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Global Risk Assessment of Aflatoxins in Maize and Peanuts: Are Regulatory Standards Adequately Protective?

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The aflatoxins are a group of fungal metabolites that contaminate a variety of staple crops, including maize and peanuts, and cause an array of acute and chronic human health effects. Aflatoxin B1 in particular is a potent liver carcinogen, and hepatocellular carcinoma (HCC) risk is multiplicatively higher for individuals exposed to both aflatoxin and chronic infection with hepatitis B virus (HBV). In this work, we sought to answer the question: do current aflatoxin regulatory standards around the world adequately protect human health? Depending upon the level of protection desired, the answer to this question varies. Currently, most nations have a maximum tolerable level of total aflatoxins in maize and peanuts ranging from 4 to 20 ng/g. If the level of protection desired is that aflatoxin exposures would not increase lifetime HCC risk by more than 1 in 100,000 cases in the population, then most current regulatory standards are not adequately protective even if enforced, especially in low-income countries where large amounts of maize and peanuts are consumed and HBV prevalence is high. At the protection level of 1 in 10,000 lifetime HCC cases in the population, however, almost all aflatoxin regulations worldwide are adequately protective, with the exception of several nations in Africa and Latin America.

Key Words: **(3–6) aflatoxin; hepatocellular carcinoma; risk assessment.**

Mycotoxin contamination of staple crops is a serious human health concern worldwide, particularly in developing countries. Mycotoxins are toxic or carcinogenic secondary metabolites produced by fungi that infect common food commodities such as maize, peanuts, and cereal grains. Many countries now regulate those mycotoxins of human health concern, including aflatoxins, fumonisins, and deoxynivalenol by setting maximum tolerable levels (MTLs) for these toxins in food. However, these regulations may still not be sufficiently protective if large amounts of maize and peanuts are consumed in a population because even if the toxin levels are relatively low, the intake of the contaminated foodstuff is high. Shephard (2008) used a risk assessment paradigm to show how MTLs for aflatoxins in some African countries where maize consumption is high may not adequately protect human health. Our study carries this work further to include an assessment for 91 countries worldwide that regulate aflatoxins.

Aflatoxins are a group of about 20 chemically related metabolites produced primarily by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxin B1, B2, G1, and G2 (AFB1, AFB2, AFG1, and AFG2) are the four major types. Aflatoxins contaminate a variety of staple foods including maize, peanuts, milk, dried fruits, and tree nuts and cause an array of acute and chronic human health disorders. For example, aflatoxin-contaminated maize was implicated in the 1981 and 2004 acute aflatoxicosis outbreaks in Kenya (Strosnider *et al.*, 2006). AFB1 is a potent liver carcinogen, causing hepatocellular carcinoma (HCC) in humans and a variety of animal species. The International Agency for Research on Cancer (IARC) has classified "naturally occurring mixes of aflatoxins" as a Group 1 human carcinogen. There is also increasing evidence that exposure to aflatoxins may cause adverse immune system effects and stunted growth in children (Gong *et al.*, 2004; Jiang *et al.*, 2005; Khlangwiset *et al.*, 2011; Mahdavi *et al.*, 2010; Okoth and Ohingo, 2004; Sadeghi *et al.*, 2009; Shuaib *et al.*, 2010; Turner *et al.*, 2003, 2007; Williams *et al.*, 2004). The conversion of aflatoxin to a reactive metabolite (aflatoxin-8,9-epoxide) in the liver appears to be responsible for many of its toxic effects (Eaton and Gallagher, 1994). Studies in rats and rainbow trout have shown that its genotoxic effects at low doses are likely nonthreshold (Eaton and Gallagher, 1994). Concomitant exposure to aflatoxin and the hepatitis B virus (HBV) is common in developing countries and greatly increases HCC risk. Individuals with both exposures often have multiplicatively greater risk of developing HCC than those exposed to aflatoxin alone (Bowers *et al.*, 1993; Groopman *et al.*, 2008; Liu *et al.*, 2012; Qian *et al.*, 1994; Yeh *et al.*, 1989).

