

Opportunities for biotechnology and policy regarding mycotoxin issues in international trade[☆]

David F. Kendra^{*}, Rex B. Dyer¹

USDA-Agricultural Research Service, National Center for Agricultural Utilization Research, 1815 N. University Street, Peoria, Illinois 61604, USA

Abstract

Despite being introduced more than a decade ago, agricultural biotechnology still remains framed in controversy impacting both the global economy and international regulations. Controversies surrounding agricultural biotechnology produced crops and foods commonly focus on human and environmental safety, intellectual property rights, consumer choice, ethics, food security, poverty reduction and environmental conservation. Originally, some consumers were reluctant to accept the first generation agricultural biotechnology products because they appeared to primarily benefit agricultural producers; however, it is clear from continued evaluations that these technologies also improved both the safety and wholesomeness of food and helped improve the environment. Plants engineered to resist insect pests and tolerate less toxic pesticides resulted in improved yields thereby enabling farmers to produce more food per acre while reducing the need for herbicides, pesticides, and water and tilling. An indirect benefit of reduced pest damage in transgenic corn expressing genes to control insect pests is lower levels of mycotoxins, most notably those caused by the genus *Fusarium*. Mycotoxins are an important regulatory issue globally because of their toxic and carcinogenic potential to humans and animals. Complicating this issue is the fact that toxicological databases for mycotoxins are relatively incomplete compared to other food contaminants. Current debates about agricultural biotechnology and mycotoxins reveal significant differences in perception of associated risks and benefits. When faced with uncertainty, regulators tend to set limits as low as possible. Additionally, some regulators invoke the “Precautionary Principle” when limited information is available or disputes over interpretation exist for possible contaminants, including mycotoxins. A major concern regarding use of the “Precautionary Principle” is the appearance that regulators can justify setting any limit on the basis of inconclusive or unknown potential hazards of a contaminant which may significantly impact global trade because mycotoxin residues vary widely between countries. This paper describes the current economic and health impact of these regulations and their impact on international trade.

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1. Introduction

Maintaining a safe global food and feed supply is a critical issue facing society. Natural contaminants, especially mycotoxins, pose a challenge because they are found in a wide range of crops and differ significantly in chemical structure and symptomatology in humans and signs of disease in animals

following exposure. Further complicating the issue is the fact that high levels of mycotoxins may be present in apparently healthy and sound commodities.

Since the original description of aflatoxin in the late 1960's, more than 100 countries have adopted regulations to limit exposure of consumers to the adverse health risks associated with selected mycotoxins ([Food and Agriculture Organization of the United Nations, 2004](#)). The 2003 Council for Agricultural Science and Technology report on mycotoxin listed the development of uniform standards and regulations for mycotoxin contamination in food and feed as one of the public policy goals for the 21st century ([Council for Agricultural Science and Technology, 2003](#)). However, controlling mycotoxins in food and feed is an evolving process due to increasing information about their occurrence, toxicology, the impact of environmental

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^{*} Corresponding author. Tel.: +1 309 681 6579; fax: +1 309 681 6689.

E-mail address: david.kendra@ars.usda.gov (D.F. Kendra).

¹ Current address: University of Illinois, College of Medicine at Peoria, 1 Illini Drive, Peoria, Illinois 61656, USA.

influences on formation and distribution and advances in agronomic, storage and transportation practices (Hensen and Caswell, 1999). Because of their ubiquitous nature and the fact that current standards focus on regulating the product rather than the process, mycotoxin contamination of food and feed is unavoidable. Current regulations are based on scientific risk assessment and legally permit small quantities of mycotoxins in food and feed if the levels are below those known to affect the health of humans and animals (Hensen and Caswell, 1999). However, differing opinions on the definition of “acceptable health risk” have led to widely divergent standards among countries. This divergence is largely based on a country’s level of economic development and the susceptibility of its crop to contamination (Food and Agriculture Organization of the United Nations, 2004; Otsuki et al., 2001).

2. Impact of genetically engineered insect resistance and mycotoxin reduction

The first generation of commercially available genetically modified corn contained traits designed to control lepidopteran insect pests and resistance to glufosinate-based herbicides. Commercial release of these varieties was opposed by some individuals who perceived these traits as benefiting only farmers and agri-chemical companies despite the fact that significant research showed that these traits helped improve the environment and food safety by allowing use of less toxic herbicides thereby controlling insect pests that vector mycotoxigenic fungi.

