IFT Institute of Food Technologists
THE Society for Food Science & Technology

Scientific Status Summary

Food Mycotoxins: An Update

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The Institute of Food Technologists has issued this Scientific Status Summary to update readers on the science of fungal toxins.

Keywords: patulin, ochratoxin, zearlenone, aflatoxin, trichothecene, fumonisin, transgenic

Unavoidable, natural contaminants in foods may have either chemical or biological origin. Mycotoxins—toxic secondary metabolites of fungi—are biological in origin. Despite efforts to control fungal contamination, toxigenic fungi are ubiquitous in nature and occur regularly in worldwide food supplies due to mold infestation of susceptible agricultural products, such as cereal grains, nuts, and fruits. Thousands of mycotoxins exist, but only a few present significant food safety challenges. The natural fungal flora associated with foods is dominated by three genera—*Aspergillus*, *Fusarium*, and *Penicillium,* which except for the *Fusarium* plant pathogens, may include commensals as well as pathogens. The chemical structures of mycotoxins produced by these fungi are very diverse (refer to Figure 1 for structures), as are the characteristics of the mycotoxicoses they can cause (ICMSF 1996).

Ergotism is the oldest identified mycotoxicosis in humans. This mycotoxin represents a group of alkaloids that grow on the heads of grasses, such as wheat and rye. Ergot was responsible for a disease of the Middle Ages known as "St. Anthony's Fire," so named for the burning sensation caused in victims' limbs. The Spartans apparently suffered an ergot epidemic in 430 B.C. and European epidemics date back as far as 857 A.D. (Bove 1970). Ergotism has also been associated with the Salem witch trials in the 1600s in Massachusetts (Caporael 1976). More recent outbreaks, associated with economic upheaval and war, have occurred in Russia (1924 and 1944), Ireland (1929), France (1953), and Ethiopia (1978). Although ergot poisoning continues to pose a challenge for the livestock industry, the toxin is less of a challenge for the food industry because current food quality control procedures screen out ergot-infected grains.

Of the thousands of existing mycotoxins, a few hundred are associated with food and only a handful present food safety challenges to the farm-to-fork food continuum. At the farm level, mold growth can result in reduced crop yields and livestock productivity stemming from illness or death due to consumption of contaminated feed. In food manufacturing, destruction of mycotoxins by conventional food processing is difficult because they are typically highly resistant and detection is complicated due to limitations in analytical methodology. In the marketplace, mycotoxins can be a hurdle to international trade, leading to increased regulation of foods and feeds that may contain them and removal from the market of commodities not meeting regulatory limits (see Table 1 for US, EU, and Codex guidance/regulations).

When present in foods in sufficiently high levels, these fungal metabolites can have toxic effects that range from acute (for example, liver or kidney deterioration), to chronic (for example, liver cancer), mutagenic, and teratogenic; and resulting symptoms range from skin irritation to immunosuppression, birth defects, neurotoxicity, and death (ICMSF 1996). Aflatoxin B_1 (AFB_1), fumonisins, and patulin are suspected human carcinogens. Deoxynivalenol and other trichothecenes as well as AFB_1 are likely to exert immunosuppressive effects, and fumonisin B_1 (FB_1) may contribute to neural tube defects. Renal dysfunction due to ochratoxin A exposure (suspected in Balkan endemic nephropathy) is also a potentially significant problem, especially as this could exacerbate impaired renal function in individuals with diabetes, a burgeoning worldwide epidemic that is highly likely to grow. There is also uncertainty related to the effects of chronic, low-level, long-term exposure to single and/or multiple mycotoxins, which may be the case even for those individuals consuming a diverse diet (Lopez-Garcia and others 1999).

Environmental factors affect mycotoxin presence in raw and stored commodities. Data on optimal temperature and water activity for toxin production by *Aspergillus*, *Penicillium*, and *Fusarium* spp. in culture are provided in Table 2. Traditionally, control of mycotoxin contamination of foods has been attempted through control of water activity, pH, and quality control of incoming ingredients. Novel control avenues are emerging, including availability of genetically modified grains with increased insect resistance and, thus, lowered rates of fungal infection; improved management of grain ingredients; and inclusion of controls for mycotoxins in food manufacturing Hazard Analysis and Critical Control Point (HACCP) plans.