The following article seeks to determine whether current regulatory standards for allowable aflatoxin in food adequately protect human health worldwide. This work addresses one of the questions posed at the end of a 50th anniversary publication of *Toxicological Sciences* on 50 years of aflatoxin research (Kensler *et al*., 2011). Table 1 shows the total aflatoxin MTLs for select countries and regions. "Total aflatoxins" in a regulatory sense refers to the sum of the concentrations of four aflatoxins: AFB1 + AFB2 + AFG1 + AFG2. Some of these countries also regulate AFB1 using a standard that is typically half the total aflatoxin MTL. For nations that provided an AFB1 standard but not total aflatoxins, we assumed total allowable aflatoxins to be twice the amount allowable for AFB1.

This analysis focuses on HCC risk as the health effect of interest (as the weight of evidence linking aflatoxin with other health effects is relatively weaker). Our quantitative analyses take into account average maize and peanut consumption per adult individual in each country, and country-specific HBV prevalence when available, because of the interactions of aflatoxin and HBV in inducing HCC. Levels of aflatoxin contamination that would result in an increased HCC risk of less than 1 in 100,000 and 1 in 10,000 cases in the population over a lifetime are calculated per country and compared with the countries' current regulatory standards.

TABLE 1
Total Aflatoxin MTLs for Select Countries and Regions

Country or region	Maize (ng/g)	Peanuts (ng/g)
Algeria	20	20
Australia and New Zealand	15	15
Brazil	30	30
Canada	15	15
China	40	40
Chile	5	5
Colombia	20	10
Egypt	20	10
Europe Union	4	4
Honduras	2	2
India	30	30
Indonesia	20	20
Iran	30	15
Israel	15	15
Japan	20	20
Jordan	30	30
Kenya	20	20
Korea	20	20
Malawi	10	10
Mexico and parts of Latin America	20	20
Morocco	20	2
Mozambique		10
Nigeria	20	20
Nepal	40	40
Philippines	20	20
Peru	15	15
Russia	10	10
South Africa	10	10
Southeast Europe	10	10
Sudan	15	15
Syria	10	10
Taiwan	15	15
Tanzania	10	10
Tunisia	4	4
Turkey	4	10
United States	20	20
Uruguay	20	20
Venezuela	20	20
Zimbabwe	10	10

Source: FAO (2004).

MATERIALS AND METHODS

From the Food and Agriculture Organization (FAO, 2004), we found 98 countries that had maximum tolerable limits for total aflatoxins in maize and peanuts. Out of these, 91 were categorized into their corresponding World Health Organization (WHO) Proposed Global Environment Monitoring System (GEMS)/Food Consumption Cluster Diets from 2006. Table 2 lists the average amounts of maize and peanuts consumed per day by an adult individual in each GEMS diet cluster. These values were used to inform calculations of the maximum amount of aflatoxin contamination that would be allowable in maize and peanuts in order for increased lifetime liver cancer risk to be less than 1 in 10^4 and 10^5 in the population.

The increased lifetime cancer risk from exposure to a carcinogen per unit time is calculated as

$$\text{Risk} = \text{LADD} \times \text{SF} \times (\text{number of years life}), \quad (1)$$

where LADD is the adult individual's lifetime average daily dose of the carcinogen, and SF is the slope factor, or cancer potency factor, of the carcinogen. Although (number of years life), or life expectancy, differs from nation to nation, we assume this value in our calculations to be 70 years.

For the slope factor SF for aflatoxin in a given nation, we took the weighted potency based on summing the proportion of HBsAg+ (hepatitis B surface antigen: a biomarker of chronic infection with HBV) and HBsAg– individuals multiplied by their respective slope factors for aflatoxin-induced HCC. As conducted by Shephard (2008) and Liu and Wu (2010), we use the values for differential slope factors from Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1998) of 0.3 cancers per year per 10^5 population per nanogram AFB1 per kilogram body weight per day for HBsAg+

TABLE 2
Amounts of Maize and Peanuts Consumed in Each GEMS/Food Consumption Cluster Diet

Diet cluster	Maize (g/day)	Peanuts (g/day)
A	82.7	7.6
B	148.4	4.3
C	135.9	3
D	31.8	1
E	33.3	5.6
F	7.5	2
G	35.2	10.6
H	298.6	2.9
I	248.1	6.6
J	57.4	30.5
K	63.1	1.3
L	58.6	1
M	85.5	9.7

Source: WHO (2006).

