBV) infection (Qian et al. 1994, Groopman et al. 2008). For individuals chronically infected with HBV, aflatoxin consumption raises the risk of liver cancer up to thirty-fold, compared with either exposure alone (Groopman et al. 2008). Unfortunately, these two risk factors – aflatoxin and HBV – are especially prevalent in poor nations worldwide (Liu and Wu 2010).

In developing countries, many people subsist largely on cereal diets. Nutritional deficiencies are very prevalent in populations consuming high levels of cereals (Bankole et al 2003), particularly children. Additionally, many children in the developing world are also exposed to high levels of mycotoxins in their diets (Cardwell et al 2001).

Aflatoxin and immunosuppression in humans has been relatively less well-characterized, but could in fact have enormous significance from a global health perspective (Williams et al. 2004). Several recent human studies have shown evidence of immunomodulation (Turner et al. 2003, Jiang et al. 2005, Jiang et al. 2008), though the actual outcomes of such immunomodulation have yet to be characterized in humans. Indeed, aflatoxin’s immunotoxicity may be one explanation for the stunted growth in children

that appears to follow a dose-response relationship with aflatoxin exposure (Wu and Khlangwiset 2010; Gong et al. 2002, 2004; Turner et al. 2003). The mechanism by which aflatoxin may result in growth impairment is not yet known; however, one possible explanation may be altered intestinal integrity through cell toxicity or immunomodulation (Gong et al. 2008).

Similarly, decades of animal studies have demonstrated that chronic exposure to aflatoxins in animals can also cause growth inhibition and immune suppression (Khlangwiset et al. 2011). Nursing animals may be affected, and aflatoxin M1 may be excreted in the milk of dairy cattle and other dairy animals. This in turn poses potential health risks to both animals and humans that consume that milk. Chronic aflatoxin exposure in animals can result in impaired reproductive efficiency, reduced feed conversion efficiency, increased mortality rates, reduced weight gain, anemia, and jaundice. In the case of laying hens, aflatoxicosis causes an enlarged fatty liver and lowered egg production (see Lubulwa and Davis 1994 for a list of effects of aflatoxicoses on livestock: poultry, beef cattle and dairy, and pigs).

Statistics on Aflatoxin and Liver Cancer

As the focus of this project is aflatoxin-related risks in Kenya and Mali, statistics for age-adjusted liver cancer incidence per 100,000 individuals in Kenya and Mali are shown in **Table 1**. Statistics for North America and Europe are included for comparative purposes.

Table 1 Liver cancer incidence per 100,000 in Kenya and Mali

Nation	Male	Female
Kenya	8.5	4.9
Mali	19.4	8.8
North America	6.8	2.2
Europe	6.5	2.2

Source: IARC GLOBOCAN 2008.

In the United States, the Food and Drug Administration (FDA) has set action levels on total level of aflatoxins allowed in human food and various types of animal feed. The human food action level is based on what is considered to be an acceptable level of liver cancer risk. These action levels are summarized in Table 2.

Table 2 FDA action levels for aflatoxins in human and animal foods.

Product or animal	Total aflatoxin action level (ppb)
Human food	20
Milk	0.5
Beef cattle	300
Swine over 100 lbs	200
Breeding beef cattle, swine, or mature poultry	100
Immature animals	20
Dairy animals	20

Source: http://www.ngfa.org/files/misc/Guidance_for_Toxins.pdf

In Kenya, mortality rates per 100,000 people of various liver diseases, as well as protein energy malnutrition, are lower than in many other regions of the world. In Mali, however, mortality rates from liver disease are, at the most, three times greater than the average mortality rates in Africa, as shown in Table 3.

Table 3 Mortality rate per 100,000 population, by region and in Kenya and Mali

	Hepatitis B	Hepatitis C	Liver cancer	Cirrhosis of the liver	Protein-energy malnutrition
WORLD	1.63	0.84	9.47	11.99	3.89
AFRICA	1.64	0.72	8.19	3.85	15.09
THE AMERICAS	0.57	0.92	4.16	12.87	4.46
EUROPE	0.83	0.52	7.33	20.94	0.54
SOUTH-EAST ASIA	2.21	0.82	3.50	12.57	3.30
WESTERN PACIFIC	1.60	0.88	21.68	9.53	0.82
KENYA	0.50	0.22	2.58	2.47	4.02
MALI	4.99	2.24	16.91	3.82	47.93

Source: (WHO, 2004)

