

Mycotoxin Risk Assessment for the Purpose of Setting International Regulatory Standards

FELICIA WU*

Department of Environmental and Occupational Health,
Graduate School of Public Health, University of Pittsburgh,
A718 Crabtree Hall, 130 DeSoto Street,
Pittsburgh, Pennsylvania 15261

The 2003 Council for Agricultural Science and Technology Mycotoxin report states that one 21st century goal is the development of uniform regulations worldwide for foodborne mycotoxin contamination. This study informs that endeavor by a risk assessment and economic analysis of two important mycotoxins: fumonisins and aflatoxins. The goals are to identify the nations that would be most heavily impacted by tighter mycotoxin regulations, examine costs and benefits as a function of regulatory stringency, and address risk–risk tradeoffs between health benefits and economic losses from compliance with those regulations. Among industrial nations, the United States would experience the heaviest economic losses from more precautionary mycotoxin standards. Environmental conditions in the developing world, however, are more conducive to mycotoxin accumulation in crops. Contrary to concerns expressed among policymakers, the less developed countries that would likely experience the greatest loss from tighter mycotoxin standards are not sub-Saharan African nations, but China and Argentina. If a fumonisin standard of 0.5 mg/kg were adopted worldwide, total export losses from fumonisins in corn may exceed \$300 million annually: 3-fold higher than if the less stringent U.S. standard of 2 mg/kg were adopted. Likewise, export losses from aflatoxins in peanuts may exceed \$450 million under the current EU regulatory standard of 4 µg/kg: almost 5-fold higher than if the U.S. standard of 20 µg/kg were adopted. Stricter standards are unlikely to improve health significantly. In developing nations such as China where hepatitis B and C are prevalent, tighter aflatoxin standards may increase health risks until improved control methods for aflatoxins are found, as high-quality crops may be exported instead of being consumed domestically.

Introduction

As early as the 11th century, the link between consumption of moldy grain and outbreaks of gangrenous disease was discovered in Europe. This disease was caused by consumption of rye contaminated with the fungus *Claviceps purpurea*, which produced a potent mycotoxin (1). Two more recent examples include an outbreak in Siberia in 1944, in which 10% of people who consumed moldy wheat and barley died

of acute toxicosis (2) and an incident in the southern United States in the mid-1930s, in which several thousand horses died from consuming moldy corn (3).

Mycotoxins are chemicals produced by fungal molds that are toxic or carcinogenic to animals and humans. While a low level of mycotoxins in food is generally regarded as safe and in any case unavoidable, conditions such as unusual weather, insect pest damage, improper breeding and harvesting, or poor storage can lead to high levels of mycotoxins in crops that can cause severe disease outbreaks. Aside from health risks, mycotoxin contamination can also reduce the price paid for crops. Losses from mycotoxins in the U.S. and other industrial nations are typically associated with market losses as opposed to illnesses or deaths from the effects of the toxins. Vardon et al. (4) calculate that total mycotoxin-related losses to agriculture in the United States are as high as \$1.4 billion annually (\$630 million to \$2.5 billion). In particular years and regions, one mycotoxin, aflatoxin, can contaminate crops so severely that farmers are forced to dispose of more than half of their total corn and peanut crop (5).

Far more severe, however, are the economic and health impacts of mycotoxins in the developing world. In these nations, many individuals are not only malnourished but are also chronically exposed to high levels of mycotoxins in their diet (6). Reported results of excess mycotoxin consumption range from deaths from severe toxicoses to various cancers to diseases of malnutrition, the last among children particularly. While industrial nations have well-developed infrastructures to monitor internal food quality standards, developing nations often lack the proper enforcement and monitoring methods to protect their people from contaminated food.

Today, the globalization of the food trade has further contributed to losses due to mycotoxins in the developing world in two important ways. First, stringent mycotoxin standards on exported foods mean that developing nations are likely to export their best-quality foods while keeping contaminated foods domestically, which inadvertently results in higher risk of mycotoxin exposure in those nations (7). Second, a large portion of even the best quality foods produced in the developing world is rejected for export at these more stringent standards, meaning millions of dollars in losses. At the 2001 United Nations Conference on the Least Developed Countries in Brussels, Secretary-General Kofi Annan noted that, "A World Bank study has calculated that the European Union regulation on aflatoxins costs Africa \$670 million each year in exports of cereals, dried fruit, and nuts. And what does it achieve? It may possibly save the life of one citizen of the European Union every two years... Surely a more reasonable balance can be found." (8)

This paper attempts to move policy decisions and international regulations toward that "more reasonable balance" by framing the problem as an economic and risk analysis that can aid policy makers in creating safe and feasible mycotoxin standards. Analysis is conducted of the risks and costs associated with two important classes of fungal mycotoxins worldwide: *fumonisins* in corn and *aflatoxins* in peanuts. While fumonisins are found in a variety of commodities such as corn, rice, and sorghum, our main concern over fumonisin exposure is its presence in corn. Aflatoxins are found in a variety of crops including corn, cotton, peanuts (groundnuts), and tree nuts such as pistachios (5). A sensitivity analysis is conducted to determine how

* Corresponding author tel: (412)624-3155; fax: (412)624-3040; e-mail: fwu@eoh.pitt.edu.

TABLE 1. FDA Guidelines to Industry for Fumonisin Concentrations in Food and Feed (17, 18)

product	recommended total fumonisin maximum level (mg/kg)
Human Food Products	
degermed dry milled corn products	2
whole or partially degermed dry milled corn products	4
dry milled corn bran	4
cleaned corn intended for masa	3
cleaned corn intended for popcorn	3
Animal Feeds^a	
equids (horses) and rabbits	5
catfish	20
swine	20
ruminants	60
poultry	100
ruminant, mink, and poultry breeding stock	30
all other livestock species and pets	10

^a It was assumed, when developing these guidelines, that corn made up no more than 20% of horse and rabbit feed and no more than 50% of other animals' feed.

differences in regulatory standards might lead to different health and economic outcomes worldwide.