individuals and 0.01 cancers per year per 10^5 population per nanogram AFB1 per kilogram body weight per day for HBsAg− individuals. These JECFA slope factor estimates were based on a variety of studies, most notably Bower et al. (1993), who used the Yeh *et al*. (1989) Guangxi data of liver cancer incidence in individuals with or without chronic HBV infection to develop a multifactor risk model that considers each of the risk factors (aflatoxin and HBV) alone and in combination. They assumed multiplicative risk, which, as described above, turned out to be a generally accurate assumption for populations with relatively high aflatoxin and/or HBV exposure, and found a statistical model that could best fit the Yeh *et al.* (1989) data. The Bowers et al. slope factors were converted from milligram to nanogram AFB1, divided by 70 years of age and multiplied by 10^5 to derive the values reported by JECFA. In this study, a sensitivity analysis was conducted assuming slope factors of 0.2 and 0.02 cancers per year per 10^5 population per nanogram AFB1 per kilogram body weight per day for HBsAg+ and HBsAg− populations, respectively.

Table 3 shows HBsAg+ prevalence ranges for each country. Liu and Wu (2010) compiled estimates of HBV prevalence based on HBsAg seroprevalence for select countries and regions. If a best estimate of HBsAg seroprevalence in the general population of a specific country could not be found in the literature, the WHO regional value was used.

LADD, in turn, is based upon the concentration of aflatoxin in the maize and peanuts, the average daily consumption rate of maize and peanuts in a given population, and average body weight of individuals in the population:

$$\text{LADD} = C_{\text{AF}} \times (M_{\text{maize}} + M_{\text{peanuts}})/\text{BW}, \quad (2)$$

where C_{AF} is the concentration of aflatoxin in nanograms per gram food, BW is the global average body weight for an adult (70 kg), M_{maize} is the mass of maize consumed in gram per day, and M_{peanuts} is the mass of total peanuts consumed in gram per day (Table 2). In this equation, we are interested in solving for C_{AF}: The allowable concentration of aflatoxin that would not increase lifetime HCC risk by more than either 1/100,000 cases in the population or 1/10,000 cases in the population.

RESULTS

Table 4 shows the allowable aflatoxin concentrations in nanograms per gram of food required for the lifetime liver cancer risk in populations to be 1/100,000 or 1/10,000, respectively, for each of two sets of slope factors. The following discussion assumes the original JECFA point estimates of the slope factors for HBsAg− and HBsAg+ populations (0.01 and 0.3, respectively). The allowable aflatoxin concentrations are smaller when a slightly higher slope factor for HBsAg− individuals (0.02) and smaller slope factor for HBsAg+ individuals (0.2) are considered; the overall conclusions do not change. If the desired level of protection is that dietary aflatoxin exposures should not cause an increase of 1/100,000 HCC cases in the relevant population over a lifetime, then allowable aflatoxin levels in maize and peanuts would have to be quite low in many nations: lower than many of these nations' current MTLs as shown in Table 1.

In GEMS diet clusters B and C, which represent Southern European and North African nations, total aflatoxin levels that achieve this level of lifetime HCC risk (2–5 ng/g) would be close to the current MTL set by the European Union of 4 ng/g aflatoxins in finished maize products. On the other hand, in many Eastern, Western, and Northern European nations (clusters D, E, and F), levels of aflatoxin in maize and peanuts could be higher than the current regulatory limit and still achieve that level of lifetime HCC risk. The aflatoxin levels in maize and peanuts that would achieve the 1/100,000 lifetime HCC risk in these nations range from 9 ng/g in Moldova (the low allowable value is due largely to a high HBV prevalence in that nation) to as high as 82 ng/g in Finland, Iceland, Norway, and Sweden (where very low HBV prevalence, and very low levels of maize and peanut consumption, make aflatoxin-related HCC unlikely).

The regions that require the lowest contamination levels of aflatoxin in maize and peanuts to prevent HCC risk from increasing substantially are in Latin American and sub-Saharan African nations, where maize (and sometimes peanut) consumption is high and HBV prevalence is high. These nations are in clusters H, I, J, and K. Ideally, aflatoxin contamination levels should be no more than 1–5 ng/g in maize and peanuts so as not to increase lifetime aflatoxin-related HCC risk above 1 in 100,000 in the population. However, this may not be feasible for a variety of reasons, including the availability and distribution of methods and technologies to reduce aflatoxins to such low levels. Another impediment to reducing aflatoxin levels is that many nations do not have regular surveillance or enforcement systems, so the size of the problem is poorly defined.

