Global Burden of Aflatoxin-Induced Hepatocellular Carcinoma: A Risk Assessment

Yan Liu and Felicia Wu

Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

BACKGROUND: Hepatocellular carcinoma (HCC), or liver cancer, is the third leading cause of cancer deaths worldwide, with prevalence 16–32 times higher in developing countries than in developed countries. Aflatoxin, a contaminant produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus* in maize and nuts, is a known human liver carcinogen.

OBJECTIVES: We sought to determine the global burden of HCC attributable to aflatoxin exposure.

METHODS: We conducted a quantitative cancer risk assessment, for which we collected global data on food-borne aflatoxin levels, consumption of aflatoxin-contaminated foods, and hepatitis B virus (HBV) prevalence. We calculated the cancer potency of aflatoxin for HBV-positive and HBV-negative individuals, as well as the uncertainty in all variables, to estimate the global burden of aflatoxin-related HCC.

RESULTS: Of the 550,000–600,000 new HCC cases worldwide each year, about 25,200–155,000 may be attributable to aflatoxin exposure. Most cases occur in sub-Saharan Africa, Southeast Asia, and China where populations suffer from both high HBV prevalence and largely uncontrolled aflatoxin exposure in food.

CONCLUSIONS: Aflatoxin may play a causative role in 4.6–28.2% of all global HCC cases.

KEY WORDS: aflatoxin, global disease burden, hepatitis, hepatocellular carcinoma, risk assessment.

Environ Health Perspect 118:818–824 (2010). doi:10.1289/ehp.0901388 [Online 19 February 2010]

Hepatocellular carcinoma (HCC), or liver cancer, is the third leading cause of cancer deaths worldwide [World Health Organization (WHO) 2008], with roughly 550,000–600,000 new HCC cases globally each year (Ferlay et al. 2004). Aflatoxin exposure in food is a significant risk factor for HCC (Wild and Gong 2010). Aflatoxins are primarily produced by the food-borne fungi *Aspergillus flavus* and *Aspergillus parasiticus*, which colonize a variety of food commodities, including maize, oilseeds, spices, groundnuts, and tree nuts in tropical and subtropical regions of the world. Additionally, when animals that are intended for dairy production consume aflatoxin-contaminated feed, a metabolite, aflatoxin M₁, is excreted in the milk (Strosnider et al. 2006).

Aflatoxins are a group of approximately 20 related fungal metabolites. The four major aflatoxins are known as B₁, B₂, G₁, and G₂. Aflatoxins B₁ and G₂ are the dihydro-derivatives of the parent compounds B₁ and G₁ (Pitt and Tomaska 2001). Aflatoxin B₁ (AFB₁) is the most potent (in some species) naturally occurring chemical liver carcinogen known. Naturally occurring mixtures of aflatoxins have been classified as a Group 1 human carcinogen by the International Agency for Research on Cancer (IARC) and has demonstrated carcinogenicity in many animal species, including some rodents, nonhuman primates, and fish [International Programme on Chemical Safety (IPCS)/WHO 1998]. Specific P450 enzymes in the liver metabolize aflatoxin into reactive oxygen species (aflatoxin-8,9-epoxide), which may then bind to proteins and cause acute toxicity (aflatoxicosis) or to DNA to cause lesions that over time increase the risk of HCC (Groopman et al. 2008).

HCC as a result of chronic aflatoxin exposure has been well documented, presenting most often in persons with chronic hepatitis B virus (HBV) infection (Wild and Gong 2010). The risk of liver cancer in individuals exposed to chronic HBV infection and aflatoxin is up to 30 times greater than the risk in individuals exposed to aflatoxin only (Groopman et al. 2008). These two HCC risk factors— aflatoxin and HBV—are prevalent in poor nations worldwide. Within these nations, there is often a significant urban–rural difference in aflatoxin exposure and HBV prevalence, with both these risk factors typically affecting rural populations more strongly (Plymoth et al. 2009).

Aflatoxin also appears to have a synergistic effect on hepatitis C virus (HCV)-induced liver cancer (Kirk et al. 2006; Kuang et al. 2005; Wild and Montesano 2009), although the quantitative relationship is not as well established as that for aflatoxin and HBV in inducing HCC. Other important causative factors in the development of HCC, in addition to HBV or HCV infection and aflatoxin exposure, are the genetic characteristics of the virus, alcohol consumption, and the age and sex of the infected person (Kirk et al. 2006).

The IPCS/WHO undertook an aflatoxin–HCC risk assessment in 1998 to estimate the impact on population cancer incidence by moving from a hypothetical total aflatoxin standard of 20 ng/g to 10 ng/g (Henry et al. 1999; IPCS/WHO 1998). Assuming that all food containing higher levels of aflatoxin than the standard was discarded and that enough maize and nuts remained to preserve consumption patterns, IPCS/WHO determined that HCC incidence would decrease by about 300 cases per year per billion people, if the stricter aflatoxin standard were followed in nations with HBV prevalence of 25%. However, in nations where HBV prevalence was 1%, the stricter aflatoxin standard would save only two HCC cases per year per billion people. This assessment associated HCC risk with particular doses of aflatoxin; however, these doses do not correspond with actual exposure in different parts of the world, and the two hypothetical values for HBV prevalence, 1% and 25%, were not intended to represent actual HBV prevalence worldwide.