Statistics on maize and groundnut production and consumption

Over the last decade, the share of maize and groundnut production by developing countries has grown; this trend is predicted to continue for the next three decades (see table 4 and 5). From 1990–1992, developing countries produced 43 percent of the world's maize. From 2001–2003, they were producing 46 percent, with projections that they will be producing nearly 50 percent by 2030. Similarly for groundnuts, from 1990–1992, developing counties produced 91 percent of the world's groundnuts; from 2001–2003, they were producing 94 percent, with projections that they will be producing 93 percent by 2030. Over the next three decades, the total amount of maize production is expected to grow, while the percentage of the world's maize produced in Kenya is will decline slowly. It is expected that groundnut production in Mali will increase somewhat by 2030 despite a slight decline in the 2001–2003 period, a time when Mali lost exports due to aflatoxin problems. (

Table 4 Production and consumption of maize by region, 1990-1992 and 2001-2003

Countries	Maize production						Maize consumption					
	1990-1992		2001-2003		2030 projected		1990-1992		2001-2003		2030 projected	
	(million tons)	(% of world production)	(million tons)	(% of world production)	(million tons)	(% of world production)	(million tons)	(% of world consumption)	(million tons)	(% of world consumption)	(million tons)	(% of world consumption)
Kenya	2.35	0.47	2.34	0.39	2.70	0.27	2.13	2.12	2.72	2.46	3.50	2.90
Mali	0.22	0.04	0.36	0.06	0.70	0.07	0.20	0.20	0.36	0.33	0.60	0.50
Africa South of Sahara	21.94	4.36	26.02	4.29	52.80	5.30	18.43	18.29	23.82	21.51	34.90	28.89
South Asia	11.47	2.28	14.45	2.38	19.30	1.94	7.84	7.78	7.48	6.75	15.80	13.08
Europe	55.29	10.99	77.09	12.71	55.90	5.61	3.93	3.90	5.11	4.61	3.80	3.15
Latin America & Caribbean	56.65	11.27	80.73	13.31	135.20	13.56	20.20	20.05	24.74	22.34	24.20	20.03
Developed Countries	287.00	57.07	327.22	53.93	507.10	50.87	13.08	12.98	16.62	15.00	8.70	7.20
Developing Countries	215.88	42.93	279.52	46.07	489.70	49.13	87.69	87.02	94.15	85.00	112.10	92.80
World	502.88	100.00	606.74	100.00	996.80	100.0	100.77	100.00	110.77	100.00	120.80	100.0
USA	210.71	41.90	242.40	39.95	462.30	46.38	3.43	3.40	3.87	3.49	4.30	3.56
China	97.38	19.36	116.64	19.22	180.80	18.14	26.77	26.57	18.96	17.11	14.20	11.75

Source: FAOSTAT, 2009 for 1990-1992 and 2001-2003 data; and IMPACT simulation data for projections for 2030 (Rosegrant et al 2009)

Table 5 Production and consumption of groundnut by region, 1990-1992 and 2001-2003

Countries	Groundnut production						Groundnut consumption					
	1990-1992		2001-2003		2030 projected		1990-1992		2001-2003		2030 projected	
	million tons	% of world production	million tons	% of world production	million tons	% of world production	million tons	% of world consumption	million tons	% of world consumption	million tons	% of world consumption
Kenya	0.01	0.05	0.03	0.09	0.02	0.05	0.01	0.12	0.03	0.21	0.04	0.25
Mali	0.16	0.68	0.14	0.42	0.22	0.50	0.01	0.18	0.02	0.11	0.04	0.25
Africa South of Sahara	4.58	19.12	8.18	23.74	10.25	23.12	1.57	19.24	2.41	18.14	3.75	22.98
South Asia	7.86	32.85	5.84	16.94	5.50	12.41	0.61	7.45	0.64	4.82	0.71	4.35
Europe	0.02	0.10	0.01	0.03	0.14	0.32	0.48	5.84	0.73	5.47	0.27	1.65
Latin America & Caribbean	0.78	3.25	1.03	2.98	1.82	4.11	0.28	3.41	0.36	2.73	0.45	2.76
Developed Countries	2.19	9.13	2.04	5.93	3.13	7.06	1.84	22.56	2.34	17.63	2.06	12.62
Developing Countries	21.75	90.87	32.41	94.07	41.20	92.94	6.33	77.44	10.95	82.37	14.26	87.38
World	23.94	100.00	34.46	100.00	44.33	100.0	8.18	100.00	13.3	100.00	16.32	100.0
USA	1.94	8.09	1.78	5.15	3.00	6.77	0.95	11.60	1.20	9.05	1.25	7.66
China	6.28	26.25	14.27	41.42	19.30	43.54	2.30	28.13	5.50	41.25	6.94	42.52

Source: FAOSTAT, 2009 for 1990-1992 and 2001-2003 data; and IMPACT simulation data for projections for 2030 (Rosegrant et al 2009)