Genotyping techniques have shed new light on mycotoxin-producing fungi and provided the foundation for advances in detection methodology. Historically, fungi have been identified on the basis of traditional taxonomic characteristics (for example, morphological features); more recently, the tools of molecular biology have enabled genetic analysis and classification on the basis of nucleic acid sequence. Since analytical methods for detecting mycotoxins have become more prevalent, sensitive, and specific, surveillance of foods for mycotoxin contamination has become more common. Table 3 provides information from surveys that have been conducted around the world with a diversity of mycotoxins detected.

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doi: 10.1111/j.1750-3841.2006.00052.x

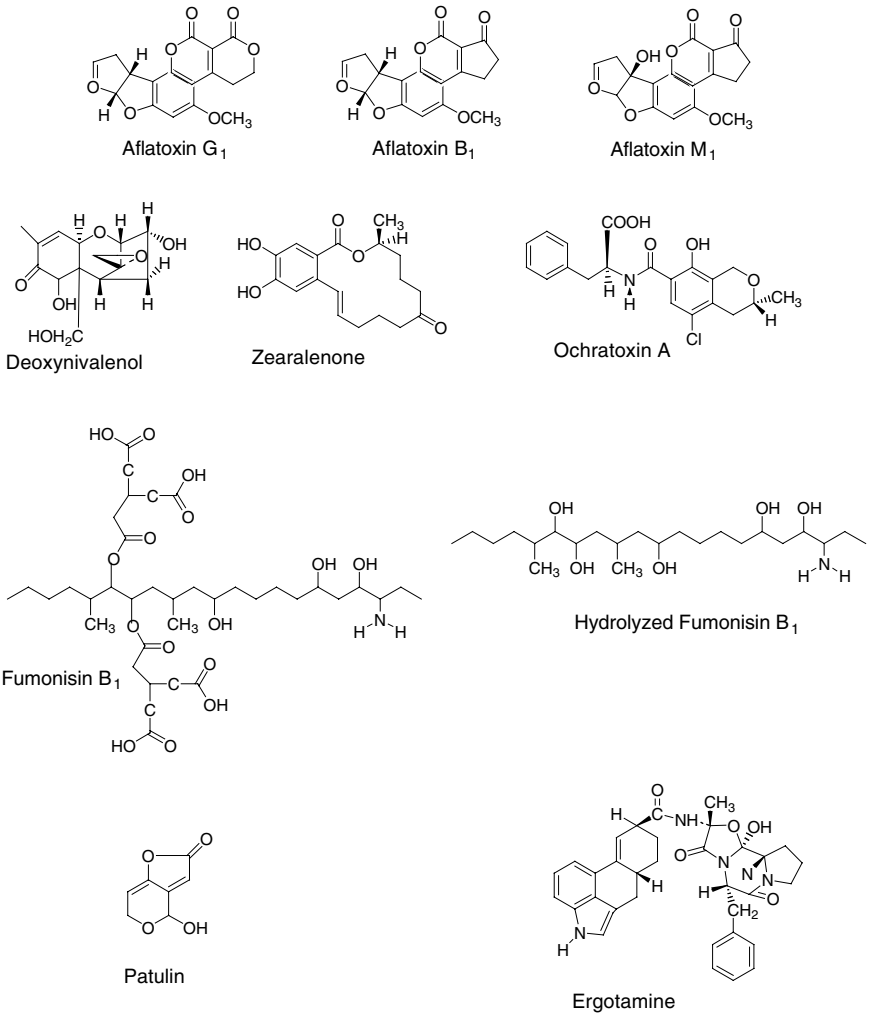

Figure 1 — Chemical structures of mycotoxins found in foods

This Scientific Status Summary addresses mycotoxins on the basis of key characteristics or scientific advances unique to each toxin. Since the publication of the previous Summary (IFT 1986) on this topic, a new type of mycotoxin—the fumonisins—produced by *Fusarium* spp. (Gelderblom and others 1988) has been isolated, and much has been accomplished in the areas of toxicology, detection, and control of mycotoxins. This Summary focuses on the scientific advances made after 1986.