If, however, the desired level of protection is that dietary aflatoxin exposures should not cause an increase of 1/10,000 HCC cases in the relevant population over a lifetime, then allowable aflatoxin levels in maize and peanuts are higher, and almost all nations currently have regulatory standards that do meet this level of protection. The only two exceptions uncovered in our analysis are Kenya and Peru. The current regulatory level for MTLs of aflatoxin in Kenya is 20 ng/g, whereas our analysis suggests that at most 9 ng/g aflatoxin in foodstuffs would cause an increase of no more than 1 HCC case per 10,000 population. This is because of the high levels of maize consumed in Kenya and the high HBV prevalence, both of which contribute to a much greater risk of aflatoxin-related liver cancer. Likewise, in Peru, the current aflatoxin regulatory standard is 15 ng/g. However, again because of high maize consumption and relatively high HBV prevalence, aflatoxin levels in foodstuffs should not exceed 10 ng/g to cause an increase of no more than 1 HCC case per 10,000 population.

DISCUSSION

To answer the question, "Do current regulatory standards for aflatoxin levels in human diets adequately protect public health?", we found that the answer depends upon the level of protection policymakers would consider "adequate." If the desired level of protection is that dietary aflatoxin exposures should not cause an increase of 1/100,000 HCC cases in the relevant population over a lifetime, then most nations' current

TABLE 3
HBsAg Seroprevalence Rates for Countries in Each WHO GEMS/Food Consumption Cluster Diet

Diet cluster	Country	Prevalence HBsAg+ (%)	References
A	Mauritius[a]	9	Johnston *et al*. (2011)
B	Cyprus	< 1	ECDC (2010)
	Greece	2–4	ECDC (2010)
	Israel	< 2	Andre (2000)
	Italy	< 2	ECDC (2010)
	Portugal	< 1	ECDC (2010)
	Spain	< 2	ECDC (2010)
	Turkey	2–8	ECDC (2010)
C	Algeria	2–7	WHO (2013)
	Egypt	2.2–10.1	Liu and Wu (2010)
	Jordan	2–7	WHO (2013)
	Morocco	< 7	Andre (2000)
	Syrian Arab Republic	2–7	WHO (2013)
	Tunisia	4–7	Hannachi *et al*. (2010)
D	Armenia	< 2	Magdzik (2000)
	Belarus	4.8	Olinger *et al*. (2008)
	Bosnia and Herzegovina	< 2	Petrovic *et al*. (2011)
	Bulgaria	3.8	Ciccozzi *et al*. (2013)
	Iran	< 2	Alavian *et al*. (2012)
	Macedonia	2–8	Magdzik (2000)
	Moldova	8	Iarovoi *et al*. (2008)
	Romania	4–6	ECDC (2010)
	The Russian Federation	2–8	Magdzik (2000)
	Serbia and Montenegro	2–7	WHO (2013)
	Ukraine	< 2	Magdzik (2000)
E	Austria	< 1	Hwang and Cheung (2011)
	Belgium	< 1	ECDC (2010)
	Croatia	< 2	Magdzik (2000)
	Czech Republic	< 1	ECDC (2010)
	Denmark	< 1	Hwang and Cheung (2011)
	France	< 1	Hwang and Cheung (2011)
	Germany	< 1	ECDC (2010)
	Hungary	< 1	Magdzik (2000)
	Ireland	< 1	ECDC (2010)
	Luxembourg	< 1	Hwang and Cheung (2011)
	Malta	2–7	WHO (2013)
	The Netherlands	< 1	ECDC (2010)
	Poland	< 2	Magdzik (2000)
	Slovakia	< 1	ECDC (2010)
	Slovenia	< 2	Magdzik (2000)
	Switzerland	< 1	Hwang and Cheung (2011)
	United Kingdom	< 1	Hwang and Cheung (2011)
F	Estonia	< 2	Magdzik (2000)
	Finland	< 1	ECDC (2010)
	Iceland	< 1	Hwang and Cheung (2011)
	Latvia	< 2	Magdzik (2000)
	Lithuania	2–8	Magdzik (2000)
	Norway	< 1	Hwang and Cheung (2011)
	Sweden	< 1	ECDC (2010)
G	China	8–10	Liu and Wu (2010)
	India	2.4–4.7	Liu and Wu (2010)
	Indonesia	2.5–5	Liu and Wu (2010)
	Malaysia	5	Liu and Wu (2010)
	Nepal	< 1	Shrestha and Shrestha (2012)
	Sri Lanka	< 2	Andre (2000)
	Thailand	4.6–8	Liu and Wu (2010)
	Vietnam	< 8	WHO (2013)
H	Guatemala	1.13	Samayoa (2010)
	Honduras	3–4	Hwang and Cheung (2011)
	Mexico	< 1	Liu and Wu (2010)
	Paraguay	< 1	Hwang and Cheung (2011)
	Peru	< 8	Hwang and Cheung (2011)
	El Salvador	< 2	WHO (2013)