Currently, > 55 billion people worldwide suffer from uncontrolled exposure to aflatoxin (Strosnider et al. 2006). What remains unknown is how many cases of liver cancer can be attributed to this aflatoxin exposure worldwide. Indeed, the Aflatoxin Workgroup (Strosnider et al. 2006), convened by the Centers for Disease Control and Prevention and WHO, identified four issues that warrant immediate attention: quantifying human health impacts and burden of disease due to aflatoxin exposure, compiling an inventory of ongoing intervention strategies, evaluating their efficacy, and disseminating the results.

Addressing this first issue is the aim of our study. We compiled available information on aflatoxin exposure and HBV prevalence from multiple nations in a quantitative cancer risk assessment, to estimate the number of HCC cases attributable to aflatoxin worldwide per year. Shephard (2008) estimated population risk for aflatoxin-induced HCC in select African nations; we expand this to include the rest of the world. We briefly describe interventions that can either reduce

Address correspondence to F. Wu, Department of Environmental and Occupational Health, Graduate School of Public Health, University of Pittsburgh, 100 Technology Dr., Rm 560, Pittsburgh, PA 15219 USA. Telephone: (412) 624-1306. Fax: (412) 624-3040. E-mail: few8@pitt.edu

We thank T. Kessler (University of Pittsburgh), J. Groopman (Johns Hopkins University), and C. Wild (International Agency for Research on Cancer) for their helpful comments. This work was funded by the Bill and Melinda Gates Foundation and the National Institutes of Health (K22 RR024153). The authors’ salaries are supported in part by the Bill & Melinda Gates Foundation.

Received 26 August 2009; accepted 19 February 2010.
aflatoxin directly in food or reduce adverse health effects caused by aflatoxin.

**Materials and Methods**

To perform a quantitative cancer risk assessment for aflatoxin-related HCC, we analyzed extensive data sets by nation or world region: food consumption patterns (of maize and peanuts), aflatoxin levels in maize and peanuts, HBV prevalence, and population size. Risk assessment is the process of estimating the magnitude and the probability of a harmful effect to individuals or populations from certain agents or activities. Four steps are involved in estimation of the risk: hazard identification, dose–response analysis, exposure assessment, and risk characterization (National Research Council 1983).

**Hazard identification.** Hazard identification is the process of determining whether exposure to an agent can increase the incidence of a particular health condition. Aflatoxin exposure is associated with an increase in incidence of HCC in humans and sensitive animal species (Groopman et al. 2008); in fact, IARC has classified AFB1 naturally occurring mixes of aflatoxins as a Group 1 carcinogen (IARC 2002).

**Dose–response analysis.** This second risk assessment step involves characterizing the relationship between the dose of an agent—in this case, aflatoxin—and incidence of HCC. 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. Although chronic HCV infection may also have synergistic effects with aflatoxin in inducing HCC, we did not include this effect in the analyses for three reasons: a) there is much less overlap worldwide between aflatoxin and HCV exposures in general; b) chronic HCV infection usually occurs later in life, whereas chronic HBV infection occurs much earlier, thus the time of overlapped exposure is less significant for aflatoxin and HCV (Groopman J, personal communication); and c) much less is known about the quantitative relationship of aflatoxin and HCV in inducing HCC.

For cancer risk assessment, it is traditionally assumed that there is no threshold of exposure to a carcinogen below which there is no observable adverse effect (National Research Council 2008). Cancer potency factors are estimated from the slope of the dose–response relationship, which is assumed to be linear, between doses of the carcinogen and cancer incidence in a population. The IPSC/WHO aflatoxin risk assessment selected two different cancer potency factors for aflatoxin: 0.01 cases/100,000/year/nanogram/kilogram body weight per 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 individuals positive for the HBV surface antigen (HBsAg; a biomarker of chronic HBV infection) and in HBsAg-negative individuals (Yeh et al. 1989), as well as other human studies that assessed cancer potency among either HBsAg-positive or HBsAg-negative individuals. We used these same potency factors for this risk assessment. Because only one of the studies (Yeh et al. 1989) specifically assessed cancer potency in both cohorts, considerable uncertainty may be associated with these potency factors. However, several epidemiological studies confirm that aflatoxin’s cancer potency is about 30 times greater among HBV-positive than among HBV-negative individuals (Kirk et al. 2005, Ok et al. 2007; Qian et al. 1994).

**Exposure assessment.** Exposure assessment involves estimating the intensity, frequency, and duration of human exposures to a toxic agent. Specifically, we sought to determine how individuals’ exposure to aflatoxin increases their risk of HCC. Aflatoxin exposure is a function not only of aflatoxin concentrations in maize and nuts but also of how much of these foodstuffs individuals consume in different parts of the world.

Aflatoxin exposure assessment has evolved significantly over the past two decades, largely due to the characterization of biomarkers for both aflatoxin exposure and effect (Groopman et al. 2005, 2008). Before these biomarkers, the primary way to estimate aflatoxin exposure was to observe how much maize and nuts people consumed on average and to measure or assume aflatoxin levels in these foods. By measuring biomarkers such as aflatoxin–albumin adducts in serum or aflatoxin-N7-guanine in urine, it is possible to improve estimations of aflatoxin exposure and how much has been biotransformed to increase cancer risk (Groopman et al. 2008).