Background on Fumonisin and Aflatoxin Standards

Fumonisin are a recently discovered class of toxins produced by the fungi *Fusarium verticillioides* (formerly *F. moniliforme*), *Fusarium proliferatum*, and some related species (9). Fumonisin were first reported in 1988 in connection with high human esophageal cancer rates in Transkei, South Africa. The following year, interest in these mycotoxins increased dramatically after unusually high horse and swine death rates in the U.S. (10). Since then, more than 28 types of fumonisins have been isolated and characterized (11). Of these, fumonisin B₁ (FB₁) is the most common in corn worldwide.

While there have been no confirmed cases of acute fumonisin toxicity in humans, epidemiological studies have linked consumption of fumonisin-contaminated grain with elevated human esophageal cancer incidence in various parts of Africa, Central America, and Asia (12) and among the black population in Charleston, SC (13). Synergistic effects between fumonisin and aflatoxin (discussed next) may also lead to increased risk of liver cancer. Studies of increased rates of neural tube birth defects in Cameron County, TX, were associated with high corn consumption after a year of high fumonisin in the crop (14). Because FB₁ reduces the uptake of folate in different cell lines, fumonisin consumption has been implicated in connection with neural tube defects in human babies (12, 14). In addition, elevated levels of fumonisins in animal feed cause diseases such as equine leukoencephalomalacia (ELEM) in horses and porcine pulmonary edema (PPE) in swine (15). They have been shown to cause liver and kidney cancer in rats (9).

To protect consumers from the harmful effects of fumonisins, a number of nations have established regulations for mycotoxins in food and animal feed (16). In the United States, the Food and Drug Administration (FDA) has set guidelines to industry for levels of fumonisin acceptable in human food and animal feed (17, 18), shown in Table 1.

At the moment, very few regulations exist in other nations regarding acceptable fumonisin levels. The 56th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2001 has, however, recommended a provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg body-weight per day. In some parts of the world, such as Latin

TABLE 2. FDA's Action Levels for Aflatoxins in Human and Animal Foods (25)

product or animal	total aflatoxin action level (µg/kg)
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

TABLE 3. National Maximum Tolerated Levels for Aflatoxins in Human Food^a

nation	total aflatoxin standard in human food (µg/kg)
Australia	5
China	20
European Union (EU), harmonized	4
Germany	4
Guatemala	20
India	30
Ireland	30
Kenya	20
Taiwan	50

^a A more complete list can be found in ref 1.

America and sub-Saharan Africa, corn is a staple in the human diet; thus, meeting the PMTDI for fumonisin would be considerably more difficult in these regions than in the United States or Europe, where corn consumption is much lower (19). At the 2002 Food and Drug Administration/Joint Institute for Food Safety and Applied Nutrition International Workshop on Mycotoxins, a draft for a new EU maximum limit on fumonisins of 0.5 mg/kg had been announced (20); thus far, however, no such limit has come into legislation.

Aflatoxins are mainly produced by the fungus *Aspergillus flavus*. Aflatoxins are the most potent chemical liver carcinogens known. Moreover, the combination of aflatoxin with hepatitis B and C, prevalent in China and sub-Saharan Africa, is synergistic, raising more than 10-fold the risk of liver cancer as compared with either exposure alone (6). Aflatoxins are associated with stunting in children (21) and possibly immune system disorders (22).

Likewise, aflatoxins can severely damage animal health. Aflatoxin B₁, the most toxic of the aflatoxins, causes a variety of adverse effects in different animal species, especially chickens. In poultry, these include liver damage, impaired productivity and reproductive efficiency, decreased egg production in hens, inferior egg shell quality, inferior carcass quality, and increased susceptibility to disease (23). In cattle, the primary symptom is reduced weight gain as well as liver and kidney damage. Milk production is also reduced (24). Unfortunately, the loss of income from lower animal production leads to greater poverty, thus reinforcing the conditions conducive to poor human health (6).

The presence of aflatoxins in foods is restricted in the U.S. to the minimum levels practically attainable by modern processing techniques. FDA's action levels for aflatoxins (25) are shown in Table 2.

Many other nations have established maximum tolerated levels of aflatoxin in food and feed. A sampling of worldwide regulations for human food is shown in Table 3. Notably, the European Commission has set a total aflatoxin standard of 4 µg/kg in food and an aflatoxin B₁ standard of 2 µg/kg,

considerably more precautionary than any national or international standards currently existing (26).

It is important to note that these maximum tolerated levels vary greatly among countries, requiring harmonization to remove the extreme variability in standards. At the moment, no international standard for aflatoxins exists. Until 1996, JECFA had recommended that dietary aflatoxin be kept to an irreducible level. After this evaluation, there have been a number of attempts to establish standards for aflatoxins in food and feed, but it has been exceedingly difficult to reach a consensus on maximum levels that should be included in these standards. Major impediments to consensus are the wide variation in contamination levels worldwide and in the relative ability of nations to reduce aflatoxin levels in a cost-effective manner.

Literature Review

The relevant body of literature concerns the economic impact of mycotoxins in the U.S. and elsewhere in the world, and specifically the economic impact of compliance with mycotoxin regulations. Vardon et al. (4) used Monte Carlo analysis to estimate the costs of three mycotoxins— aflatoxin, deoxynivalenol (primarily in wheat), and fumonisin—in various crops and found that total annual costs within the U.S. were likely to exceed \$1 billion. Their calculations included the costs of market rejection at current FDA regulations, which made up about 99% of the total cost, and a relatively small amount of loss of livestock productivity. In addition, Robens and Cardwell (5) estimated that the costs to manage mycotoxins in the United States, which includes research and testing, are in the tens of millions of U.S. dollars.

In the developing world, market, human health, and animal health losses from mycotoxins are all significant. Lubulwa and Davis (26) calculated the total social costs of aflatoxin in three developing Asian nations—the Philippines, Thailand, and Indonesia—to be \$900 million U.S. dollars (2003 dollars). Combined market losses in these nations totaled \$200 million, livestock losses totaled \$200 million, and human health losses made up the most significant portion of loss at \$500 million. The study assumed an international standard that would allow for aflatoxin concentrations of up to 50 $\mu\text{g}/\text{kg}$ in food; in fact, standards are much stricter now.