TABLE 3—*Continued*

Diet cluster	Country	Prevalence HBsAg+ (%)	References
I	Kenya	11–15	Liu and Wu (2010)
	Malawi	8	WHO (2013)
	Mozambique	4.5–10.6	Liu and Wu (2010)
	South Africa	3.3–10.4	Liu and Wu (2010)
	United Republic of Tanzania	5–9	Liu and Wu (2010)
	Zimbabwe	10–15	Liu and Wu (2010)
J	Nigeria	13.2	Liu and Wu (2010)
	Sudan	6–26	Liu and Wu (2010)
K	Barbados	< 2	Tanaka (2000)
	Belize	2–7	WHO (2013)
	Brazil	2.1–3.4	Liu and Wu (2010)
	Colombia	< 8	Hwang and Cheung (2011)
	Costa Rica	< 2	Tanaka (2000)
	Cuba	< 2	Tanaka (2000)
	Dominican Republic	3–4	Hwang and Cheung (2011)
	Jamaica	< 2	Tanaka (2000)
	Suriname	2–7	Tanaka (2000)
	Venezuela	< 8	Hwang and Cheung (2011)
L	Japan	< 2	Andre (2000)
	Republic of Korea	4–5	Liu and Wu (2010)
	The Philippines	5–16	Liu and Wu (2010)
M	Argentina	< 2	Liu and Wu (2010)
	Australia	< 1	Liu and Wu (2010)
	Canada	< 2	Liu and Wu (2010)
	Chile	< 1	Hwang and Cheung (2011)
	New Zealand	< 1	Hwang and Cheung (2011)
	United States	< 2	Liu and Wu (2010)
	Uruguay	< 2	Tanaka (2000)

Note. [a]Prevalence among injecting drug users.

aflatoxin regulatory standards are not adequately protective. Ironically, the nations that could afford a more relaxed aflatoxin regulatory standard are European nations because of low HBV prevalence and relatively low consumption rates of the foodstuffs that are commonly contaminated with aflatoxin (especially in Finland, Iceland, Norway, and Sweden). Yet European nations currently have some of the strictest aflatoxin regulatory standards in the world.

On the other hand, if the desired level of protection is that aflatoxin exposures should not cause an increase of 1/10,000 HCC cases over a lifetime, then the vast majority of current aflatoxin regulatory standards are adequately protective. The only exceptions found in our study are Kenya and Peru. Kenya's aflatoxin standards are the same as those of the United States (MTL of 20 ng/g); however, maize consumption is much higher in Kenya, and HBV prevalence is relatively high. Peru's aflatoxin standards are actually stricter than those in the United States (15 ng/g). However, similar to Kenya, maize consumption and HBV prevalence are relatively high in Peru such that the current aflatoxin standards would not protect the population at the level of less than 1/10,000 additional lifetime HCC cases.

However, aflatoxin contamination in foods is not necessarily at or near the level of nations' current regulatory standards, so the risk estimates for aflatoxin exposure and subsequent HCC are upper bounds in many cases. In some nations, even if a relatively relaxed aflatoxin standard exists, maize and peanuts may routinely have much lower levels of aflatoxin than the allowable limit; hence, the population is not highly exposed overall. In other nations, particularly where a large proportion of subsistence farmers produce and consume food that never enters formal inspection, regulatory standards have little effect on the overall amount of aflatoxin exposure in the population.