Linking consumption with Aflatoxin exposure to measure health impacts

Very few studies have attempted to quantify the impacts on human health associated with consumption of foods contaminated with aflatoxins. In 1998, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) conducted a quantitative risk assessment of aflatoxin using existing data from epidemiological studies in China and from animal toxicity studies in order to estimate the impact of different regulatory standards on aflatoxin-induced liver cancer in populations with or without chronic HBV infection. The JECFA aflatoxin risk assessment selected two different cancer potency factors for aflatoxin: 0.01 cases per 100,000 per year per ng/kg bw/day aflatoxin exposure for individuals without chronic HBV infection and 0.30 corresponding cases for individuals with chronic HBV infection. This was based on one cohort study that estimated cancer potency in both HBsAg+ (HBV surface antigen: a biomarker of chronic HBV infection) and HBsAg- individuals (Yeh et al. 1989), as well as other human studies that assessed cancer potency in either HBsAg+ or HBsAg- individuals. Assuming that all food containing higher than standard aflatoxin levels was discarded, and that enough maize and nuts would remain to preserve consumption patterns, JECFA determined that HCC incidence would decrease by about 300 cases per billion people per year if the stricter aflatoxin standard (10 ppb vs. 20 ppb) was followed in nations with HBV prevalence of 25 percent. However, in nations where HBV prevalence was 1 percent, the stricter aflatoxin standard would only save 2 HCC cases per billion people per year (Henry et al. 1999).

Shephard (2008) combined the estimates of JECFA with exposure assessments based on data collected from various studies in Africa on staple food consumption and estimated the population risk for aflatoxin-induced HCC in select sub-Saharan African nations. Given the limited data available, a Monte Carlo method was used to determine the distribution of toxin exposure in different communities. Dietary exposure was estimated following the formula below, which relates aflatoxin contamination levels in the food consumed, amounts of each relevant foodstuff consumed per day, and body weight:

Exposure (ng kg^{-1} bodyweight/day) = (Contamination level) (Amount Consumed) / (Body weight)

This analysis showed that for a number of countries, there was a very high population risk for primary liver cancer based on exposure to aflatoxin. These results should encourage risk managers to consider action among population groups likely to be exposed (Shephard 2008).

Liu and Wu (2010) used a quantitative cancer risk assessment methodology to estimate the total number of liver cancer cases worldwide that could be directly attributable to aflatoxin (as opposed to other risk factors for liver cancer). Dose-response data were used to derive aflatoxin's cancer potency factors both in individuals without chronic HBV and individuals with chronic HBV. HBV prevalence and aflatoxin exposure data were gathered from multiple countries worldwide; these exposures were extrapolated to neighboring nations in which aflatoxin exposure data were not available. Based on these aflatoxin cancer potency factors and exposure data, it was estimated that anywhere from 25,200–155,000 liver cancer cases worldwide are attributable to aflatoxin. This makes up 4.8–28.2 percent of all cases.

The magnitude of the economic impacts of the health consequences associated with consumption of aflatoxin-contaminated food in developing countries is not known due to a lack of good data. It is our view that if we can quantify economic losses and estimate the effects of aflatoxin on health, this will encourage Health Ministries to enforce standards and provide crucial advocacy to benefit the rural poor, such as improving their level of education about aflatoxin exposure. Further, it is possible that stakeholders along the value chain may be more interested in implementing measures to alter their families' exposure to aflatoxin if they were made aware of the potential impacts.

METHODS

The analyses we will conduct under *Objective 1* are to estimate the burden of aflatoxin-induced liver cancer globally using secondary data from the WHO GEMS food consumption database; then at more detail in Kenya using data from the Kenya Integrated Household Budget Survey (KIHBS), 2004/05 which includes extensive consumption data, and in Mali if a similar data set is available. Once primary data is collected from the prevalence, household, and value chains surveys within other activities, we will see if we can update the analysis. Using risk analysis (under *Objective 3* of the Aflacontrol project), we will then recalculate our estimates of the economic impact of health effects associated with aflatoxin and look at the cost effectiveness of various control efforts as maize and groundnuts products move through the value chain using the primary data collected under objective 2 of the Aflacontrol project.