Mycotoxins Impacting Food Production and Manufacturing

Patulin

Apricots, grapes, peaches, pears, apples, olives, cereals, and low-acid fruit juices (notably apple, grape, and pear) are the commodities most commonly infected by the pathogens that produce patulin (Speijers 2004). Patulin is not found in intact fruit because it is damage to the surface of fruit that makes it vulnerable to *Penicillium* infection (Sewram and others 2000). Thus, the critical point for controlling fruit quality is the point at which the fruit enters the processing line.

Recent studies have determined that patulin is not carcinogenic, thereby causing a decline in research interest (Wouters and Speijers 1996). Hence, most of the patulin toxicity research conducted since 1995 has focused on genotoxicity.

Historically, apple juice has been a product of high concern with regard to patulin contamination. Therefore, many of the investigations on patulin stability during food processing have focused on apple juice. Bissessur and others (2001) reported that filtration to clarify juices and concentrates reduced patulin levels up to 40%. Lipowska (1990) observed that patulin was unstable during fermentation of apple juice to cider and was completely destroyed by treatment with 0.125% sulfur dioxide. However, findings pertaining to the effect of heat on the toxin vary. Although Woller and Majreus (1982) reported no loss of patulin in thermal processing of apple juice, Wheeler and others (1987) reported partial patulin destruction using high temperature-short time pasteurization, and Kadakal and Nas (2003) reported a 25% loss in naturally contaminated apple juices during pasteurization or evaporation conditions (70 to 100 °C). It is thought that the pH of the apple juices lends heat stability to patulin, accounting for the variability in results. Because of this, it is important to assess the effectiveness of conditions specific to each process before implementing a process control measure.

Ochratoxin

Ochratoxin is present in a large variety of foods because it is produced by several fungal strains of the *Penicillium* and *Aspergillus* species that have varied physiologies and ecologies. The presence of chlorine in its structure (Figure 1) makes it unique. Ochratoxin is considered to be nephrotoxic, teratogenic, and immunotoxic, and

Table 1 — Guidance and regulations on mycotoxins in food and feed

Country/Region	Mycotoxin	Food/Feed	Action level	Source
United States	Patulin	Apple juice, apple juice concentrate, and apple juice products	50 ppb	http://www.fda.gov/ora/compliance_ref/cpg/cpgfod/cpg510-150.htm
	Fumonisin $B_1+B_2+B_3$	Degermed dry milled corn products	2 ppm	http://www.cfsan.fda.gov/dms/fumongu2.html
		Whole or partially degermed dry milled corn products	4 ppm	
		Dry milled corn bran	4 ppm	
		Cleaned corn intended for masa production	4 ppm	
		Cleaned corn intended for popcorn	3 ppm	
		Corn and corn by-products intended for:		
		Equids and rabbits	5 ppm	
		Swine and catfish	20 ppm	
		Breeding ruminants, poultry, and mink (includes lactating dairy cattle and hens laying eggs for human consumption)	30 ppm	
		Ruminants ≥3-mo old being raised for slaughter and mink for pelt production	60 ppm	
		Poultry being raised for slaughter	100 ppm	
		All other species or classes of livestock and pet animals	10 ppm	
	Aflatoxin $B_1+B_2+G_1+G_2$	Foods	20 ppb	http://www.cfsan.fda.gov/lrd/fdaact.html
		Brazil nuts, pistachio nuts, peanuts, and peanut products	20 ppb	
	Aflatoxin M_1	Milk	0.5 ppb	
	Aflatoxin $B_1+B_2+G_1+G_2$	*Corn and peanut products intended for:*		
		Finishing beef cattle	300 ppb	
		Finishing swine ≥100 lb	200 ppb	
		Breeding beef cattle, breeding swine, or mature poultry	100 ppb	
		Corn, peanut products, and other animal feeds and feed ingredients but excluding cottonseed meal, intended for immature animals	100 ppb	
		Corn, peanut products, cottonseed meal, and other animal feed ingredients intended for dairy animals, for animal species, or when the intended use is unknown	20 ppb	
		Cottonseed meal for beef cattle, swine, poultry	300 ppb	
	DON	Finished wheat products	1 ppm	http://www.cfsan.fda.gov/comm/cp07002.html
European Union	Ochratoxin A	Raw cereal grains	5 ppb	http://europa.eu.int/eur-lex/pri/en/oj/dat/2002/l_075/l_07520020316en00180020.pdf
		All products derived from cereals	3 ppb	
		Dried vine fruit (currants, raisins, sultanas)	10 ppb	
	Patulin	Apple juice and other foods derived from apples	50 ppb	http://europa.eu.int/eur-lex/en/archive/2004/l_07420040312en.html
		Solid apple products, for example, purees, compotes	25 ppb	
		Apple juice and solid apple products intended for infant foods	10 ppb	
	Aflatoxin B_1	Spices (*Capsicum* and *Piper* spp., nutmeg, ginger, and turmeric)	5 ppb	http://europa.eu.int/eur-lex/pri/en/oj/dat/2002/l_075/l_07520020316en00180020.pdf
	Aflatoxin $B_1+B_2+G_1+G_2$	Spices (*Capsicum* and *Piper* spp., nutmeg, ginger, and turmeric)	10 ppb	
	Aflatoxin B_1	Groundnuts, nuts, dried fruit, and processed products thereof intended for direct consumption or as an ingredient	2 ppb	http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_077/l_07720010316en00010013.pdf