A recent World Bank study (27) estimated that compliance with the EU's aflatoxin B₁ standard of 2 $\mu\text{g}/\text{kg}$ in peanuts (about 70% of total aflatoxins are accounted for by aflatoxin B₁) could result in a trade flow between Africa and the EU that is 63% lower than the Codex Alimentarius standard of 15 $\mu\text{g}/\text{kg}$ total aflatoxins, which would imply an equivalence of 9 $\mu\text{g}/\text{kg}$ aflatoxin B₁. A companion study estimated that the EU aflatoxin B₁ standard of 2 $\mu\text{g}/\text{kg}$ would result in a \$670 million loss to Africa (28). On the basis of these two studies, United Nations Secretary General Kofi Annan made his statement about unreasonable losses to Africa through stringent mycotoxin standards (see Introduction). The calculations, however, were not based on actual aflatoxin concentrations in African crops nor volume of trade; rather, it was assumed that African exports would decrease in log-linear form with increased aflatoxin standards.

This current study takes the research described previously further in several important ways. First, it identifies the nations worldwide that would experience the most significant effects from new international mycotoxin standards. Second, it integrates existing data on fumonisin and aflatoxin concentrations in those nations, from which a sensitivity analysis on compliance costs with respect to mycotoxin standards is conducted. Third, it addresses the risk-risk tradeoff between human lives saved (or lost, as the case may be) and economic losses from the stringent regulations that account for the marginal improvement in food quality.

Mycotoxin Exposure Worldwide and Implications of Regulations

As explained in the seminal National Academy study on risk assessment in the federal government (29), risk assessment is one important component of regulatory action. It consists of some or all of the following four steps: hazard identification, analysis of effects, exposure assessment, and risk characterization—the description of the nature and often the magnitude of risk, including attendant uncertainty. The hazards and effects of fumonisins and aflatoxins are described previously; exposure to mycotoxins in various parts of the world is also important to consider. Differences in environmental conditions in the crop-growing regions of the world, as well as differences in control methods used to prevent or decontaminate mycotoxins, lead to vastly different levels of mycotoxin exposure and consequent economic and health risks. For example, growing and storage environments in the United States usually lend themselves to lower human and animal exposure to mycotoxins than in crop-producing regions of the developing world such as China and Africa.

In most years and in most parts of the U.S., the current FDA guidelines for fumonisins are not difficult to meet. In the 1990s, 0.5–10.5% of corn grown in the north central U.S. had fumonisin B₁ levels of 5 mg/kg or higher. However, only about 3.5% of U.S. corn, that devoted to dry milling, masa, popcorn, and corn fed to horses, must meet the lowest recommended fumonisin levels (30). Fumonisin levels rarely are so high that they are rejected for use in other animal feed. Within the animal feed sector, however, the majority of corn is fed to livestock on-farm, without going to market. This means that the majority of corn fed to livestock is not inspected for potentially dangerous fumonisin levels.

Throughout the U.S., aflatoxins develop on crops primarily when droughts occur, followed by periods of rain before crops are harvested. Crops from anywhere in the U.S. may be affected, depending on the growth, harvesting, and storage conditions involved; however, aflatoxin contamination is particularly high in warm, dry regions of the Southeast. A study of 2510 peanut butter samples from 1982 to 1989 showed that about 10% exceeded the FDA action level for aflatoxin (31).

Impacts in the developing world, both economically and healthwise, can be far more severe. Poor quality seed, lack of pest control, and suboptimal storage conditions all increase the risk of mycotoxin accumulation in food. Furthermore, in the poorest regions of the world, agriculture is largely in the form of subsistence farming rather than commercial operations. Thus, most of the corn and peanuts grown is consumed within the farming families and communities without any form of outside inspection or regulatory control. A 2001 JECFA study (32) showed that in sub-Saharan Africa, over half the diets sampled contained high levels of fumonisin. Exposure to aflatoxins in West Africa is equally alarming: over 90% of corn samples collected from households were contaminated with *A. flavus* (the aflatoxin-producing fungus), and 99% of children tested had aflatoxins in their blood (33). Further complicating the problem is that for the given level of exposure, health effects are more severe than they would be in the industrial world because of the prevalence of hepatitis B and C. A study in China associated fumonisin concentrations in corn from particular regions with increases in esophageal cancer rates (34), although a more recent report of the International Agency for Research on Cancer (IARC) shows that a causal relationship between fumonisins and esophageal cancer has not been proven (9). High aflatoxin concentrations in other Chinese regions have been linked with liver cancer risk (35).

From the standpoint of compliance with international regulations, Africa exports a relatively small volume of

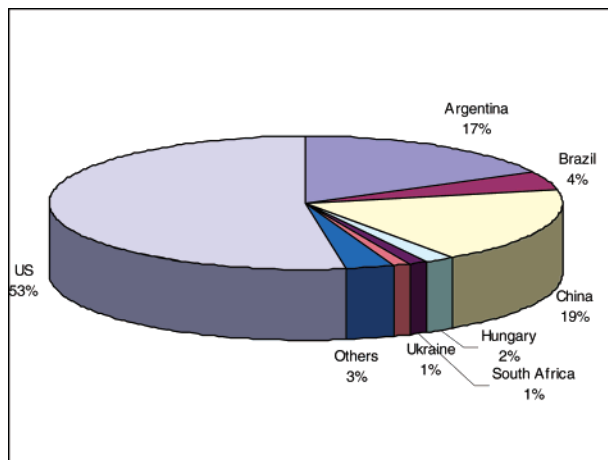


FIGURE 1. Relative corn-export market volumes of prominent corn-exporting nations, 2002/2003 (see ref 36).