Because aflatoxin biomarker data worldwide are limited, we collected data on estimated HBV prevalence in these countries and on maize and nut consumption patterns in different world regions and estimated average aflatoxin exposure or contamination levels in the maize and nuts in different world regions. Where aflatoxin exposure data were not already estimated, we used food consumption patterns and aflatoxin contamination levels to estimate exposure. The studies estimating HBV prevalence were based on HBsAg detection among males and among females in both urban and rural settings across all age groups. Data on maize and peanut consumption in different world regions are adapted from the WHO Global Environment Monitoring System (GEMS)/Food Consumption Cluster Diets database (WHO 2006). We estimated aflatoxin exposure data in different nations from multiple sources through literature searches.

**Risk characterization.** This final step of risk assessment integrates dose–response and exposure data to describe the overall nature and magnitude of risk. For our study, this final step consisted of quantifying, across the globe, the burden of aflatoxin-related liver cancer. For each nation, we estimated total number of individuals with or without chronic HBV by multiplying prevalence by population size. To estimate aflatoxin-induced HCC rates within these two populations (with and without chronic HBV infection), we multiplied the corresponding cancer potency factor by aflatoxin exposure estimates. Then we multiplied these values by each nation’s HBV-positive and HBV-negative population sizes to derive total number of aflatoxin-induced HCC cases in each nation. We summed across all world regions to arrive at an estimate for global burden of aflatoxin-induced HCC.

**Results**

Table 1 lists the prevalence of chronic HBV infection by world region, as measured by HBsAg in different parts of the world. Although these different estimates involve uncertainty and variability, all data are from literature published in or after 2000, to ensure that the HBV prevalence estimates are as current and as relevant as possible. Countries are grouped by WHO designated regions (WHO 2005): Africa, North America and Latin America, Eastern Mediterranean, Southeast Asia, Western Pacific, and Europe. Some regions were divided into subgroups because of significantly varied aflatoxin exposure and HBV prevalence within the region.

Table 2 provides calculations of maize and peanut consumption in select countries of the world. The GEMS/Food Consumption Cluster Diets database divides countries of the world into 13 groups based on diets. For each group cluster, the GEMS food consumption database has estimated the amount of cereals, nuts, and oilseeds consumed. We thus estimated average maize and nut consumption by individual country. There are limitations to these data because of the clustering into 13 groups (with potentially wide ranges among nations within a group), as well as variability in data quality regarding diet and aflatoxin exposure estimates.

We estimated (based on Tables 1 and 2) or found in the literature the average aflatoxin exposure in different world regions and then calculated the estimated incidence of aflatoxin-induced HCC, with and without the synergistic impact with HBV, in the corresponding populations of each nation and world region (Table 3). Within each WHO-designated region, we found aflatoxin exposures in the most populous nations. The “in general” rows in Table 3 represent a small proportion of each region: nations in which aflatoxin data were not available, or very
small nations. For these, we assumed a range for aflatoxin exposure that incorporated the ranges of the nations within the region for which we found aflatoxin data.

These data provide the necessary information to calculate the total estimated cases of aflatoxin-induced HCC cases annually, worldwide. Table 4 lists populations for each relevant nation and world region. Accounting for chronic HBV infection prevalence as shown in Table 1, and the risk estimates for HBV-positive versus HBV-negative individuals in Table 3, the numbers of cases of aflatoxin-induced HCC can be estimated in each world region. These are then summed to produce a global estimate of the number of annual aflatoxin-induced HCC cases. Our estimate is that anywhere from 25,200 to 155,000 annual HCC cases worldwide may be attributable to aflatoxin exposure.

Figure 1 illustrates the distribution of HCC cases attributable to aflatoxin globally.

The categories denote WHO world regions. Sub-Saharan Africa is the most important region for HCC cases attributable to aflatoxin; Southeast Asia and China (in the Western Pacific region) are also key regions where aflatoxin-related HCC is an important risk. Relatively fewer cases occur in the Americas, Eastern Mediterranean, and Europe. Although Australia and New Zealand are grouped with the Western Pacific region, these nations also have low aflatoxin-induced HCC incidence. It is notable that in Mexico, where HBV prevalence is relatively low but aflatoxin contamination in food is relatively high, aflatoxin appears to be a significant risk factor for HCC among those without HBV (an estimated 152–924 HCC cases per year per 100,000 people).

### Discussion

Aflatoxin contamination in food is a serious global health problem, particularly in developing countries. Although it has been known for several decades that aflatoxins cause liver cancer in humans, the exact burden of aflatoxin-related HCC worldwide was unknown. This study represents a first step in attempting to estimate that burden. We find that at its lower estimate, aflatoxin plays a role in about 4.6% of total annual HCC cases; at its upper estimate, aflatoxin may play a role roughly 28.2% of all HCC cases worldwide. This large range stems from the considerable uncertainty and variability in data on cancer potency factors, HBV prevalence, aflatoxin exposure, and other risk factors in different world regions. The most heavily afflicted parts of the world are sub-Saharan Africa, Southeast Asia, and China.