(continued on next page)

Table 1 – (continued from previous page)

Country/Region	Mycotoxin	Food/Feed	Action level	Source
		Groundnuts to be subjected to sorting or other physical treatment before human consumption or use as ingredient	8 ppb	
		Nuts and dried fruit to be subjected to sorting or other physical treatment before human consumption or use as ingredient	5 ppb	
		Cereals and processed products thereof intended for direct consumption or as an ingredient	2 ppb	
	Aflatoxin $B_1+B_2+G_1+G_2$	Groundnuts, nuts, dried fruit, and processed products thereof intended for direct consumption or as an ingredient	4 ppb	
		Groundnuts to be subjected to sorting or other physical treatment before human consumption or use as ingredient	15 ppb	
		Nuts and dried fruit to be subjected to sorting or other physical treatment before human consumption or use as ingredient	10 ppb	
		Cereals and processed products thereof intended for direct consumption or as an ingredient	4 ppb	
	Aflatoxin M_1	Milk (raw, for manufacture of milk-based products, and heat-treated)	0.05 ppb	
Codex Alimentarius Commission	Patulin	Apple juice and apple juice ingredients in other beverages	50 ppb	Codex Standard 235 to 2003 http://www.codexalimentarius.net/web/standard_list.do?lang=en
	Aflatoxin $B_1+B_2+G_1+G_2$	Peanuts intended for further processing	15 ppb	Codex Standard 209 to 2001 http://www.codexalimentarius.net/web/standard_list.do?lang=en
	Aflatoxin M_1	Milk	0.5 ppb	Codex Standard 232 to 2001 http://www.codexalimentarius.net/web/standard_list.do?lang=en

has been classified by the IARC as a Class 2B carcinogen, probable human carcinogen.

Ochratoxin A, the main toxin in this group, is found in wheat, corn, and oats having fungal infection and in cheese and meat products of animals consuming ochratoxin-contaminated grains (Aish and others 2004). *A. ochraceus* is found on dry foods such as dried and smoked fish, soybeans, garbanzo beans, nuts, and dried fruit. *A. carbonarius* is the major pathogen in grapes and grape product including raisins, wines, and wine vinegars. Although reported to occur in foods around the world, the main regions of concern are Europe and, for some foods, Africa. The Joint Expert Committee on Food Additives of the Food and Agriculture Organization of the United Nations and the World Health Organization (JECFA 2001) presented data indicating that cereals, wine, grape juice, coffee, and pork are the major sources of human ochratoxin exposure, at levels of 58%, 21%, 7%, 5%, and 3% of total ochratoxin intake, respectively. Levels reported range from 100 to 700 ng/kg in cereals, 30 to 9000 ng/L in European wines, 170 to 1300 ng/kg in coffee, and 150 to 2900 ng/kg in pork (Sage and others 2004). Ochratoxin presence in European wines is a relatively recent concern, with red wines typically containing higher ochratoxin levels than rosé or white wines.