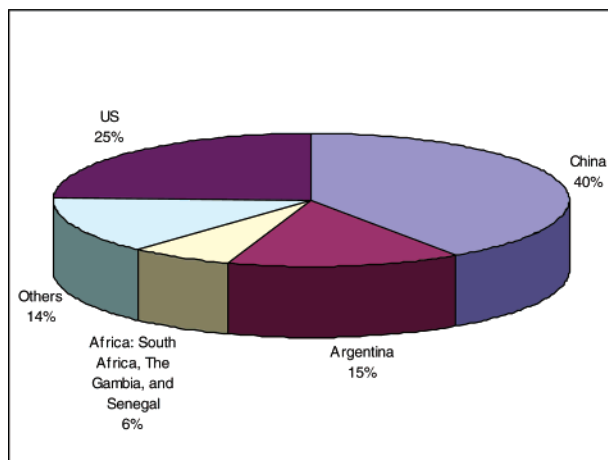


FIGURE 2. Relative peanut-export market volumes of prominent peanut-exporting nations, 2002/2003 (see ref 37).

peanuts and virtually no corn (with the exception of South Africa), whereas China exports large volumes of both. The top corn exporting nations worldwide are (in order) the U.S., China, and Argentina, together accounting for 89% of the total volume of exported corn (36). The top peanut exporting nations are (in order) China, the U.S., and Argentina, together accounting for 78% of the total volume of exported peanuts (37). Hence, these three nations will experience the most serious economic challenges with tightened mycotoxin standards in corn and peanuts. Figures 1 and 2 show the relative sizes of export markets among major corn-exporting and peanut-exporting nations, respectively. By contrast, the European Union is not a major exporter of either of these crops; rather, it is a net importer of corn and peanuts.

Empirical Economic Model and Sensitivity Analysis

A nation's total export loss of a particular food crop, given a particular internationally imposed mycotoxin standard, can be calculated as the product of the price of the food crop per unit volume on the world market, the total volume of that crop exported by a particular nation, and the fraction of that nation's food export crop that is rejected as a result of a worldwide mycotoxin standard

$$\text{export loss}_{i,j,k} = P_i W_{i,j} f_{i,j,k} \quad (1)$$

where i is the crop (corn, peanuts); j is the nation; k is the international mycotoxin standard (fumonisin, aflatoxin); P_i is the world price for food crop i per unit volume; $W_{i,j}$ is the

total export weight (in metric tons) of crop i from nation j ; and $r_{i,j,k}$ is the fraction of export volume of crop i from nation j rejected at international mycotoxin standard k .

The study does a sensitivity analysis on k : how do export losses for food crops in particular nations change as a function of k ? Values for $r_{i,j,k}$ are calculated by fitting probability density functions $PDF_{i,j,k}$, based on the relevant literature, of concentrations of fumonisins and/or aflatoxins in crop i in nation j . The particular nations j to study are chosen by looking at the most important exporting nations of crop i as shown in Figures 1 and 2. In this model, the assumption is made that a shipment that is rejected for import has zero value in that particular exchange; that is, it is not accepted at a lower price for another use. (It can, however, be diverted elsewhere for trade with another market or returned to the nation of origin.) Cumulative distribution functions are estimated from the probability density functions of percentage of crop having mycotoxin levels at or lower than a given concentration. Then the percentage of export volume rejected at that given concentration is

$$r_{i,j,k} = 1 - \int PDF_{i,j,k} dk \quad (2)$$

where $PDF_{i,j,k}$ is the probability density function of percentage of crop i from nation j having mycotoxin levels at or lower than standard k , and its integral over k represents the cumulative distribution function.

Table 4 includes the model parameters, their descriptions, and references for calculating economic impacts of fumonisin regulations in corn worldwide. Uncertainties are estimated by reviewing the literature available on the particular parameter, giving weight to the quality of the work, and fitting a distribution to the available data based on its quality and measurements of uncertainty.

Results

Figure 3 shows the export losses to the three major corn-exporting nations—the United States, China, and Argentina—as a function of varying international fumonisin regulations in food.

Imposing a precautionary fumonisin standard would have the greatest impact on the United States, as it is the largest exporter of corn in the world. As U.S. corn is of generally high quality, though, any international fumonisin standard less stringent than 2 mg/kg (or parts per million, ppm, as Figure 3 shows) means that U.S. export losses would be roughly comparable with those of China and Argentina. If the current FDA guideline of 2 mg/kg fumonisins in food were adopted internationally, the export losses to each of these three nations would range between \$20 million and \$40 million annually, with a total loss of about \$100 million. However, if more stringent fumonisin regulations such as the formerly proposed EU standard of 0.5 mg/kg become a worldwide norm, the estimated corn export losses will rise to \$170 million in the U.S., \$60 million in China, and \$70 million in Argentina for a total of about \$300 million lost export markets annually. The loss in this case would more than quadruple for the U.S., where most of the corn produced has fumonisin levels below the current FDA standard of 2 mg/kg but higher than 0.5 mg/kg.

Figure 4 shows expected peanut export losses to those same three nations (also the world's top exporters in peanuts) as well as Africa—represented by major peanut export nations South Africa, Gambia, and Senegal—as a function of international aflatoxin regulations in food.

Throughout the range given for possible worldwide aflatoxin standards, China's expected export loss is greatest because it has the largest peanut export market and also has large variability in peanut quality. Although African peanut