As indicated in Table 3, populations in developing countries in tropical and subtropical areas are nearly ubiquitously exposed to moderate to high levels of aflatoxin. Aflatoxin is a controllable risk factor in food, yet the parts of the world in which the risk is particularly high have limited resources to implement most aflatoxin control strategies. Much

### Table 1. Estimates of HBV prevalence in select countries based on HBsAg seroprevalence.

| WHO region/country | References | Chronic HBV prevalence (%) |
|--------------------|------------|-----------------------------|
| Africa             |            |                             |
| Democratic Republic of Congo | Batina et al. 2007, Mbendi et al. 2001 | 6–10 |
| Ethiopia           | Abbe et al. 2003, Shimelis et al. 2008 | 6–7 |
| The Gambia         | Kirk et al. 2004, Valt et al. 1990 | 15–20 |
| Kenya              | Kiire 1998, Tuen 1994 | 11–15 |
| Mozambique         | Chuna et al. 2007 | 4.5–10.6 |
| Nigeria            | Fasola et al. 2008 | 13.2 |
| South Africa       | Custer et al. 2004, Kiire 1996 | 3.3–10.4 |
| Tanzania           | Hasegawa et al. 2006, Matee et al. 2006, Miller et al. 1998 | 5–9 |
| Zimbabwe           | Kiire 1996, Tsawa et al. 1996 | 10–15 |
| Others             | Kiire 1996, Matee et al. 2006, Tayou et al. 2009 | 9–20 |
| North America and Latin America |            |                             |
| Canada             | Minuk and Uhanova 2001, Zhang et al. 2001 | 1–2 |
| United States      | CDC 2009, Cohen et al. 2008; WHO 2005 | 0.3–2 |
| Argentina          | Paraná and Almeida 2005, Torres 1996 | 0.8–1.1 |
| Brazil             | Paraná and Almeida 2005, Torres 1996 | 2.1–3.4 |
| Mexico             | Roman et al. 2009 | <0.3 |
| Others             | Paraná and Almeida 2005, Torres 1996 | 0.5–3 |
| Eastern Mediterranean |            |                             |
| Egypt              | Ismail et al. 2009, Lehman and Wilson 2009, Youssouf et al. 2009 | 2.2–10.1 |
| Iran               | Kafi-Abad et al. 2009a, 2009b | 0.41–0.56 |
| Pakistan           | Butt and Amin 2008, Khattak et al. 2002 | 3.3 |
| Sudan              | Elsheikh et al. 2007 | 6–26 |
| Others             | Abou et al. 2009, Batayneh and Bdlour 2002; Ameen et al. 2005; WHO 2005 | 0.65–10 |
| Southeast Asia     |            |                             |
| India              | Behal et al. 2008, Tandon et al. 1996 | 2.4–4.7 |
| Indonesia          | Hong et al. 2001, Merican et al. 2000; van Hattum et al. 2003 | 2.5–5 |
| Thailand           | Tanprasert and Somjitja 1993 | 4.6–8 |
| Others             | Alam et al. 2007, Ali et al. 2009, Jafri et al. 2006, WHO 2005 | 2–7 |
| Western Pacific    |            |                             |
| Australia          | WHO 2007 | <1 |
| China              | Merican et al. 2000, WHO 2007 | 8–10 |
| Malaysia           | Merican et al. 2000, WHO 2007 | 5 |
| Philippines        | Domingo 1997, Lassang 1996, WHO 2007 | 5–16 |
| Korea              | Song et al. 2009, WHO 2007 | 4–5 |
| Others             | Gust 1996, Merican et al. 2000, Nakata et al. 1994 | 1–10 |
| Europe             |            |                             |
| Eastern Europe     | Majdzik 2000, Resuli et al. 2009 | 2–7 |
| Southern Europe    | Da Villa 1998, Gogos et al. 2003; WHO 2005 | 2–7 |
| Western Europe     | Hahn et al. 2004; WHO 2005; Jig et al. 2001 | 0.5–1 |

### Table 2. Maize and peanut consumption in select countries.

| WHO region/country | Maizea (g/person/day) | Peanutb (g/person/day) |
|--------------------|-----------------------|------------------------|
| Africa             |                        |                        |
| Democratic Republic of Congo | 57 | 52 |
| Ethiopia           | 83 | 13 |
| The Gambia         | 57 | 52 |
| Kenya              | 248 | 11 |
| Mozambique         | 248 | 11 |
| Nigeria            | 57 | 52 |
| South Africa       | 248 | 11 |
| Tanzania           | 248 | 11 |
| Zimbabwe           | 248 | 11 |
| North America and Latin America | 18 | 17 |
| Canada             | 96 | 17 |
| United States      | 86 | 17 |
| Argentina          | 63 | 2 |
| Brazil             | 300 | 5 |
| Mexico             | 136 | 5 |
| Pakistan           | 35 | 18 |
| Sudan              | 57 | 52 |
| Southeast Asia     |                        |                        |
| India              | 35 | 18 |
| Indonesia          | 35 | 18 |
| Thailand           | 35 | 18 |
| Western Pacific    |                        |                        |
| Australia          | 86 | 17 |
| China              | 35 | 18 |
| Malaysia           | 35 | 18 |
| Philippines        | 59 | 2 |
| Republic of Korea  | 59 | 2 |
| Europe             |                        |                        |
| Eastern Europe     | 32 | 2–10 |
| Southern Europe    | 148 | 7 |
| Western Europe     | 33 | 10 |

Data are adapted from GEMS/Food Consumption Cluster Diets database (WHO 2008). *Including maize, flour and germ. **Including groundnuts in shell and shelled.
agricultural land in Africa and Asia lies in climatic regions favorable for *A. flavus* and *A. parasiticus* proliferation. Suboptimal field practices and poor drying/storage conditions make crops vulnerable to fungal infection and aflatoxin accumulation. Maize and groundnuts, the two crops most conducive to *Aspergillus* infection, are staples in many African and Asian diets. Because the very poor in these regions cannot afford much food variety, these staples make up a significant portion of their diets, increasing aflatoxin exposure.