Because of the large variety of food matrices in which ochratoxin has been found, there is no universally suitable method of analysis. Differences in extraction conditions and clean-up are as varied as the foods. Analysis is typically accomplished by high performance liquid chromatography, although liquid chromatography—mass spectrometry— is an important secondary confirmation technique.

The impact of processing on ochratoxin A-contaminated foods is not very well understood. Polishing and milling of wheat (to remove outer layers for white flour production) lowered ochratoxin levels; however, no effect was seen for whole-wheat flours (Osborne and others 1996). Chelkowski and others (1981) reported equal distribution of ochratoxin A into the bran and flour fractions upon dry milling of wheat and barley. Van der Stegen and others (2001) reported that ochratoxin was relatively stable during heat processing; however, toxin levels were reduced 70% to 96% during coffee bean roasting, and Heilmann and others (1999) reported similar reductions during decaffeination. Wet milling of corn resulted in reductions of ochratoxin levels in germ and grits of 96% and 49%, respectively (Wood 1982). And McKenzie and others (1997) reported that ozonolysis is effective in destroying ochratoxin in aqueous model systems.

Zearalenone

A myco-estrogen, zearalenone, has attracted recent attention due to concerns that environmental estrogens have the potential to disrupt sex steroid hormone functions. Occasional outbreaks of zearalenone mycotoxicosis in livestock are known to cause infertility. Alternatively, derivatives of zearalenone are used in some livestock feeds for growth promotion (for example, Ralgro® in beef cattle), as alternatives to the more potent and controversial synthetic estrogen, diethylstilbestrol.

This toxin is found almost entirely in grains and in highly variable amounts ranging from a few nanograms per gram to thousands of nanograms per gram. The appearance of mold on grain plants cannot be relied upon to warn of toxin production because *Fusarium*-infected grain does not necessarily appear visibly moldy in the presence of high concentrations of mycotoxins (Murphy and others 1996). The average human intake of zearalenone was estimated to be approximately 0.02 μg/kg bw/d on the basis of limited data obtained in Canada, the United States, and Scandinavian countries, but it is likely that intakes are greater in countries from the regions of the world having less well-controlled grain storage systems.

Table 2—Examples of optimal conditions for mycotoxin production

Microorganism (mycotoxin)	Temp (°C)	A_w	Reference
Aspergillus flavus, A1 parasiticus (aflatoxin)	33	0.99	Hill and others 1985
Aspergillus ochraceus (ochratoxin)	30	0.98	Ramos and others 1998
Penicillium verrucosum (ochratoxin)	25	0.90 to 0.98	Cairns and others 2003
Aspergillus carbonarius (ochratoxin)	15 to 20	0.85 to 0.90	Mitchell and others 2003
Fusarium verticillioides, F1 proliferatum (fumonisin)	10 to 30	0.93	Marin and others 1999
Fusarium verticillioides, F. proliferatum (DON)	11	0.90	Hope and Magan 2003
Fusarium graminearum (zearalenone)	25 to 30	0.98	Sanchis 2004
Penicillium expansum (patulin)	0 to 25	0.95 to 0.99	Sanchis 2004

[a]The majority of data generated on environmental optima for mycotoxin production was obtained from cultures rather than actual field or storage environments.

Genotoxicity is a reported concern with respect to zearalenone. Although this estrogenic compound showed no mutagenicity in Ames tests (1 to 500 μg zearalenone/agar plate), the substance induced chromosomal anomalies in some lymphocyte, oocyte, and kidney cell cultures when present within a range of 0.1 to 20 μM (Stopper and others 2005). This dose range is difficult to extrapolate to likely human exposures because no human bioavailability estimates are available. With estimated human intake of approximately 1 to 2 μg per person, however, occurrence of blood or tissue concentrations remotely close to 0.1 M (approximately 30 μg/L) seems extremely unlikely.