TABLE 4. Model Parameters, Descriptions, Values, and References for Empirical Model of Mycotoxin Costs

model parameter	description	value	ref
P_{corn}	world price of corn per metric ton (t)	\$102/t	38
$P_{peanuts}$	world price of peanuts per metric ton	\$389/t	39
$W_{corn,US}$	total weight of U.S. corn exported for food (t)	uniform[41M, 50M]	36
$W_{corn,China}$	total weight of China corn exported for food (t)	uniform[7M, 15M]	36
$W_{corn,Argentina}$	total weight of Argentina corn exported for food (t)	uniform[8M, 14M]	36
$W_{peanut,US}$	total weight of U.S. peanuts exported for food (t)	uniform[200K, 350K]	37
$W_{peanut,China}$	total weight of China peanuts exported for food (t)	uniform[350K, 650K]	37
$W_{peanut,Argentina}$	total weight of Argentina peanuts exported for food (t)	uniform[130K, 230K]	37
$W_{peanut,Africa}$	total weight of Africa peanuts exported for food (t)	uniform[45K, 80K]	37
$PDF_{corn,US}$	fumonisin level in U.S. corn (mg/kg)	log-normal[0.8, 2.5]	30, 40–42
$PDF_{corn,China}$	fumonisin level in China corn (mg/kg)	log-normal[1.2, 4]	34, 43
$PDF_{corn,Argentina}$	fumonisin level in Argentina corn (mg/kg)	log-normal[1.6, 2]	44–46
$PDF_{peanut,US}$	aflatoxin level in U.S. peanuts (μ g/kg)	log-normal[7, 2.4]	31, 47
$PDF_{peanut,China}$	aflatoxin level in China peanuts (μ g/kg)	log-normal[10, 2.3]	48
$PDF_{peanut,Argentina}$	aflatoxin level in Argentina peanuts (μ g/kg)	log-normal[8, 2.5]	49
$PDF_{peanut,Africa}$	aflatoxin level in Africa peanuts (μ g/kg)	log-normal[20, 2]	estimate

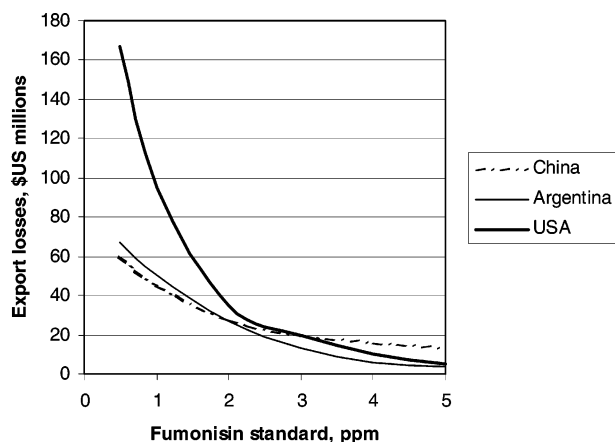


FIGURE 3. Expected export losses to the top three corn-exporting nations as a function of internationally imposed fumonisin standards in food.

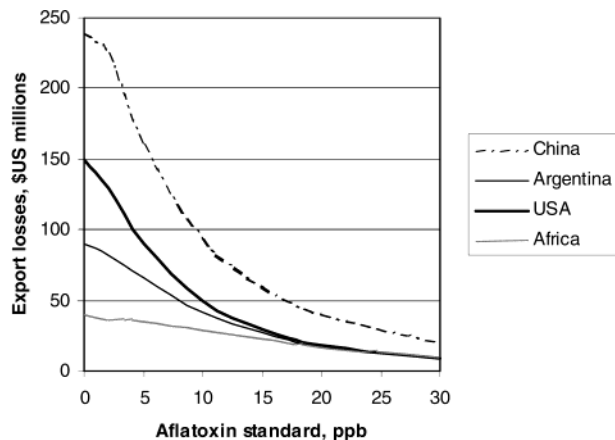


FIGURE 4. Expected export losses to top peanut-exporting regions as a function of internationally imposed aflatoxin standards in food.

concentrations of aflatoxins are expected to be significantly higher than in these other three nations, their total export losses are relatively lower because their share of the peanut export market is smaller. If the U.S. standard of 20 μ g/kg (or parts per billion, ppb, as Figure 4 shows) aflatoxins in food were adopted worldwide, export losses to these four regions would total about \$92 million. At the EU standard of 4 μ g/kg, U.S. export losses would total \$120 million, Argentina's \$75 million, Africa's \$40 million, and China's \$215 million for a combined peanut export loss in these four regions of about \$450 million annually.

On the other hand, importers of corn and peanuts should expect to benefit the most healthwise by stringent mycotoxin standards. The question is whether this health benefit is significant. A JECFA study has estimated that where hepatitis B and C incidence are low, reducing aflatoxin in food from 20 to 10 μ g/kg would reduce the risk of mortality by 2 in 1 billion annually—undetectable by epidemiological standards (50). Thus, nations that would benefit most from more stringent mycotoxin standards are those that are net importers of corn and peanuts and have high prevalence of hepatitis B and C. The top importers of corn worldwide are Japan, Korea, Mexico, Egypt, Canada, and Taiwan (36), and the top importers of peanuts are the European Union, Indonesia, Japan, and Canada (37). With the possible exception of Korea, all these nations have low hepatitis B and C incidences.

Discussion

Precautionary regulations on food contaminants are typically justified by the health benefits that would result from those stricter standards. At the same time, it is important to consider the cost of compliance with such regulations, particularly when creating harmonized international standards that could significantly affect both industrial and developing world export markets. This study has analyzed a number of the challenges that face policymakers in attempting to create those harmonized international standards for mycotoxins.

The nations that would be most heavily affected by international fumonisin and aflatoxin regulations are those that have the largest export markets in corn and peanuts—the crops most frequently contaminated by these mycotoxins. With over 50% of the total corn export market, the United States will experience the greatest impact from an international fumonisin standard. China and Argentina are the other top corn exporters, at 19% and 17%, respectively. Thus far, these nations have suffered few export losses due to fumonisin contamination because very few nations have developed fumonisin guidelines. If the current U.S. (FDA) guideline of 2 mg/kg were to be adopted worldwide, the total expected loss to these three nations is about \$100 million through corn rejected for excessively high fumonisin levels. U.S. export losses in this case would be relatively low because its corn is generally of high quality. On the other hand, if a standard of 0.5 mg/kg were adopted as an international standard, U.S. losses would skyrocket, as most of its corn has naturally occurring fumonisin levels between 0.5 and 2 mg/kg. Total export losses to U.S., China, and Argentina under these circumstances would triple to \$300 million.

Unlike the scenario for fumonisins, many nations have already adopted their own aflatoxin regulations; the challenge is to arrive at an internationally accepted standard. The harmonized standard will prove crucial to peanut exporters.