Relationships between insect mediated damage in corn ears and fungal ear rots are well documented for several lepidopteran and coleopteran pests (Christensen and Schneider, 1950; Dowd, 1995, 2000). The first generation of insect resistant transgenic corn varieties contains a gene from the soil bacterium, *Bacillus thuringiensis*, encoding the crystal (Cry) protein which is toxic to lepidopteran corn pests, most notably the European Corn Borer (ECB) (*Ostrinia nubilalis* (Hubner)). Second generation transgenic insect resistant maize contain Cry proteins that protect against a wider variety of insect pests including fall army worm (*Spodoptera frugiperda* (J.E. Smith)), corn ear worm (*Helicoverpa zea* (Boddie)), Southwestern corn borer (*Diatraea grandiosella* Dyar), Western bean cutworm (*Richia albicosta* (Smith)) and Sugarcane borer (*Diatraea saccharalis* (Fabricius)) (Hammond et al., 2005).

In addition to reducing contamination by mycotoxigenic fungi, second generation insect resistant corn is less susceptible to environmental stresses in the field due to a more developed and healthy root system that can more efficiently adsorb water and nutrients thereby protecting the plant against drought stress. Herbicide resistant corn varieties also improve water and nutrient availability and reduce diseases by reducing weeds which compete for water and nutrients and also serve as alternative hosts for diseases, including mycotoxigenic fungi (Jefferson-Moore and Traxler, 2005).

Two of the most important mycotoxins in corn, aflatoxin, and fumonisin, are produced primarily by *Aspergillus flavus*, and *Fusarium verticillioides*, respectively. In the United States production of these toxins is strongly influenced by climate with

fumonisin occurring primarily in the heart of the US Corn Belt, and aflatoxin primarily in the Southeastern and Gulf Coast states.

2.1. *A. flavus* and aflatoxin

Aflatoxins are a group of structurally related mycotoxins that are among the most potent naturally occurring substances and are the most potent chemical liver carcinogen known. Aflatoxins are produced by *A. flavus* and *A. parasiticus* and can infect important food and feed crops both pre- and post-harvest. Aflatoxin contamination is a world wide problem especially on major commodities including corn, peanuts, cottonseed and tree nuts.

Globally, aflatoxins are very important due to their role in aflatoxicosis in both domestic and non-domestic animals including cattle, horses, rabbits, and other non-primates. Aflatoxicosis is also reported for humans most notably in developing countries.

Oral exposure resulting from contaminated diets, is the main route of entry for aflatoxins for both humans and animals. The toxicological effects of aflatoxins are generally divided into two categories and are based on exposure dose and symptomology/signs — acute and chronic toxicity. Acute toxicity occurs when large doses of aflatoxins are ingested and is most often observed in livestock resulting in liver necrosis (Council for Agricultural Science and Technology, 2003). Chronic toxicity results from long term exposure of low to moderate concentrations of aflatoxins and symptoms often include reduced weight gain, reduced milk or egg production, immuno-suppression and liver damage, including tumors (Robens and Richard, 1992). Aflatoxin is also known to act synergistically with hepatitis B virus resulting in hepatic tumors which is a major problem in China and African countries where dietary exposure to aflatoxins and incidence of hepatitis B virus is high (Kirk et al., 2006).

Because of its carcinogenic properties, the Food and Drug Administration (FDA) established guidelines for specific uses of aflatoxin contaminated commodities. Extensive research indicates that aflatoxin-contaminated corn with concentrations at or below the action levels will not affect the health of the specific animals listed but is dependent on factors such as age, sex and general health of the animals. Aflatoxins are often present in highest concentration in broken and cracked kernels; however, apparently healthy and sound kernels may also contain levels significantly exceeding the allowable limits (Windstrom et al., 1975).

Commercial corn hybrids currently available contain little, if any resistance to infection by *A. flavus* and aflatoxin contamination (Wiatrak et al., 2005) and no commercially available detoxification methods for corn have received approval nor are sanctioned by the FDA. Current research indicates that management practices that improve plant health, such as proper irrigation and nutrients, strongly suppress aflatoxin contamination in the field. Additionally, drought tolerant corn hybrids generally have lower aflatoxin concentrations than non-tolerant hybrids under conditions favoring aflatoxin contamination. More recently, experimental corn hybrids developed in breeding programs that simultaneously select for both stress tolerance and resistance to *A.*

flavus infection and aflatoxin contamination, show better overall plant health than currently available commercial hybrids. This strategy offers a promising approach to reduce aflatoxin levels in corn grown in environments conducive for disease and contamination (Xu et al., 2004).