Data is needed on the following factors in order to estimate the economic impacts of the human health problems associated with aflatoxin consumption:

- Aflatoxin concentrations in maize and groundnuts in Mali and Kenya, modeled as probability density functions (PDFs);
- Hepatitis B prevalence in the populations of these countries;
- Expected mortality from acute aflatoxicosis and liver cancer;
- Disability-adjusted life years (DALYs) associated with liver cancer
- Consumption patterns of maize and groundnuts in these countries;
- Cancer potency factors for aflatoxin in HBV+ and HBV- individuals;

Based on these data, we will use quantitative risk assessment tools to estimate exposure and health effects based on aflatoxin concentrations in food. We will assess both the dose-response and exposure of individuals to aflatoxin from maize and groundnuts, respectively, in Kenya and Mali so as to determine the burden of these different diseases and conditions that can be specifically attributable to aflatoxin exposure from these commodities in the study countries. We will then compare the relative contribution of aflatoxin in these conditions to other risk factors that can cause the same conditions.

We will not assess the burden associated with particular health impacts – acute aflatoxicosis, immune suppression, liver cirrhosis, or childhood stunting – for the following reasons. In the case of acute aflatoxicosis, the difficulty in quantifying a burden is due to the fact that there are insufficient data. It may be possible to estimate an aflatoxin dose that could cause aflatoxicosis, but it is virtually impossible to know how often humans around the world are exposed to that dose from sporadic high occurrences in food. Acute aflatoxicoses may be occurring regularly around the world, and may be mistaken for other conditions (Wu 2010). In the case of immune suppression, it is currently impossible to estimate the global burden of disease caused by aflatoxin-induced immunomodulation because immunomodulation is not in and of itself a meaningful health endpoint. Immunology is inherently extremely complex, and up-regulation or down-regulation of particular cytokines and/or antibodies cannot currently be linked to an increase in a particular disease incidence. In the case of liver cirrhosis, studies and experts conflict as to whether an association between aflatoxin exposure and cirrhosis exists. Two studies indicate that there is evidence for aflatoxin's association with cirrhosis. Kuniholm et al. (2008) estimated an average odds ratio of 2.8 for Gambians who self-reported "high lifetime consumption" of groundnuts (implicitly consuming more aflatoxin), while the odds ratio was 3.8 for those who had a particular mutation in the p53 tumor suppressor gene (at codon 249) associated with aflatoxin-induced DNA damage. Sun et al. (1999) estimate a relative risk of 2.8 in a cohort of HBV+ Chinese men who had detectable aflatoxin M1 in urine. On the other hand, older studies explicitly state that aflatoxin does not appear to cause cirrhosis (Newberne and

Wogan 1968; Kew and Popper 1984). In animals, aflatoxin does not cause cirrhosis (Dr. Thomas Kensler, personal communication). Table 9 summarizes the effects we will and will not evaluate in Objective 1. In the case of childhood stunting, limited dose-response data exist linking stunting prevalence to aflatoxin-albumin adduct levels in children (Gong et al. 2002), but these studies were carried out on 480 children in Togo and Benin in West Africa. It is impossible to extrapolate these results from the study population to other populations, given multiple co-factors and confounders that would be involved in such extrapolations.

Table 6 Aflatoxin health effects to be evaluated and those that will not be evaluated.

Evaluated in this study	Not evaluated in this study
• Aflatoxin-induced liver cancer	• Acute aflatoxicosis • Aflatoxin-associated immune suppression • Liver cirrhosis • Aflatoxin-associated stunting in children

The methods described here are used specifically for our liver cancer calculation (Liu and Wu 2010). We begin by compiling available information on aflatoxin cancer potency and exposure from the study countries so as to conduct a quantitative cancer risk assessment. This will enable us to estimate the number of aflatoxin-induced liver cancer cases in the study countries per year and to determine the relative importance of aflatoxin as a risk factor in liver cancer for each of these countries. This approach is an extension of the work done by Shephard (2008) in which we will estimate population risk for aflatoxin-induced HCC in Kenya and Mali and estimate precise numbers of aflatoxin-induced cases.

We will compile and analyze extensive datasets by country—food consumption patterns, aflatoxin concentrations in food, HBV prevalence, and population size—in order to perform a quantitative cancer risk assessment for aflatoxin-induced liver cancer. Risk assessment is the process of quantifying the probability of a harmful effect on individuals or populations from certain human activities. Four steps are involved in estimation of the risk: hazard identification, dose-response analysis, exposure quantification, and risk characterization (National Research Council 1983). Much of the work is adapted from the analyses of Liu and Wu (2010).

Hazard Identification

Hazard identification, the first step in risk assessment, is the process of determining whether exposure to an agent can cause an increase in the incidence of a particular health condition. It is already well established that aflatoxin induces hepatocellular carcinoma in humans and other animals (Groopman et al. 2008); indeed, the International Agency for Research on Cancer has classified aflatoxin B1 as a Group 1 “known” human carcinogen (IARC 2002).