A related fungal metabolite, α-zearalenol, which has about 3-fold more estrogenic potency than zearalenone, was recently shown to inhibit atherogenesis, lowering plasma LDL-cholesterol and limiting aortic plaque formation in ovariectomized rabbits fed a high dose of cholesterol. The effective estrogenic dose of α-zearalenol was >0.5 mg/kg/d for 12 wk (Dai and others 2004). Except as a potential pharmaceutical, such a large dose is of little practical value. Common human exposure levels for zearalenone or related compounds would not be expected to exert such health benefits.

Aflatoxins

Aflatoxins may contaminate many crops including peanuts, corn, cottonseed, Brazil nuts, pistachios, spices, copra (dried coconut), and figs with widespread contamination in hot and humid regions of the world. These mycotoxins occur in several chemical forms, designated aflatoxin B_1, B_2, G_1, G_2, and M_1 (Figure 1). "B" and "G" refer to the blue or green fluorescence observed upon exposure of the toxin to ultraviolet irradiation. M_1 is the predominant metabolite of AFB_1 in milk from lactating humans and animals that consume AFB_1-contaminated food or feed. According to the IARC, there is sufficient evidence to conclude that AFB_1 and mixtures of B_1, G_1, and M_1 are proven human carcinogens, thereby warranting Group 1 carcinogen status. M_1 and B_2 are designated as Group 2B probable human carcinogens (IARC 1993a).

AFB_1 is metabolized by the liver through the cytochrome P450 enzyme system to the major carcinogenic metabolite AFB_1-8,9-epoxide (AFBO), or to less mutagenic forms such as AFM_1, Q_1, or P_1 (Crespi and others 1991, Shimada and Guengerich 1989). As shown in Figure 2, there are several pathways that AFBO can take, one resulting in cancer, another in toxicity, and others in AFBO excretion. The exo-form of AFBO readily binds to cellular macromolecules including genetic material, for example, proteins and DNA, to form adducts. It is the formation of DNA-adducts, such as with N^7-guanine, that leads to gene mutations and cancer. One such mutation is suspected to occur in the human p53 tumor suppression gene at codon 249 (AGG, Eaton and Gallagher 2004). Studies have shown that AFBO induces conversions from G (guanine) to T (thymine) at the 3rd nucleotide of the codon, making it a mutational "hotspot." This mutation has been found with greater frequency among patients with hepatocellular carcinomas in areas of high-risk aflatoxin exposure (IARC 1993a,b). The AFB_1-N^7-guanine adduct is excreted in the urine of those infected. Urinary excretion not only serves as evidence that humans have the necessary biochemical pathways for carcinogenesis (IARC 1993a,b), but also provides a reliable biomarker for exposure to AFB_1 (Groopman and Kensler 2005).

Inhibition of AFBO formation (through disruption of the cytochrome P450 system) and/or adduct formation are important strategies for prevention of these damaging mutations. In animal models, metabolic detoxification of AFBO is facilitated by induction of glutathione S-transferase (GST). This enzyme catalyzes the reaction that binds glutathione to AFBO and renders it noncarcinogenic. It is interesting to note that mice, which are resistant to aflatoxin carcinogenesis, have GST activity levels 3 to 5 times higher than rats, which are susceptible—and humans have lower GST activity than rats. Synthetic dithiolthione compounds, such as oltipraz (an FDA approved antischistosomal drug), and antioxidants, such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and ethoxyquin, are among the most effective against aflatoxin carcinogenesis (Bammler and others 2000, IARC 1993a,b, Kwak and others 2001). Human clinical trials in China showed that a daily dose (125 mg/d) of oltipraz significantly increased excretion of AFB_1-mercapturate, a derivative of GST reaction with AFB_1 (Kwak and others 2001); chlorophyllin has also been shown to protect against human AFB_1 toxicity (Kensler and others 2004). It remains to be seen if long-term administration of oltipraz could lessen human risk for AFB_1 carcinogenesis; reduction of aflatoxin intake, however, would result in reduced liver cancer rates.