The link between transgenic insect resistance and aflatoxin production is not clear. In the geographic areas where aflatoxin is a chronic problem, feeding damage may result from a wide variety of insects and toxin levels in transgenic insect resistant corn are highly variable. Preliminary data from second generation transgenic insect resistant corn, that control many of the insect species that vector *Aspergillus*, generally contain less aflatoxin than their non-insect resistant isogenic counterparts. It is unclear if this reduction is due to fewer wound sites available for *Aspergillus* colonization or if it is due to an overall increase in plant health (Hammond et al., 2005). Further complicating the disease process is the fact that under favorable conditions and without insect damage, *Aspergillus* can colonize silk tissues, invade healthy kernels and produce aflatoxin.

2.2. *Fusarium graminearum* and deoxynivalenol

F. graminearum occurs frequently in the northern corn production areas of the United States, and eastern Canada and produces deoxynivalenol, the most important mycotoxin occurring in these regions. In transgenic insect resistant hybrids commercially available in Canada, the mean concentration of deoxynivalenol was reduced by 59% compared to non-transgenic commercial hybrids under high ECB pressure (Schaafsma et al., 2002). Baute et al (2002) found in Ontario Canada that under low ECB pressure, transgenic insect resistant corn did not differ in performance from non-transgenic corn and was economical only when insect pressure was high. They concluded that the economic benefit was directly related only to insect control. No correlation was observed between transgenic insect resistance and deoxynivalenol concentrations in early maturing European corn hybrids which led Magg et al. (2002) to speculate that resistance to *Fusarium* ear rot is independently inherited from resistance to insect pests. They recommended that plant breeding efforts are urgently needed to improve *Fusarium* resistance in maize germplasm to help ensure that farmers meet legal mycotoxin standards for food and feed.

2.3. *F. verticillioides* and fumonisins

Fumonisins are a group of mycotoxins produced by several *Fusarium* species, including *F. verticillioides* and *F. proliferatum*, pathogens of several important crops including corn, sorghum, rice, and cereals (Munkvold and Desjardins, 1997). *F. verticillioides* is the most common corn pathogen world wide and can cause disease at any developmental stage. Correlation between visual mold symptoms and fumonisin production is poor and intact corn kernels may contain both the fungus and the toxin but show no sign of the fungal contamination. However, fumonisin levels are highest generally in damaged and unsound kernels and kernel fragments so sound management practices often are sufficient to reduce concentrations to below acceptable levels.

Evidence supports the role of fumonisins in both human and animal diseases including human esophageal cancer, equine leukoencephalomalacia (ELEM), and porcine pulmonary edema (Munkvold and Desjardins, 1997).

Currently there are no corn hybrids resistant to *F. verticillioides* or fumonisin. Commercial corn hybrids vary in their susceptibility to *Fusarium* but no hybrid is classified as completely resistant. Environmental conditions strongly influence both fungal infection and fumonisin formation. Dry weather early in the season, followed by wet weather during pollination along with insect infestation is often associated with increased disease and fumonisin levels in harvested grain. Yield is generally not significantly affected by infection by *F. verticillioides*. However, if conditions favorable for fungal growth persist to harvest, fumonisin levels in grain may exceed levels recommended for certain animals. Factors that influence fumonisin production in corn are not well understood at this time; but it is clear that insect damage provides an avenue for infection. Hybrids genetically engineered to resist insects may have lower levels of fumonisins depending on environmental conditions and level of insect pressure (Hammond et al., 2005; Munkvold and Desjardins, 1997; Munkvold et al., 1999; Papst et al., 2005); however, other infection pathways may also function, including wind or splash dispersion of spores and systemic infection (Munkvold and Desjardins, 1997). Plants engineered with enzymes to degrade fumonisin were evaluated but are not yet commercialized (Hammond et al., 2005). This technology provides an *in planta* control strategy to reduce or eliminate fumonisins in a pre-harvest manner.

3. Risk-benefit perceptions and mycotoxin regulations

As countries move to lower trade barriers and increase the exchange of goods across national borders, governing bodies have developed regulations to ensure competitive trade and domestic food safety. An underlying feature of food safety regulations is the use of scientific assessment of risks to assure that regulations are based on sound science and are not protectionist. Unfortunately, scientific risk assessment is influenced by both politics and culture (Post, 2006).