Dose-response / health effects assessment

This second risk assessment step involves characterizing the relationship between the dose of an agent—in this case, aflatoxin— and the incidence of HCC. In this case, because of the synergistic impact of aflatoxin and HBV in inducing HCC, the assessment must be done separately for populations with and without chronic HBV infection. Though chronic HCV infection would likely also have a synergistic effect with aflatoxin in inducing HCC, we did not include this for three reasons: 1) there is much less overlap worldwide between aflatoxin and HCV exposures in general; 2) chronic HCV infection usually occurs later in life, while chronic HBV infection occurs relatively earlier; hence, the time of exposure is less significant for aflatoxin and HCV (Dr. John Groopman, personal communication); and 3) much less is known about the quantitative relationship of aflatoxin and HCV in inducing HCC.

For the cancer risk assessment specifically, it is traditionally assumed that there is no threshold of exposure to a carcinogen below which there is no observable adverse effect (NRC 1983). Cancer potency factors are calculated based on the slope of the linearized dose-response curve of the relationship between the carcinogenic agent and the incidence of cancer in a population. The JECFA (1998) aflatoxin risk assessment selected, based on a review of multiple studies examining cancer potency in human populations, two different cancer potency factors for aflatoxin: 0.01 cases per 100,000 per year for every ng (kg bw)$^{-1}$day^{-1} aflatoxin exposure for individuals without chronic HBV infection and 0.30 corresponding cases for individuals with chronic HBV infection.

We will use these same potency factors to estimate the number of aflatoxin-induced HCC cases in different regions of the world, based on HBV prevalence in those different regions, and specifically in Kenya and Mali (depending on the availability of secondary data in both countries). Because only one of the studies (Yeh et al. 1989) specifically assessed cancer potency in both cohorts, there may be considerable uncertainty associated with these potency factors. However, several epidemiological studies confirm that aflatoxin's cancer potency is about 30 times greater in HBV+ compared with HBV- individuals (Ok et al. 2007, Kirk et al. 2005, Qian et al. 1994) (Liu and Wu 2010).

Exposure assessment

Exposure assessment involves estimating the intensity, frequency, and duration of human (or animal) exposures to a risky agent. Specifically, we aim to determine how individuals' exposure to aflatoxin increases their risk of HCC, which, as described above, depends on whether they are chronically infected with HBV. Moreover, aflatoxin exposure is a function not only of aflatoxin concentrations in maize and groundnuts, but also of how much of these aflatoxin-contaminated foodstuffs individuals consume in different parts of the world.

Aflatoxin exposure assessment has evolved significantly over the last two decades, in large part due to the characterization of biomarkers for both aflatoxin exposure and effect (Groopman et al. 2008). Prior to measuring these biomarkers, the primary way by which human aflatoxin exposure was estimated was by observing how much maize and groundnuts people consumed on average by region and by taking measurements of, or making assumptions about, how much aflatoxin was in that food in different parts of the world. From these values, one could derive an estimate for daily aflatoxin exposures. However, by measuring biomarkers such as aflatoxin-albumin adducts in serum or aflatoxin-N7-guanine in urine, it is possible to get much more accurate estimations of how much aflatoxin is in people's diet and how much has been biotransformed to increase cancer risk (Groopman et al. 2008). As data do not exist on aflatoxin biomarker levels in most parts of the world, we will instead collect data on estimated HBV prevalence and maize and groundnut consumption patterns in these countries; these data will be used to estimate average aflatoxin exposure or contamination levels in maize and groundnuts in different regions and in Mali and Kenya specifically.

We will use primary data gathered in the field and through household studies to estimate individuals' average exposure to aflatoxin in Kenyan maize and in Malian groundnuts. We will also gather data from the literature on estimated HBV prevalence in these two countries in order to estimate aflatoxin-related liver cancer risk to HBV+ and HBV- populations.

Risk characterization

This final step of risk assessment involves integrating the dose-response and exposure data to describe the overall nature and magnitude of risk. For our study, this will consist of quantifying the burden of aflatoxin-induced liver cancer across the globe. Where aflatoxin exposure data are not already estimated around the world, we will use food consumption patterns and aflatoxin contamination levels to estimate exposure. For each nation in which data is available, we will estimate the total number of people with or without chronic HBV infection by multiplying the prevalence by population size. To estimate aflatoxin-induced HCC cases per 100,000 in the two sets of populations

(those with and without chronic HBV infection), we will multiply the corresponding cancer potency factor by the exposure estimates. Then we will multiply these values by the nations' HBV+/HBV- population sizes, divided by 100,000, to derive the total number of aflatoxin-induced HCC cases in each nation. Finally, we will sum across all nations and regions to arrive at an estimate for the global burden of aflatoxin-induced HCC.