Even within the same nation, aflatoxin-induced HCC risk can vary significantly among different populations, hence the large national ranges for risk shown in Table 4. Rural populations generally have higher levels of aflatoxin exposure than do urban dwellers in developing countries (Wild and Hall 2000), because urban populations typically consume more diversified diets than do rural dwellers and may have food that is better controlled for contaminants. In addition, there is a strong seasonal variation in aflatoxin exposure that correlates with food availability (Gnonlonfin et al. 2008; Tajkarimi et al. 2007). Moreover, HBV prevalence is generally higher in rural areas than in urban ones, and higher among males than among females in most places (Plymoth et al. 2009). We present our collected data of HBsAg seroprevalence as a range for countries or populations (Table 1), to account for these variations.

Although many nations that suffer from both high aflatoxin exposures and high HBV prevalence have nominally established maximum allowable aflatoxin standards in food, there is little if any enforcement of these standards in many rural areas. Indeed, the food in subsistence farming and local food markets is rarely formally inspected. Strict aflatoxin standards can even lead to large economic losses for poor food-exporting nations when trading with other nations (Wu 2004). Subsistence farmers and local food traders sometimes have the luxury of discarding

| Table 3. Estimated HCC incidence attributable to aflatoxin, by WHO region. |
|--------------------------|
| WHO region/country | Reference | Aflatoxin exposure (ng/kg body weight/day) | Estimated annual HCC (per 100,000) |
|--------------------------|
| Africa | | | |
| Democratic Republic of Congo | Manjula et al. 2009<sup>6</sup> | 0.07–27 | 0.0007–0.27 | 0.02–8.10 |
| Ethiopia | Ayalew et al. 2006<sup>6</sup> | 1.4–36 | 0.01–0.36 | 0.42–10.8 |
| The Gambia | Hall and Wild 1994; Shephard 2008 | 4–115 | 0.04–1.15 | 1.20–34.5 |
| Kenya | Hall and Wild 1994; Shephard 2008 | 3.5–133 | 0.04–1.33 | 1.05–39.9 |
| Mozambique | Hall and Wild 1994 | 39–180 | 0.39–1.80 | 11.7–54.0 |
| Nigeria | Bandypadhyay et al. 2007; Bankole and Mabiekoje 2004<sup>6</sup> | 139–227 | 1.39–2.27 | 41.7–68.1 |
| South Africa | Hall and Wild 1994; Shephard 2003 | 0–17 | 0–0.17 | 0–5.10 |
| Tanzania | Manjula et al. 2009<sup>6</sup> | 0.02–50 | 0.0002–0.50 | 0.06–15.0 |
| Zimbabwe | IPCS/WHO 1998 | 17.5–42.5 | 0.18–0.43 | 5.25–12.8 |
| In general<sup>6</sup> | Hall and Wild 1994; Shephard 2008 | 0–100 | 0.10–1.80 | 3.0–54.0 |
| North America | | | |
| Canada | Kuiper-Goodman 1995 | 0.2–0.4<sup>6</sup> | 0.002–0.004 | 0.06–0.12 |
| United States | IPCS/WHO 1998 | 0.26 | 0.003 | 0.08 |
| In general<sup>6</sup> | | 0.26–1 | 0.003–0.01 | 0.08–0.3 |
| Latin America | | | |
| Argentina | Etchoverry et al. 1999; Solovey et al. 1999<sup>6</sup> | 0–4 | 0–0.04 | 0–1.20 |
| Brazil | IARC 2002; Midio et al. 2001; Oliveira et al. 2009; Vargas et al. 2001<sup>6</sup> | 0.23–50 | 0.002–0.50 | 0.07–15.0 |
| Mexico | Garcia and Heredia 2000; Guzmán-de-Peña and Peña-Caballier 2005; Torres et al. 1995<sup>6</sup> | 14–86 | 0.14–0.86 | 4.20–25.5 |
| In general<sup>6</sup> | | 20–50 | 0.20–0.50 | 6.0–15.0 |
| Eastern Mediterranean | | | |
| Egypt | Anwar et al. 2008<sup>6</sup> | 7–57 | 0.07–0.57 | 2.1–17.1 |
| Iran | Hadiani et al. 2009; Mazaheri 2009<sup>6</sup> | 5–8.5 | 0.05–0.09 | 1.50–2.95 |
| Pakistan | Munir et al. 1998<sup>6</sup> | 7–0.5 | 0.07–0.50 | 2.10–15.0 |
| Sudan | Omer et al. 1998 | 19–186 | 0.19–1.86 | 5.70–55.8 |
| In general<sup>6</sup> | | 10–80 | 0.10–0.80 | 3.00–24.0 |
| Southeast Asia | | | |
| India | Vasanthis et al. 1998 | 4–100 | 0.04–1.00 | 12.30–30.0 |
| Indonesia | Ali et al. 1998; IARC 2002; Noviandi et al. 2001<sup>6</sup> | 9–122 | 0.09–1.22 | 2.76–36.8 |
| Thailand | Hall and Wild 1994; Lipigorngoson et al. 2003<sup>6</sup> | 53–73 | 0.53–0.73 | 15.9–21.9 |
| In general<sup>6</sup> | | 30–100 | 0.30–1.00 | 9.00–30.0 |
| Western Pacific | | | |
| Australia | NHMRC 1992; Pitt and Tomaska 2001 | 0.15–0.18 | –0.022 | –0.05 |
| China | Li et al. 2001; Qian et al. 1994; Wang and Liu 2007; Wang et al. 2001<sup>6</sup> | 17–37 | 0.17–0.37 | 5.10–11.1 |
| Malaysia | Ali et al. 1998; IARC 2002<sup>6</sup> | 15–140 | 0.15–1.4 | 4.5–42.6 |
| Philippines | Ali et al. 1998; IARC 2002; Sales and Yoshizawa 2005<sup>6</sup> | 44–54 | 0.44–0.54 | 13.2–16.2 |
| Republic of Korea | Ok et al. 2007; Park et al. 2004 | 1.2–6 | 0.01–0.06 | 0.36–1.80 |
| In general<sup>6</sup> | | 15–50 (except Australia and New Zealand) | 0.15–0.50 | 4.5–15.0 |
| Europe | | | |
| Eastern Europe | Malir et al. 2006<sup>6</sup> | 3.5–4 | 0.04 | 1.20 |
| Southern Europe | Battilani et al. 2008; Giray et al. 2007<sup>6</sup> | 0–4 | 0–0.04 | 0–1.20 |
| Western Europe | IARC 2002 | 0.3–1.3 | 0.003–0.01 | 0.09–0.39 |
| In general<sup>6</sup> | | 0–4 | 0–0.04 | 0–1.20 |
Table 4. Estimated annual global burden of HCC cases attributable to aflatoxin exposure in HBsAg-positive and HBsAg-negative populations.