Because mycotoxin contamination of food and feed is a world-wide problem, more than 100 countries have established formal regulations to minimize exposure (Food and Agriculture Organization of the United Nations, 2004). Development of these regulations is influenced by both scientific and socio-economic factors including: i. the availability of scientifically sound toxicological data; ii. availability of occurrence data in commodities; iii. knowledge of the distribution and concentrations of toxins in commodities; iv. availability of detection methods, including conformational and analytical; v. governmental legislation between countries where trade contracts exist and vi. the need for a sufficient food supply (Food and Agriculture Organization of the United Nations, 2004).

Generally, food safety regulations, including those for mycotoxins, are reactive rather than proactive focusing on the product rather than the production and marketing processes. Enforcing such standards imposes costs on both producers and

consumers including costs for surveillance monitoring, destruction of the commodity or diversion to a lower valued market. (Shoemaker, 2001). Nations most economically affected by international mycotoxin standards are those that are the largest exporter of a given crop, most notably corn and peanuts (Wu, 2004). The United States, China and Argentina export more than 89% of the world's corn and 78% of the world's peanuts therefore these three nations will experience the greatest economic impact due to import regulations for fumonisins and aflatoxins (Wu, 2004). However, in developing nations where agriculture is primarily of a subsistence nature, market, human and animal health losses due to mycotoxin contamination are always significant and are generally severe. Education and a cultural environment that rewards farmers for improving pest and weed control and grain storage conditions will significantly reduce mycotoxin contamination and is the focus of several international agricultural programs.

Toxicological databases for mycotoxins are often incomplete compared to other food contaminants such as pesticides or heavy metals consequently the maximum tolerated limits for regulated mycotoxins vary greatly among countries. To foster international trade, the harmonization of standards based on risk assessment was proposed in order to remove the extreme variability (Council for Agricultural Science and Technology, 2003). Current debates about agricultural biotechnology and mycotoxins reveal significant differences in perception of associated risks and benefits. When faced with uncertainty, regulators tend to set limits as low as possible. The Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives (JECFA) provides scientific advice on mycotoxins to the Codex Alimentarius Commission (CAC), primarily through its general subject committee, the Codex Committee on Food Additives and Contaminants (CCFAC). The main purposes of CAC is to protect consumer health and ensure fair trade practices in the food trade, and promote the coordination of all food standards by international organizations. In the European Union (EU), the first harmonized regulations for mycotoxins in food went into effect in 1998 and included sampling protocols and criteria for methods of analysis. Harmonized regulations have since been expanded to additional mycotoxins in different foodstuffs. A significant expansion for EU-harmonized mycotoxin regulations for foods and feeds began in 2004 and continues to today. For foods, regulations are being considered or are approved for patulin, aflatoxin B₁, aflatoxin M₁, ochratoxin A and deoxynivalenol in infant formula; ochratoxin A in beer, cocoa, cocoa products, coffee, grape juice, and wine; trichothecenes (T-2 and HT-2, in addition to deoxynivalenol), fumonisins and zearalenone in cereal-based foodstuffs.

Recently, Wu (2006) expanded economic calculations to more accurately predict the economic benefits and detriments of strict food standards. She showed that the current EU regulation limiting total aflatoxin in food to 4 µg/kg total may result in significant economic loss to both the EU food processing industries and consumers due to drastically reduced food supplies resulting in increased market prices which must be passed on to the consumers. She also noted that health benefits from this strict standard are insignificant (Wu, 2006). Export markets may also

benefit from strict regulations but depend on several conditions including 1.) a consistently high-quality product, 2.) a global arena with a high degree of difference in quality between multiple exporters to allow for market shifts, and 3.) the lack of a competing export market from the EU. If these conditions are not present then export markets are likely to suffer due to the strict EU aflatoxin standard (Wu, 2006).

Further complicating the regulatory process is the fact that some regulators invoke the "Precautionary Principle" when information of possible contamination is limited or disputes over interpretation exist. A major concern regarding the use of the "Precautionary Principle" is the perception that regulators can justify setting any limit on the basis of inconclusive or unknown potential hazards of a contaminant which could significantly impact global trade because mycotoxin residues vary widely between countries. Care must be taken to ensure that political considerations do not outweigh scientific risk assessment data when determining a national or regional position on allowable limits for mycotoxins. Implementation of process standards based on good agricultural practices (GAP), good management practices (GMP) and hazard analysis critical control points (HACCP) will significantly help minimize mycotoxins contamination in food and feed.

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