Sensitivity analysis

Calculating how liver cancer risk is a function of average daily aflatoxin consumption depends on several factors that have considerable uncertainty and variability associated with them. Hence, in this regard, it is important to conduct sensitivity analyses on those factors. One factor is the relationship between aflatoxin's cancer potency factor and chronic HBV infection. Our model will use the aflatoxin cancer potency factors gathered from the literature in a sensitivity analysis for both HBV+ and HBV- individuals. It will calculate beyond the two scenarios for HBV prevalence calculated in the JECFA report (1 percent and 25 percent) to account for the real nation-by-nation HBV prevalence as of 2008 (WHO 2008):

*Population liver cancer risk = Potency * Intake*, where

Potency = [Aflatoxin cancer potency factor in HBV+ persons][% HBV+ persons] + [Aflatoxin cancer potency factor in HBV- persons]*[% HBV- persons*]

Intake of aflatoxin will be calculated as a function of both the average maize and groundnut consumption per nation (FAOSTAT 2006) and the aflatoxin concentration in those foods. Potency is calculated by factoring in both proportions of HBV+ and HBV- individuals per nation (WHO 2008) because in this calculation, we are interested in each nation's population cancer risk attributable to aflatoxin. Moreover, because the aflatoxin cancer potency factor in those chronically infected with HCV is uncertain, a sensitivity analysis will be conducted on this variable with ranges both above and below the aflatoxin cancer potency factor for HBV.

Disability-Adjusted Life Years (DALYs).

The DALY is a measure of the burden associated with a disease or condition. It extends the concept of potential years of life lost due to premature death to include equivalent years of "healthy" life lost in states of less than full health, broadly termed disability (Havelaar 2007). One DALY can thus be thought of as one lost year of healthy life. 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) (Wu and Khlangwiset 2010):

$$DALY = YLL + YLD$$

For this project, we choose the health endpoint of aflatoxin-induced HCC. DALYs for any given disease are estimated separately for high-income, middle-income, and low-income nations, based on assumptions about how many years individuals will live with a disability in different parts of the world and what resources are available to alleviate disability. Because we are focusing on health outcomes in Kenya and Mali, we will use DALY estimates for HCC in low-income nations. We will develop estimates of burden of disease in terms of DALYs for Kenya and Mali, specifically, from aflatoxin-contaminated maize and groundnuts respectively, when the prevalence data become available. We will use these prevalence data to estimate average daily dose of aflatoxin in Kenyan and Malian diets, and thus to estimate lifetime cancer risk. This risk will be extrapolated to the general populations of Kenya and Mali, from which a DALY calculation will be made

REFERENCES

Adhikari M, Ramjee G, Berjak P, Aflatoxin, kwashiorkor, and morbidity(1994) *Natural Toxins*. 2:13.

Azziz-Baumgartner E, Lindblade K, Gieseker K, Schurz Rogers H, Kieszak S, Njapau H, Schleicher R, McCoy LF, Misore A, DeCock K, Rubin C, Slutsker L, Aflatoxin Investigative Group (2005). Case-Control Study of an Acute Aflatoxicosis Outbreak, Kenya, 2004. *Environmental Health Perspectives* 113:1779-1783.

Bankole, S. and Adebanjp A, Mycotoxin in food in West Africa: current situation and possibilities of controlling it (2003). *African Journal of Biotechnology* vol 2 (9) 254-263 Sept.

Cardwell,A Desjardins, S. Henry, G. Munkvold, and J Robens (2001) *APSNET*, Mycotoxins: The Costs of Achieving Food Security and Quality..

CDC 2004. Outbreak of Aflatoxin Poisoning --- Eastern and Central Provinces, Kenya, January--July September 3, 2004 / 53(34);790-793.

FAOSTAT (2006). Food Security Statistics: Food Consumption and Population Growth. Rome, FAO Press, http://www.fao.org/es/ess/faostat/foodsecurity/index_en.htm.

Gong Y, Turner PC, Hall AJ, CP W. 2008. Aflatoxin exposure and impaired child growth in West Africa: An unexplored international public health burden? In: *Mycotoxins: Detection Methods, Management, Public Health and Agricultural Trade*, (Leslie JF, Bandyopadhyay R, Visconti A, eds). Oxfordshire, UK: CAB International, 53-65.

Gong YY, Egal S, Hounsa A, , Turner PC, Hall AJ, Cardwell K Wild, CP (2003). Determinants of aflatoxin exposure in young children from Benin and Togo, West Africa: the critical role of weaning, *International Journal of Epidemiology*; 32:556-562.

Gong YY, Cardwell K, Hounsa A, Egal S, Turner PC, Hall AJ, Wild, CP. (2002). Dietary aflatoxin exposure and impaired growth in young children from Benin and Togo: cross sectional study. *BMJ* 325(7354): 20-21.