Simultaneous hepatitis B and AFB_1 infections commonly occur in regions with high rates of hepatocellular carcinoma (HCC). A cohort study of more than 18000 individuals in China clearly showed a relative risk (measure of how much a particular risk factor [for example, AFB_1] influences the risk of a specified outcome [for example, HCC]) for HCC of 3.4 in subjects who showed AFB_1 exposure (urinary AFB_1-N^7-guanine; due to AFB_1 exposure, a person is 3.4 times more likely to develop HCC), whereas relative risk for subjects positive for hepatitis B antigen was 7.3; combination of hepatitis B and AFB_1 exposure increased relative risk for HCC to 59 (Qian and others 1994). Thus, AFB_1 is an independent and possibly strongly potentiating factor for human HCC.

Human aflatoxicoses continue to be an occasional, serious problem. For example, a severe outbreak was reported in Kenya in 2002 (CDC 2004). Half of the maize food samples tested in districts associated with this outbreak had AFB_1 levels >20 ppb (the action level for AFB_1 in Kenya), with 3% to 12% of samples, depending on the district, containing >1000 ppb and some samples containing as much as 8000 ppb AFB_1. This outbreak had at least a 39% incidence of death (317 cases with 125 deaths) resulting from acute hepatotoxicity.

Immunotoxicity seems a likely effect of human AFB_1 exposure due to the numerous animal studies in which lymphocyte (T-cell,

Table 3—Worldwide mycotoxin surveys

Country	Food/Feed type	Deoxynivalenol (mg/kg)	Nr of positive samples/Nr of samples tested	Other mycotoxins detected[a]	Detection method (limit of detection)[b]	References
China	Raw corn	<0.5 to 2.7	7/12	FB_1, FB_2, FB_3, 15ADON	GC/MS (0.5 mg/kg)	Groves and others (1999)
	Cornmeal	<0.5 to 1.6	8/13			
	Cooked pancakes	<0.5 to 1.5	4/14			
China	Wheat	0.016 to 51.45	8/8	NIV, 3ADON, ZEA	GC/MS (trichothecenes 0.01 mg/kg)	Li and others (1999)
	Barley	0.132 to 3.521	2/2	NIV, ZEA	HPLC (fumonisins 0.05 mg/kg)	
	Corn	0.256 to 21.200	2/2	NIV, ZEA, FB_1, FB_2, FB_3, 15ADON		
Nepal	Corn grain	nd to 11.00	10/58	Fumonisins	Immunoassay (1.0 mg/kg)	Desjardins and others (2000)
	Corn flour	nd to 3.00	1/8	Fumonisins	Quantitative fluorometry (1.0 mg/kg)	
	Cornflakes	nd	0/2			
Portugal	Bran cereal	<0.1 to >5.001	16/24	—	HPLC (0.1 mg/kg)	Martins and Martins (2001)
	Wheat flakes	<0.1 to 5.000	16/20			
	Wheat and fruit cereal	<0.1 to 5.000	32/44			
Germany	White wheat flour	0.239 ± 0.228	28/28	NIV, ZEA	GC/MS (0.002 to 0.012 mg/kg)	Schollenberger and others (2002)
	White wheat flour	0.234 ± 0.215	12/13	NIV, HT-2, ZEA		
	Whole wheat flour	0.404 ± 0.427	19/19	NIV, 3ADON, 15ADON, HT-2, T-2, ZEA		
Germany	Wheat flour	0.394 mean 0.956 (90^{th} %)	59/60	Discussed but not reported	GC/MS (0.007 mg/kg)	Schollenberger and others (2003)
	Wheat bread	0.125 mean 0.247 (90^{th} %)	127/141			
	Noodles	0.275 mean 1.149 (90^{th} %)	61/67			
	Rice	0.058 mean	14/26			
	Oats and products	0.024 mean	12/23			
	Corn and products	0.034 mean	25/36			
Canada	Oat-based infant cereals	0.052 mean 0.090 max.	33/53	OTA	GC/MS (limit of quantification) LOQ DON 0.020 mg/kg	Lombaert and others (2003)
	Barley-based infant cereal	0.260 mean 0.980 max.	29/50	ZEA, OTA ZEA, OTA, FB		
	Soy-based infant cereal	0.116 mean 0.240 max.	8/8	ZEA, OTA, FB ZEA, OTA, FB		
	Multi-grain infant cereals	0.116 mean 0.400 max.	62/86			
	Rice-based infant cereals	nd	0/9	ZEA, OTA, FB		
	Teething biscuits	0.060 mean 0.120 max.	18/24	nd nd		
	Soy formulas	nd	0/1			
	Creamed corn	nd	0/6			
United States	Durum wheat	nd to 23.0	123 tested	15ADON (nd to 0.8) NIV nd	GC LOD (limit of detection) not reported	Manthey and others (2004)
United States	Hard winter wheat	0.8 mean 7.6 max.	94/194	Not reported	ELISA (0.5 mg/kg)	Trucksess and others (1995)
	Soft winter wheat	1.4 mean 14.6 max	50/59			
	Hard spring wheat	3.7 mean 18.4 max.	180/201			
	Soft white wheat	0.1 mean 0.7 max.	8/28			