Again, U.S., China, and Argentina are the three main exporters of peanuts. Although Africa's share in the peanut export market is relatively small as compared with these three nations, the aflatoxin standard will also prove important in this region, as peanuts are one of Africa's few export commodities, and aflatoxin is a serious problem throughout the continent. China, however, as the world's largest exporter of peanuts, will be most affected by a new aflatoxin regulation. If the U.S. standard of 20 $\mu\text{g}/\text{kg}$ aflatoxins in food were adopted worldwide, export losses to these four regions would total about \$92 million. If the EU standard of 4 $\mu\text{g}/\text{kg}$ were adopted, however, the combined peanut export loss in these four regions would approach \$450 million annually: almost a 5-fold increase in loss over the previous scenario. Despite the claims of the World Bank articles (27, 28), this study shows that the loss to Africa in this case would be about \$40 million—smaller than the \$670 million stated by Kofi Annan but nonetheless a significant portion of Africa's agricultural economy. It is, however, also important to consider economic consequences of discouragement when unattainable standards are imposed externally. The loss to African and other peanut-exporting nations may be even greater than the estimates shown here, if their food production in general were discouraged by infeasible aflatoxin goals.

Do the health benefits from stricter mycotoxin standards justify the potential costs? In the short term, the opposite may be true—that excessively precautionary mycotoxin standards may even jeopardize human health in certain areas of the world. In any case, health quality would not be expected to increase significantly. The standards are meant to protect populations in nations that are net importers of corn and peanuts and that have high prevalence of hepatitis B and C, as hepatitis and aflatoxin interact to increase liver cancer incidence synergistically. However, most of the top importers of corn and peanuts worldwide—Japan, Mexico, Egypt, Canada, Taiwan, and the European Union—have low hepatitis B and C incidences. Hence, a change in aflatoxin standards from 20 to 10 $\mu\text{g}/\text{kg}$, much less from 10 to 2 $\mu\text{g}/\text{kg}$, would likely reduce the risk of mortality by an amount so small that it would not be detected by epidemiological standards.

On the other hand, areas with high incidence of hepatitis B and C—namely, China and sub-Saharan Africa—could very well have greater levels of health risks due to stringent international mycotoxin standards. Until improved agricultural methods of controlling these mycotoxins in crops are available and affordable, such standards would encourage the exportation of their best-quality crops to preserve their export markets. Thus, the poor-quality crops would be left for domestic consumption, inadvertently increasing the risk of liver cancer among hepatitis-infected populations.

Several control methods, both preharvest and postharvest, are being developed. The U.S. Department of Agriculture, for example, is conducting research on methods of biocontrol, host-plant resistance enhancement, bioengineered crops, and integrated pest management systems as means to reduce mycotoxin contamination preharvest (51). Postharvest control methods include nixtamalization (processing corn in an alkaline solution), which has been shown to significantly reduce concentrations of fumonisin in corn (52), and ammoniation processes, by which aflatoxin in crops is converted to less harmful chemicals (53). With the exception of nixtamalization in Latin America, these technologies have yet to find widespread use in less developed countries.

Indeed, it is important for policymakers to consider the implications of both health and economic outcomes when developing international standards for mycotoxins. As creation of these standards is one of the goals in mycotoxin research and regulation for the 21st century, the time is right for risk and economic analyses to be included in the decision-making process.

Acknowledgments

This research was funded in part by RAND Science and Technology, although the opinions are those of the author alone. The author is deeply grateful to Dr. J. David Miller of Carleton University, Canada, for his comments, suggestions, and encouragement. Thanks also go to Drs. Elizabeth Casman, Hans van Egmond, Scott Farrow, Bruce Hammond, David Kendra, Robert Klein, Cristina McLaughlin, John Richard, Ronald Riley, and anonymous reviewers.