| WHO region/country | Population (millions)* | HBsAg-negative | HBsAg-positive |
|--------------------|------------------------|----------------|---------------|
| Africa             |                        |                |               |
| Democratic Republic of Congo | 68                      | 1–173          | 1–551         |
| Ethiopia           | 95                     | 11–288         | 21–643        |
| The Gambia         | 1.7                    | 1–17           | 3–117         |
| Kenya              | 38                     | 11–450         | 44–2,270      |
| Mozambique         | 21                     | 73–361         | 111–1,200     |
| Nigeria            | 149                    | 1,800–2,940    | 8,200–13,400  |
| South Africa       | 48                     | 0–79           | 0–255         |
| Tanzania           | 41                     | 1–195          | 1–554         |
| Zimbabwe           | 13                     | 19–50          | 68–249        |
| Total region       | 755                    | 2,150–9,300    | 9,230–50,600  |
| North America      |                        |                |               |
| Canada             | 33                     | 1              | 1             |
| United States      | 300                    | 8              | 1–5           |
| Total region       | 333                    | 9              | 2–5           |
| Latin America      |                        |                |               |
| Argentina          | 40                     | 0–16           | 0–5           |
| Brazil             | 190                    | 4–930          | 3–969         |
| Mexico             | 109                    | 152–924        | 14–83         |
| Total region       | 562                    | 589–2,980      | 84–2,060      |
| Eastern Mediterranean |                        |                |               |
| Egypt              | 81                     | 51–452         | 37–1,400      |
| Iran               | 66                     | 33–56          | 4–8           |
| Pakistan           | 172                    | 116–832        | 119–851       |
| Sudan              | 41                     | 58–717         | 140–5,950     |
| Total region       | 569                    | 446–3,720      | 341–13,200    |
| Southeast Asia     |                        |                |               |
| India              | 1,150                  | 438–11,200     | 331–16,200    |
| Indonesia          | 237                    | 203–2,820      | 160–4,340     |
| Thailand           | 63                     | 307–439        | 461–1,100     |
| Total region       | −1,734                 | 1,740–17,300   | 1,460–27,600  |
| Western Pacific region |                    |                |               |
| Australia          | 21                     | 0–1           | 0–1           |
| China              | 1,300                  | 1,990–4,430    | 5,300–14,400  |
| Korea              | 50                     | 5–29          | 4–65         |
| Malaysia           | 28                     | 40–372        | 63–588       |
| Philippines        | 90                     | 333–462       | 594–2,330    |
| Total region       | −1,740                 | 2,710–6,510   | 6,310–21,200  |
| Europe             |                        |                |               |
| Eastern Europe     | 290                    | 94–114        | 61–244        |
| Southern Europe    | 144                    | 0–56          | 0–121        |
| Western Europe     | 183                    | 5–24          | 1–7          |
| Total region       | 617                    | 99–184        | 62–372       |
| Total (world)      | 6,280                  | 7,700–40,000  | 17,500–115,000 |
| Total annual HCC cases attributable to aflatoxin worldwide | 25,200–155,000 |

*Data from Central Intelligence Agency 2009.

Figure 1. Distribution of HCC cases attributable to aflatoxin in different regions of the world.

Multiple public health interventions exist to control the burden of aflatoxin in the body and to prevent HCC. These interventions, described in greater detail in Wu and Khlangwiset (2010), can be grouped into three categories: agricultural, dietary, and clinical. Agricultural interventions can be applied either in the field (preharvest) or in storage and transportation (postharvest) to reduce aflatoxin levels in key crops. They can thus be considered primary interventions. Dietary and clinical interventions can be considered secondary interventions. They cannot reduce actual aflatoxin levels in food, but they can reduce aflatoxin-related illness, either by reducing aflatoxin’s bioavailability in the body or by ameliorating aflatoxin-induced damage. Because aflatoxin-mediated mutations may precede HCC by several years, the effects of reducing aflatoxin exposure on HCC incidence may take time to become apparent (Szymanska et al. 2009).