Further, the MTLs established by countries may be of little value because aflatoxin surveillance and enforcement systems are often not in place. However, on a more global level, aflatoxin regulations do affect trade patterns of aflatoxin-contaminated commodities worldwide (Wu and Guclu, 2012), with the likelihood that higher quality foods are channeled to nations with stricter standards and more aflatoxin-contaminated foods going to nations with more relaxed (or no) standards. Moreover, these standards can affect the quality of products remaining in exporting countries and sent to importing countries.

There are a number of limitations in our study. The first is the reliance on the slope factors determined by JECFA (1998) to apply to increased HCC risk from aflatoxin exposure in HBV− and HBV+ individuals. There is a great deal of uncertainty and variability around these estimates, and these were not quantified although a sensitivity analysis was conducted in the JECFA study. These slope factors were based upon a study that assumed a multiplicative interaction of aflatoxin and HBV in causing liver cancer, which appears to be accurate for populations in high-risk areas such as many parts of Asia and Africa

TABLE 4

MTLs of Total Aflatoxins in Food (Rounded to the Nearest Integer) Required for Liver Cancer Risk to be Increased by 1 out of 100,000 and 1 out of 10,000 in a Lifetime in the Population, For Countries in Each WHO GEMS/Food Consumption Cluster Diet

		Aflatoxin MTL (ng aflatoxin/g food)			
		Slope factors: 0.01 and 0.3		Slope factors: 0.02 and 0.2	
Diet cluster	Country	Lifetime risk of 1/100,000	Lifetime risk of 1/10,000	Lifetime risk of 1/100,000	Lifetime risk of 1/10,000
A	Mauritius	3	31	3	31
B	Cyprus	5	51	3	30
	Greece	4	41	3	28
	Israel	4	41	3	28
	Italy	4	41	3	28
	Portugal	5	51	3	30
	Spain	4	41	3	28
	Turkey	4	41	3	28
C	Algeria	5	46	3	31
	Egypt	4	44	3	30
	Jordan	5	46	3	31
	Morocco	2	24	2	22
	Syrian Arab Republic	5	46	3	31
	Tunisia	3	33	3	26
D	Armenia	19	193	13	129
	Belarus	13	127	11	106
	Bosnia and Herzegovina	19	193	13	129
	Bulgaria	15	145	11	114
	Iran	19	193	13	129
	Macedonia	19	193	13	129
	Moldova	9	92	9	89
	Romania	14	141	11	112
	The Russian Federation	19	193	13	129
	Serbia and Montenegro	19	193	13	129
	Ukraine	19	193	13	129
E	Austria	20	199	12	118
	Belgium	20	199	12	118
	Croatia	16	163	11	109
	Czech Republic	20	199	12	118
	Denmark	20	199	12	118
	France	20	199	12	118
	Germany	20	199	12	118
	Hungary	20	199	12	118
	Ireland	20	199	12	118
	Luxembourg	20	199	12	118
	Malta	16	163	11	109
	The Netherlands	20	199	12	118
	Poland	16	163	11	109
	Slovakia	20	199	12	118
	Slovenia	16	163	11	109
	Switzerland	20	199	12	118
	United Kingdom	25	250	13	127
F	Estonia	67	666	45	446
	Finland	82	816	48	483
	Iceland	82	816	48	483
	Latvia	67	666	45	446
	Lithuania	67	666	45	446
	Norway	82	816	48	483
	Sweden	82	816	48	483
G	China	7	66	6	63
	India	13	129	9	90
	Indonesia	13	127	9	89
	Malaysia	9	89	8	75
	Nepal	17	169	10	100
	Sri Lanka	14	138	9	93
	Thailand	9	94	8	77
	Vietnam	7	66	6	63