Literature Cited

- (1) Council for Agricultural Science and Technology (CAST). *Mycotoxins: Risks in Plant, Animal, and Human Systems*; Task Force Report No. 139: Ames, IA, 2003.
- (2) Kotsonis, F. N. Food Toxicology. In *Casarett & Doull's Toxicology: The Basic Science of Poisons*; Klaassen, C. D., Ed.; McGraw-Hill: New York; pp 909–949.
- (3) McCue, P. M. Equine Leukoencephalomalacia. *Compend. Continuing Educ. Pract. Vet.* **1989**, *11* (5), 646–650.
- (4) Vardon, P.; McLaughlin, C.; Nardinelli, C. Potential Economic Costs of Mycotoxins in the United States. In *Council for Agricultural Science and Technology (CAST). Mycotoxins: Risks in Plant, Animal, and Human Systems*; Task Force Report No. 139: Ames, IA, 2003.
- (5) Robens, J.; Cardwell, K. The Costs of Mycotoxin Management to the USA: Management of Aflatoxins in the United States. *J. Toxicol., Toxin Rev.* **2003**, *2–3*, 143–156.
- (6) Miller, J. D.; Marasas, W. F. O. Ecology of Mycotoxins in Maize and Groundnuts. *Suppl. LEISA Magazine* **2002**, 23–24.
- (7) Cardwell, K. F.; Desjardins, A.; Henry, S. H.; Munkvold, G.; Robens, J. *Mycotoxins: The Cost of Achieving Food Security and Food Quality*, 2001. www.apsnet.org/online/feature/mycotoxin/top.html (accessed May 2004).
- (8) Annan, K. *Third United Nations Conference on the Least Developed Countries*, 2001. <http://www.globalpolicy.org/soecon/un/unctad/2001/anna0514.htm> (accessed December 2003).
- (9) IARC (International Agency for Research on Cancer). *Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*. Monograph Volume 82, 2002. <http://monographs.iarc.fr/htdocs/indexes/vol82index.html> (accessed November 2003).
- (10) Marasas, W. F. O. Fumonisin: History, World-Wide Occurrence, and Impact. In *Fumonisin in Food*; Jackson, L., Ed.; Plenum Press: New York, 1996.
- (11) Rheeder, J. P.; Marasas, W. F.; Vismser, H. F. Production of fumonisin analogues by *Fusarium* species. *Appl. Environ. Microbiol.* **2002**, *68*, 2101–2105.
- (12) Marasas, W. F. O.; Riley, R. L.; Hendricks, K. A.; Stevens, V. L.; Sadler, T. W.; Gelineau-van Waes, J.; Missmer, S. A.; Cabrera, J.; Torres, O.; Gelderblom, W. C. A.; Allegood, J.; Martinez, C.; Maddox, J.; Miller, J. D.; Starr, L.; Sullards, M. C.; Roman, A. V.; Voss, K. A.; Wang, E.; Merrill, A. H., Jr. Fumonisin disrupt sphingolipid metabolism, folate transport, and neural tube development in embryo culture and in vivo: A potential risk factor for human neural tube defects among populations consuming fumonisin-contaminated maize. *J. Nutrition* **2004**, *134*, 711–716.
- (13) Sydenham, E. W.; Shephard, G. S.; Thiel, P. G.; Marasas, W. F. O.; Stockenstrom, S. Fumonisin Contamination of Commercial Corn-Based Human Foodstuffs. *J. Agric. Food Chem.* **1991**, *39*, 2014–2018.
- (14) Hendricks, K. Fumonisin and neural tube defects in south Texas. *Epidemiology* **1999**, *10*, 198–200.
- (15) Ross, P. F.; Rice, L. G.; Osweiler, G. D.; Nelson, P. E.; Richard, J. L.; Wilson, T. M. Review and update of animal toxicoses associated with fumonisin-contaminated feeds and production of fumonisins by *Fusarium* isolates. *Mycopathologia* **1992**, *17*, 109–114.
- (16) Van Egmond, H. P. Worldwide regulations for mycotoxins. *Adv. Exp. Med. Biol.* **2002**, *504*, 257–269.
- (17) FDA (2000a). *Background Paper in Support of Fumonisin Levels in Corn and Corn Products Intended for Human Consumption*. <http://www.cfsan.fda.gov/~dms/fumonbg3.html>.
- (18) FDA (2000b). *Background Paper in Support of Fumonisin Levels in Animal Feed*. <http://vm.cfsan.fda.gov/~dms/fumonbg2.html>.
- (19) Shephard, G. S. Mycotoxins Worldwide: Current Issues in Africa. In *Meeting the Mycotoxin Menace*; Barug, D., van Egmond, H.