One highly effective clinical intervention to reduce aflatoxin-related HCC is vaccination against HBV. Vaccinating children against HBV has, over the past 30 years, significantly decreased HBV infection in several regions, including Europe (Bonanni et al. 2003; Williams et al. 1996), Taiwan (Chen et al. 1996), and Thailand (Jutavijittum et al. 2005). This vaccine will, over time, lessen the global carcinogenic impact of aflatoxin, because removing the synergistic impact between HBV and aflatoxin exposure would significantly reduce HCC risk. However, there are currently roughly 360 million chronic HBV carriers worldwide, and HBV vaccination is still not incorporated into many national immunization programs (Wild and Hall 2000). Thus, adopting measures to reduce dietary exposure to aflatoxins is crucial for public health.

Our study highlights the significant role of aflatoxin in contributing to global liver cancer burden. Most cases occur in sub-Saharan Africa, Southeast Asia, and China, where populations suffer from both high HBV prevalence and largely uncontrolled exposure to aflatoxin in the food. Not all risk factors for HCC, including synergistic roles between aflatoxin and other carcinogens, are clearly understood; hence, these estimates for number of global aflatoxin-induced HCC cases have a large range. Although it is impossible to completely eliminate aflatoxin in food worldwide, it is possible to significantly reduce levels and dramatically reduce liver cancer incidence worldwide. The challenge remains to deliver these interventions to places of the world where they are most needed.
BMC Public Health 6:21; doi:10.1186/1471-2458-6-21 [online 30 January 2006].

Mazaheri M. 2009. Determination of aflatoxins in imported rice to
Iran. Food Chem Toxicol 47(8):2004–2006.

Mbbem Nombi C, Longo-Mbemba B, Mbandu Nkusi S, Muyembe Tamfum JI, Situkubanza Nannita H, Vangu Ngoma D. 2001. Prevalence of HIV and HBs antigen in
blood donors. Residual risk of contamination in blood recipients in East Kinshasa, Democratic Republic of the Congo. Med Trop (Mars) 61(2):139–142.

Mericari C, Guarn R, Amarapaku D, Alexander MJ, Chutquatte A, Chien RN, et al. 2000. Chronic hepatitis B virus infection in
Indonesia. J Gastroenterol Hepatol 15(10):1356–1361.

Midio AF, Campos RR, Sabino M. 2001. Occurrence of aflatoxins
B1, B2, G1 and G2 cooked food components of meats
in market food foods of the city of Sao Paulo, SP, Brazil. Food Addit Contam Part A 18(5):445-448.

Miller WC, Shao JF, Weaver DJ, Shimokura GH, Paul DA, Lallinger GJ. 1998. Seroprevalence of viral hepatitis in
Asian travelers. Trop Med Int Health 3(9):757–763.

Minuk GY, Uhanova J. 2001. Chronic hepatitis B infection in
Canada. J Can J Infect Dis 12(5):351–356.

Munir M, Saleem M, Malik ZH, Ahmad M, Ali A. 1989. Incidence of aflatoxin contamination in non-perishable food commodities.
J Pak Med Assoc 39(6):154–157.

Nakata S, Song P, Duc DD, Nguyen XQ, Murata K, Tsuda F, et al. 1994. Hepatitis C and B virus infections in populations at low risk for HBV in Ho Chi Minh and Hanoi, Vietnam. J Gastroenterol Hepatol 9(4):416–419.

National Health and Medical Research Council. 1992. The 1990
National Health Survey. Canberra:National Health and Medical Research Council.

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

National Research Council. 2000. Science and Decisions:
Advancing Risk Assessment. Washington, DC:National Academy Press.

Nevada CT, Raza R, Ezaz A, Agha B, Juulz HW, Weddeshi S, et al. 2001. Natural occurrence of aflatoxin B1 in some
Indonesian food and feed products in Yogyakarta in year 1998–1999. Mycotoxin Res 3(1):3–10.

Oh HK, Kim HJ, Jo Shim DH, Oh H, Bae DH, Chang DH, et al. 2007. Natural occurrence of aflatoxin B1 in marketed foods
and risk estimates of dietary exposure in Koreans. J Food Prot 70(12):2624–2628.

Oliveira CA, Gonçalves NB, Rosim RE, Fernandes A. 2009. Determination of aflatoxins in peanut products in the
northeast region of São Paulo, Brazil. Int J Mol Sci 10(1):174–183.

Omer RE, Baitser MI, van’t Veer P, Hoogenboom RL, Coromina E, et al. 1990. Risk factors for transmission of hepatitis B virus to Gambian children. Lancet 336(8723):1107–1109.

Pitt JI, Tomaska L. 2001. Are mycotoxins a health hazard in
Paraná R, Almeida D. 2005. HBV epidemiology in Latin America.

Román S, Panduro A, Aguilar-Güiterrez Y, Maldonado M, Qidong, China. Cancer Epidemiol Biomarkers Prev 3:3–10.

Shephard GS. 2008. Aflatoxin and food safety: recent African
and risk estimates of dietary exposure in Koreans. Epidemiol Infect 134(1):137–141.