Gong, Y., Hounsa, A., Egal, S (2004). Postweaning exposure to aflatoxin results in impaired child growth: a longitudinal study in Benin, West Africa. *Environmental Health Perspective* 112: 1334-38.

Groopman JD, Kensler TW, Wild CP (2008). "Protective Interventions to Prevent Aflatoxin-Induced Carcinogenesis in Developing Countries." *Ann Rev Public Health* 29:187-203.

Havelaar A. 2007. *Methodological choices for calculating the disease burden and cost-of-illness of foodborne zoonoses in European countries*. EU Report No. 07–002.

Henry SH, Bosch FX, Troxell TC, Bolger PM. 1999. Public health: Reducing liver cancer--global control of aflatoxin. *Science* 286(5449):2453-2454.

IARC (2002). *Some traditional herbal medicines, some mycotoxins, naphthalene and styrene*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 82: 171-300.

ICRISAT (2004) *On Farm Management of Aflatoxin Contamination of Groundnut in West Africa*. ICRISAT flyer.

JECFA. 1998. *Safety evaluation of certain food additives and contaminants*, WHO Food Additives Series 40, Aflatoxins. In: The forty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization.

Jiang Y, Jolly P, Ellis WO, Wang JS, Phillips TD, Williams JH. (2005). Aflatoxin B1 albumin adduct levels and cellular immune status in Ghanaians. *Int Immunol* 17(6): 807-814.

Jiang Y, Jolly P, Preko P, Wang JS, Ellis WO, Phillips TD, et al. (2008). Aflatoxin-related immune dysfunction in health and in human immunodeficiency virus disease. *Clin Dev Immunol* 1-12.

Jolly P, Jiang Y, Ellis WO, Wang JS, Afriyie-Gyawu E, Phillips TD, et al. (2008). Modulation of the human immune system by aflatoxin. In: *Mycotoxins: Detection Methods, Management, Public Health and Agricultural Trade* (Leslie JF BR, Visconti A, ed). Oxfordshire, UK: CAB International, 41-52.

Kew MC, Popper H. 1984. Relationship between hepatocellular carcinoma and cirrhosis. *Semin Liver Dis* 4:136-46.

Kirk GD, Bah E, Montesano R (2006). Molecular epidemiology of human liver cancer: Insights into etiology, pathogenesis and prevention from The Gambia. *Carcinogenesis* 27:2070-82.

Khlangwiset P, Shephard GS, Wu F (2011). Aflatoxins and growth impairment: A review. *Critical Reviews in Toxicology*, submitted.

Kocabas CN, Coskun T, Yurdakok M, Haziroglu R. The effects of aflatoxin B1 on the development of kwashiorkor in mice. *Human Experimental Toxicology* 2003;22:155-8.

Kuniholm MH, Lesi OA, Mendy M, Akano AO, Sam O, Hall AJ, Whittle H, Bah E, Goedert JJ, Hainaut P, Kirk GD (2008). Aflatoxin exposure and viral hepatitis in the etiology of liver cirrhosis in The Gambia, West Africa. *Environ Health Perspect* 116:1553-7.

Lamplugh SM, Hendrickse RG. Aflatoxins in the livers of children with kwashiorkor. *Annals of Tropical Paediatrics* 1982;2:101-4.

Lewis, L., M. Onsongo, H. Njapau, H. Schurz-Rogers, G. Luber, S. Kieszak, J. Nyamongo, L. Backer, A. Dahive, A. Misore, K. DeCock, C. Rubin, and the Kenya Aflatoxicosis Investigation Group (2005)"Aflatoxin Contamination of Commercial Maize Products during an Outbreak of Acute Aflatoxicosis in Eastern and Central Kenya," *Environ Health Perspect.* December; 113(12): 1763–1767.

Liu Y, Wu F (2010). "Global Burden of Aflatoxin-Induced Hepatocellular Carcinoma: A Risk Assessment." *Environmental Health Perspectives* 118:818-24.

Lubulwa, A. S. G., and J. S. Davis. 1998. Esti*mating the social costs of the impacts of fungi and aflatoxins in maize and peanuts*. Proceedings of the 6th International Working Conference on Stored-Product Protection, Volume 2.

National Research Council. (1983). *Risk Assessment in the Federal Government: Managing the Process.* Washington, DC: National Academy Press.

Newberne PM, Wogan GM. 1968. Sequential Morphologic Changes in Aflatoxin B1 Carcinogenesis in the Rat. *Cancer Research* 28:770-781.