- P., Lopez-Garcia, R., van Osenbruggen, W. A., Visconti, A., Eds.; Wageningen Academic: Wageningen, The Netherlands, 2004; pp 81–88.
- (20) Food Standards Agency, *Contaminated maize meal withdrawn from sale*, 2003. www.food.gov.uk/news/newsarchive/maize (last accessed May 2004).
- (21) Gong, Y. Y.; Cardwell, K.; Hounsa, A.; Egal, S.; Turner, P. C.; Hall, A. J.; Wild, C. P. Dietary aflatoxin exposure and impaired growth in young children from Benin and Togo: cross-sectional study. *Brit. Med. J.* **2000**, *325*, 20–21.
- (22) Turner, P. C.; Moore, S. E.; Hall, A. J.; Prentice, A. M.; Wild, C. P. Modification of immune function through exposure to dietary aflatoxin in Gambian children. *Environ. Health Perspect.* **2003**, *111*, 217–220.
- (23) Wyatt, R. D. Poultry. In *Mycotoxins and animal foods*; Smith, J. E., Henderson, R. S., Eds.; CRC Press: Boca Raton, FL, 1991; pp 553–606.
- (24) Keyl, A. C. Aflatoxicosis in cattle. In *Mycotoxic Fungi, Mycotoxins, Mycotoxicoses, Vol. 2*; Wyllie, T. D., Morehouse, L. G., Eds.; Marcel Dekker: New York, 1978; pp 9–27.
- (25) FDA 1994 Sec. 683.100. *Action Levels for Aflatoxins in Animal Feeds (CPG 7126.33)*; www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg683-100.html.
- (26) Lubulwa, A. S. G.; Davis, J. S. Estimating the social costs of the impacts of fungi and aflatoxins in maize and peanuts. In *Stored Product Protection: Proceedings of the 6th International Working Conference on Stored-product Protection*; Highley, E., Wright, E. J., Banks, H. J., Champ, B. R., Eds.; CAB International: Wallingford, UK, 1994; pp 1017–1042.
- (27) Otsuki, T.; Wilson, J. S.; Sewadeh, M. What price precaution? European harmonization of aflatoxin regulations and African groundnut exports. *Eur. Rev. Agric. Econ.* **2001**, *28*, 263–283.
- (28) Otsuki, T.; Wilson, J. S.; Sewadeh, M. Saving Two in a Billion: Quantifying the Trade Effect of European Food Safety Standards on African Exports. *Food Policy* **2001**, *26*, 495–514.
- (29) National Research Council. *Risk Assessment in the Federal Government: Managing the Process*; The National Academy Press: Washington, DC, 1983.
- (30) Munkvold, G. P. Potential Impact of FDA Guidelines for Fumonisin in Foods and Feeds. In *Mycotoxins: The Cost of Achieving Food Security and Food Quality*, 2001. www.apsnet.org/online/feature/mycotoxin/top.html (accessed May 2004).
- (31) Gagliardi, S. J.; Cheatle, T. F.; Mooney, R. L.; Llewellyn, G. C.; O'Rear, C. E. Occurrence of Aflatoxin in Peanut Butter from 1982 to 1989. *J. Food Protect.* **1991**, *54*, 627–631.
- (32) Joint FAO/WHO Expert Committee on Food Additives (JECFA). *Safety evaluation of certain mycotoxins in food*; WHO Food Additives Series 47, FAO food and Nutrition Paper 74; JECFA: Geneva, 2001.
- (33) Cardwell, K. F.; Hounsa, A.; Egal, S.; Wild, C.; Turner, P. C.; Gong, Y.; Hall, A. Costs of Aflatoxin Contaminated Foods in West Africa. In *Mycotoxins: The Cost of Achieving Food Security and Food Quality*, 2001. www.apsnet.org/online/feature/mycotoxin/top.html (accessed May 2004).
- (34) Yoshizawa, T.; Yamashita, A.; Luo, Y. Fumonisin occurrence in corn from high- and low-risk areas for human esophageal cancer in China. *Appl. Environ. Microbiol.* **1994**, *60*, 1626–1629.
- (35) Zhang, J. Y.; Wang, X.; Han, S. G.; Zhuang, H. Case-control study of risk factors for hepatocellular carcinoma in Henan, China. *Am. J. Trop. Med. Hygiene* **1998**, *59*, 947–951.
- (36) United States Department of Agriculture (USDA). *World Corn Trade*; Foreign Agricultural Service: Production, Supply & Distribution, 2003. http://www.fas.usda.gov/psd/complete_tables/GF-table7-88.htm.
- (37) USDA. *Peanut Oilseed: World Supply and Distribution*; Foreign Agricultural Service: Production, Supply & Distribution, 2003. http://www.fas.usda.gov/psd/complete_tables/OIL-table2-171.htm.
- (38) USDA. *World Coarse Grains Situation and Outlook*; Foreign Agricultural Service (FAS) online, 2003. http://www.fas.usda.gov/grain/circular/2003/10-03/cgra_txt.htm (accessed November 2003).
- (39) USDA. *Oilseed Prices*. Foreign Agricultural Service (FAS) online, 2003. <http://www.fas.usda.gov/oilseeds/circular/2003/03-10/PRICES.pdf> (accessed November 2003).
- (40) USDA. *Mycotoxin levels in the 1995 midwest preharvest corn crop*; Animal and Plant Health Inspection Service (APHIS), 1996. www.aphis.usda.gov/vs/ceah/cahm/mycotxt.htm (accessed November 2003).
- (41) USDA. *Mycotoxin levels in the 1996 midwest preharvest corn crop*; Animal and Plant Health Inspection Service (APHIS), 1997. www.aphis.usda.gov/vs/ceah/cahm/mycotxt96.htm (accessed November 2003).
- (42) USDA. Fumonisin B1 Mycotoxin in Horse Grain/Concentrate on US Horse Operations." Animal and Plant Health Inspection Service (APHIS), Info Sheet: Veterinary Services, 2000. <http://www.aphis.usda.gov/vs/ceah/cahm/Equine/eq98fumonisin.htm> (accessed November 2003).
- (43) Li, F. Q.; Yoshizawa, T.; Kawamura, O.; Luo, X. Y.; Li, Y. W. Aflatoxins and fumonisins in corn from the high-incidence area for human hepatocellular carcinoma in Guangxi, China. *J. Agric. Food Chem.* **2001**, *49*, 4122–4126.
- (44) Broggi, L. E.; Resnik, S. L.; Pacin, A. M.; Gonzelez, H. H. L.; Cano, G.; Taglieri, D. Distribution of fumonisins in dry-milled corn fractions in Argentina. *Food Additives Contamin.* **2002**, *19*, 465–469.
- (45) Solovey, M. M. S.; Somoza, C.; Cano, G.; Pacin, A.; Resnik, S. Survey of fumonisins, deoxynivalenol, zearalenone, and aflatoxins contamination in corn-based food products in Argentina. *Food Additives Contamin.* **1999**, *16*, 325–329.
- (46) Sydenham, E. W.; Shephard, G. S.; Thiel, P. G.; Marasas, W. F. O.; Rheeder, J. P.; Peralta Sanhueza, C. E.; Gonzalez, H. H. L.; Resnik, S. L. Fumonisin in Argentinian field-trial corn. *J. Agric. Food Chem.* **1993**, *41*, 891–895.
- (47) Dorner, J. W.; Blankenship, P. D.; Cole, R. J. Performance of two immunochemical assays in the analysis of peanuts for aflatoxin at 37 field laboratories. *J. Assoc. Official Agric. Chemists Int.* **1993**, *76*, 637–643.
- (48) Wang, J. S.; Huang, T.; Su, J.; Liang, F.; Wei, Z.; Liang, Y.; Luo, H.; Kuang, S. Y.; Qian, G. S.; Sun, G.; He, X.; Kensler, T. W.; Groopman, J. D. Hepatocellular carcinoma and aflatoxin exposure in Zhuqing Village, Fusui County, People's Republic of China. *Cancer Epidemiol. Biomarkers* **2001**, *10*, 143–146.
- (49) Fernandez Pinto, V.; Patriarca, A.; Locani, O.; Vaamonde, G. Natural co-occurrence of aflatoxin and cyclopiazonic acid in peanuts grown in Argentina. *Food Additives Contamin.* **2001**, *18*, 1017–1020.
- (50) Henry, S. H.; Bosch, F. X.; Troxell, T. C.; Bolger, P. M. Reducing Liver Cancer—Global Control of Aflatoxin. *Science* **1999**, *286*, 2453–2454.
- (51) Cleveland, T. E.; Dowd, P. F.; Desjardins, A. E.; Bhatnagar, D.; Cotty, P. J. United States Department of Agriculture—Agricultural Research Service research on preharvest prevention of mycotoxins and mycotoxigenic fungi in U.S. crops. *Pest Manage. Sci.* **2003**, *59*, 629–642.
- (52) Dombrink-Kurtzman, M. A.; Dvorak, T. J.; Barron, M. E.; Rooney, L. W. Effect of nixtamalization (alkaline cooking) on fumonisin-contaminated corn for production of masa and tortillas. *J. Agric. Food Chem.* **2000**, *48*, 5781–5786.
- (53) Park, D. L.; Price, W. D. Reduction of Aflatoxin Hazards using Ammoniation. *Rev. Environ. Contamin. Toxicol.* **2001**, *171*, 139–175.

Received for review December 4, 2003. Revised manuscript received May 6, 2004. Accepted May 10, 2004.

ES035353N