Sossey ALM, Thomas TP, Heldrick RP, et al. 2009. Characteristics of blood donors and donated blood in sub-Saharan francophone Africa. Transfusion 49(6):1592–1599.

Torres Espinosa E, Acuña Askar K, Naccha Torres LR, Montoya T, et al. 2009. Aflatoxin A contamination in corn distributed in the city of Monterrey, Mexico. J Food Addit Contam Part A 27:496; doi 10.1080/19440040903437865 [Online 4 April 2010].

Vall Mayans M, Hall AJ, Inskim HK, Chotard J, Lindsey SW. 2003. Correlation of aflatoxins with milk aflatoxin M1 contamination in milk in five regions in Iran. J Food Prot 66(9):1333–1339.

Webhastri S, et al. 2001. Natural occurrence of aflatoxin B1
in some Indonesian food and feed products in Yogyakarta in year 1998–1999. Mycotoxin Res 17(0):174–177.

Womenking J, van Hattum J, Boland GJ, Jansen KG, Kleinpenning AS, Kunert J. 1998. Aflatoxin and liver cancer in
Korea. Intervirology 41(4):238–243.

WHO. 2006. Global Environment Monitoring System—Food
Contamination Monitoring and Assessment Programme (GEMS/FOOD). Available: http://www.who.int/foodsafety/chem/gems/en/index.html [accessed 20 August 2009].

WHO. 2007. Western Pacific Regional Plan for Hepatitis B Control through Immunization. Manila, Philippines:World Health Organization, Regional Office for the Western Pacific.

WHO. 2008. The Global Burden of Disease: 2004 Update. Geneva:World Health Organization. Available: http://www. who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html [accessed 27 April 2010].

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

Wild CP, Hall AJ. 2000. Primary prevention of hepatocellular carcinoma in developing countries. Mutat Res Rev Mutat Res 462(2–3):171–183.

Williams JH. 2008. Institutional stakeholders in mycotoxin
issues—past, present and future. In: Mycotoxins: Detection Methods, Management, Public Health and Agricultural Trade (Leslie JF, Bandyopadhyay R, edfs). Oxfordshire, UK:CAAB International, 349–358.

Williams J, Nokes DJ, Medley GF, Anderson RM. 1996. The transmission dynamics of hepatitis B in the UK: a mathe-

Zhuqing Village, Fusui County, People’s Republic of China. Cancer Epidemiol Biomarkers Prev 10(2):143–146.

Wang J, Liu XM. 2007. Contamination of aflatoxins in different
kinds of foods in China. Biomed Sin Enviro(2008):483–487.

WHO. 2005. Vaccine Product Selection Menu: A Guide for National Immunization Managers when Introducing GAVI/ The Vaccine Fund Supported Vaccines. Available: http://www. who.int/immunization_development/new_vaccines/4. CoreimmunisationHepatitis%20b.pdf [accessed 27 April 2010].

WHO. 2006. Global Environment Monitoring System—Food
Contamination Monitoring and Assessment Programme (GEMS/FOOD). Available: http://www.who.int/foodsafety/chem/gems/en/index.html [accessed 20 August 2009].

WHO. 2007. Western Pacific Regional Plan for Hepatitis B Control through Immunization. Manila, Philippines:World Health Organization, Regional Office for the Western Pacific.

WHO. 2008. The Global Burden of Disease: 2004 Update. Geneva:World Health Organization. Available: http://www. who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html [accessed 27 April 2010].

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

Wild CP, Hall AJ. 2000. Primary prevention of hepatocellular carcinoma in developing countries. Mutat Res Rev Mutat Res 462(2–3):171–183.

Wild CP, Montesano R. 2009. A model of interaction: aflatoxins and hepatitis viruses in liver cancer aetiology and preven-
tion. Cancer Lett 281(1):22–30.

Williams JH. 2008. Institutional stakeholders in mycotoxin
issues—past, present and future. In: Mycotoxins: Detection Methods, Management, Public Health and Agricultural Trade (Leslie JF, Bandyopadhyay R, edfs). Oxfordshire, UK:CAAB International, 349–358.

Williams J, Nokes DJ, Medley GF, Anderson RM. 1996. The transmission dynamics of hepatitis B in the UK: a mathe-

Wu F. 2004. Mycotoxin risk assessment for the purpose of setting international regulatory standards. Environ Sci
Technol 38(19):4004–4005.

Wu F, Khlangwiset P. 2010. Health economic impacts and cost-
effectiveness of aflatoxin reduction strategies in Africa: studies in biocontrol and postharvest interventions. Food Addit Contam Part A 27:496-496; doi:10.1080/02652030802309815 [Online 4 April 2010].

Yeh FS, Yu MC, Mo CC, Luo S, Tong MJ, Henderson BE. 1989. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in southern Guangxi, China. Cancer Res 49(8):2506–2509.

Youssef A, Yano Y, Usutumi T, Abd El-alah EM, Abd El-Hameed AE, Serwah AH, et al. 2009. Molecular epidemiological study of hepatitis viruses in Ismailia, Egypt. Intervirology 52(6):391–396.

Zhang J, Zou S, Giulivi A. 2001. Hepatitis B in Canada. Can
Dis Dis Rep 27(suppl 3):S13–S20. Available: http://www. phac-aspc.gc.ca/publicat/cdr-rmtc/cdr01vs27/27s327s3e. html [accessed 27 April 2010].