TABLE 4—*Continued*

		Aflatoxin MTL (ng aflatoxin/g food)			
		Slope factors: 0.01 and 0.3		Slope factors: 0.02 and 0.2	
Diet cluster	Country	Lifetime risk of 1/100,000	Lifetime risk of 1/10,000	Lifetime risk of 1/100,000	Lifetime risk of 1/10,000
H	Guatemala	2	25	2	15
	Honduras	2	18	1	13
	Mexico	3	26	2	15
	Paraguay	3	26	2	15
	Peru	1	10	1	10
	El Salvador	2	21	1	14
I	Kenya	1	9	1	10
	Malawi	1	12	1	11
	Mozambique	2	17	1	14
	South Africa	2	20	2	15
	Tanzania	2	16	1	14
	Zimbabwe	1	10	1	10
J	Nigeria	2	24	3	26
	Sudan	4	42	4	37
K	Barbados	10	98	7	66
	Belize	10	98	7	66
	Brazil	10	97	7	65
	Colombia	5	47	5	45
	Costa Rica	10	98	7	66
	Cuba	10	98	7	66
	Dominican Republic	8	83	6	61
	Jamaica	10	98	7	66
	Suriname	10	98	7	66
	Venezuela	5	47	5	45
L	Japan	11	106	7	71
	Republic of Korea	8	78	6	62
	The Phillippines	7	68	6	58
M	Argentina	7	66	4	45
	Australia	8	81	5	48
	Canada	7	66	4	45
	Chile	8	81	5	48
	New Zealand	8	81	5	48
	United States	7	66	4	45
	Uruguay	7	66	4	45

(Liu *et al*., 2012) but may not be accurate for populations where both risk factors are low (Wu *et al*., 2009). Second, the data for maize and peanut consumption were based on the WHO GEMS cluster diets, which aggregate clusters of nations that have, again, uncertainty and variability in consumption patterns that are not captured in the analysis. Third, these results assume current estimates of HBV prevalence in the nations, which affects the cancer potency of aflatoxin (and hence the "acceptable" levels of exposure); but HBV prevalence is likely to decline in the future based on increased HBV vaccination in infants and children worldwide. Nonetheless, these results represent a first effort using this approach in understanding whether current regulatory standards for dietary aflatoxin, if enforced, protect against aflatoxin-related liver cancer in different parts of the world.

These analyses used slope factors for aflatoxin-related HCC that assume a no-threshold model of effect. There is increasing evidence that even genotoxic carcinogens may exhibit thresholds (Greim and Albertini, 2012), which means that if a different model was assumed, the risk assessment may look very different. Indeed, different models will lead to different conclusions, but the currently available data are too incomplete to allow rigorous comparisons of the different hypothetical models. However, Eaton and Gallagher (1994) have implied that aflatoxin-induced HCC may indeed have a no-threshold response.

Setting more stringent aflatoxin standards in these countries is not likely to be the best method to reduce aflatoxin exposure and HCC risk. Establishing stricter standards may discourage food companies, which in turn may give up trying to control aflatoxin altogether. Further, developing countries should not have to impose stricter standards just because their populations rely more heavily on maize and peanuts. Because many of the highest consumers of maize or peanuts also have higher HBV prevalence, one method to reduce HCC risk would be to prevent HBV infection through vaccination (Henry *et al*., 1999; JECFA, 1998).

Other strategies, summarized in Khlangwiset and Wu (2010), may be implemented pre- or postharvest in order to directly reduce or prevent aflatoxin contamination of maize and peanuts. Preharvest strategies include planting the most robust crop varieties, which are resistant to fungal infection and other environmental stressors, or using nontoxigenic strains of *Aspergillus* to outcompete those that produce aflatoxins, a method called biocontrol (Cotty *et al*., 2007; Dorner and Horn, 2007; Holbrook *et al*., 2006). However, postharvest methods may be the least resource intensive for developing countries to implement. Postharvest strategies could include the use of visual cues to physically separate infected kernels or peanuts from relatively uninfected ones, as well as improved crop handling and storage (Turner *et al*., 2005). Additionally, special food additives and constituents that can reduce the bioavailability of aflatoxin could in theory be introduced into diets in high-risk populations (Kensler *et al*., 2003). Maize processing techniques such as nixtamalization (soaking maize in a lye solution) used by indigenous cultures in Mexico and Central America to make masa can reduce aflatoxin contamination (Khlangwiset and Wu, 2010). Outreach to agricultural communities in developing nations is essential in order to educate them about the proper implementation of these strategies and to help build self-efficacy. Reducing aflatoxin exposure and its associated health risks may be best achieved through a combination of the above pre- and postharvest methods and revisiting policy measures.

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