Probst C, H. Njapau, and Cotty, P (2007). Outbreak of an Acute Aflatoxicocosis in Kenya in 2004: Identification of the Causal Agent, *Applied and Environmental Microbiology*, April, p 2762-2764

Qian GS, Ross RK, Yu MC, Yuan JM, Gao YT, Henderson BE, Wogan GN, Groopman JD (1994). "A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China, Cancer Epidemiology." *Biomarkers and Prevention* 3:3-10.

Shephard, G. S . 2003. Aflatoxin and food safety: recent African perspectives. *Journal of Toxicology* 22(2&3#) 267-286.

Shephard GS. 2008. Risk assessment of aflatoxins in food in Africa. Food Additives & Contaminants: Part A: Chemistry, Analysis, Control, Exposure & Risk Assessment 25(10): 1246 – 1256.

Strosnider H, Azziz-Baumgartner E, Banziger M, Bhat RV, Breiman R, Brune M, DeCock K, Dilley A, Groopman J, Hell K, Henry SH, Jeffers D, Jolly C, Jolly P, Kibata GN, Lewis L, Liu X, Luber G, McCoy L, Mensah P, Miraglia M, Misore A, Njapau H, Ong C, Onsongo MTK, Page SW, Park D, Patel M, Phillips T, Pineiro M, Pronczuk J, Schurz Rogers H, Rubin C, Sabino M, Schaafsma A, Shephard G, Stroka J, Wild C, Williams JT, Wilson D (2006). "Workgroup Report: Public Health Strategies for Reducing Aflatoxin Exposure in Developing Countries." *Environmental Health Perspectives*, 114:1989-1903.

Sun Z, Lu P, Gail MH, Pee D, Zhang Q, Ming L, Wang J, Wu Y, Liu G, Wu Y, Zhu Y. 1999. Increased risk of hepatocellular carcinoma in male hepatitis B surface antigen carriers with chronic hepatitis who have detectable urinary aflatoxin metabolite M1. *Hepatology* 30:379-83.

Turner PC, Moore SE, Hall AJ, Prentice AM, Wild CP. (2003). Modification of immune function through exposure to dietary aflatoxin in Gambian children. *Environ Health Perspect* 111(2): 217-220.

Wild, CP, Fen Y., Turner, PC. (2000). Environmental and genetic determinants of aflatoxin-albumin adducts in the Gambia, *International Journal of Cancer*; 86:1-7

Wild CP, Gong YY. 2010. Mycotoxins and human disease: a largely ignored global health issue. *Carcinogenesis* 31:71-82.

WHO (2008). World Health Statistics (2008). WHO Press, Geneva, http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf.

Wu F (2010). *The global burden of disease caused by foodborne aflatoxin.* WHO Commissioned Report, Foodborne Disease Burden Epidemiology Reference Group (FERG).

Wu F, Khlangwiset P. (2010). Health economic impacts and cost-effectiveness of aflatoxin reduction strategies in Africa: Case studies in biocontrol and postharvest interventions. . *Food Additives & Contaminants* 27:496-509.

Yeh F-S, Yu MC, Mo C-C, Luo S, Tong MJ, Henderson BE. 1989. Hepatitis B Virus, Aflatoxins, and Hepatocellular Carcinoma in Southern Guangxi, China. *Cancer Res* 49(9):2506-2509

INTERNATIONAL FOOD POLICY RESEARCH INSTITUTE
2033 K Street, NW • Washington, DC 20006-1002 USA
T +1 (202) 862-5600 • F +1 (202) 467-4439
Skype: ifprihomeoffice • ifpri@cgiar.org

AUTHORS: Felicia Wu, Assistant Professor, Department of Environmental and Occupational Health, University of Pittsburgh, 100 Technology Dr, Pittsburgh, PA 15219

Clare Narrod, Senior Research Fellow, International Food Policy Research Institute (IFPRI), 2033 K Street NW, Washington, DC, 20006

Marites Tiongco, Research Fellow, International Food Policy Research Institute (IFPRI), 2033 K Street NW, Washington, DC, 20006

Yan Liu, Graduate Research Assistant, Department of Environmental and Occupational Health, University of Pittsburgh, 100 Technology Dr, Pittsburgh, PA 15219

For more information about the Aflacontrol Project, please visit www.ifpri.org/afla/afla.asp.

Aflacontrol is a collaborative research project funded by the Bill & Melinda Gates Foundation and managed by the International Food Policy Research Institute.

Project Partners: International Maize and Wheat Improvement Center (CIMMYT); International Crops Research Institute for Semi-Arid Tropics (ICRISAT); ACDI-VOCA; University of Pittsburgh; United States Uniformed Services University of the Health Sciences (USU); Institut d'Economie Rurale (IER); and Kenya Agricultural Research Institute (KARI)