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Table 3—(continued from previous page)

Country	Food/Feed type	Deoxynivalenol (mg/kg)	Nr of positive samples/Nr of samples tested	Other mycotoxins detected[a]	Detection method (limit of detection)[b]	References
	Mixed wheat barley	2.3	1/1			
		3.0 mean 14.0 max.	79/118			
	Malting barley	9.0 mean 25.8 max.	29/29			
Italy	Cereals, whole meals, flours	0.065 median (0.065 to 0.930 range)	111/111	FB_1, FB_2	GC/ECD (0.007 mg/kg)	Cirillo and others (2003)
	Breads	0.046 median (0.007 to 0.270)	19/24	FB_1, FB_2		
	Durum wheat pasta	0.019 median (0.009 to 0.077)	7/17	FB_2		
		0.023 median (0.012 to 0.047)	9/14	FB_1, FB_2		
	Breakfast cereals	0.040 median (0.016 to 0.150)	16/24	FB_1, FB_2		
	Biscuits	0.035 median (0.007 to 0.166)	7/12	nd		
	Baby and infant foods					
Denmark	Wheat	0.144 mean 0.527 max.	75/88	NIV, HT-2, T-2, ZEA	GC-ECD (0.020 mg/kg)	Rasmussen and others (2003)
	Rye	0.043 mean 0.257 max.	41/69	NIV, HT-2, T-2, ZEA		
	Durum wheat	1.155 mean 2.591 max.	33/33	NIV, T-2		
United Kingdom	Polenta	0.587 mean ± 0.135 sd	2/2	ZEA, FB_1, FB_2, FB_3	GC/MS (0.050 LOQ)	FSA (2005)
	Corn cereals	0.227 mean ± 0.306 sd	15/44	ZEA, FB_1, FB_2, FB_3, NIV		
	Snacks	0.157 mean ± 0.077 sd	19/38	ZEA, FB_1, FB_2, FB_3, OTA		
United Kingdom	Cereals	0.138 mean ± 0.355 sd	42/60	3ADON, 15ADON, FUSX, NIV, T-2, HT-2, ZEA NIV, ZEA	GC/MS (0.010 LOQ)	FSA (2003)
	Cookies	0.033 mean ± 0.044 sd	49/60	NIV, ZEA		
	Bread	0.058 mean ± 0.062 sd	57/60			
	Cakes	0.024 mean ± 0.015 sd	19/40	NIV		
	Flour	0.061 mean ± 0.091 sd	36/40	15ADON, NIV, ZEA		
	Polenta	0.175 mean ± 0.139 sd	7/8	3ADON, 15ADON, NIV, ZEA ZEA		
	Snacks	0.251 mean ± 0.269 sd	36/40	NIV, HT-2, ZEA		
	Corn flour	-	0/8			
	Baby food	0.047 mean ± 0.044 sd	13/17	15ADON, NIV, ZEA		
	Snacks (2nd survery)	0.092 mean ± 0.0073 sd	37/44			

[a]FB = fumonisin; 15ADON = 15-acetyl-deoxynivalenol; NIV = nivalenol; 3ADON = 3-acetyl-deoxynivalenol; ZEA = zearalenone; OTA = ochratoxin A; FUSX = fusarenon X; T-2 = T-2 toxin; HT-2 = HT=2 toxin; sd = standard deviation.
[b]GC/MS = gas chromatography/mass spectrometry; HPLC = high performance liquid chromatography; ELISA = enzyme-linked immunosorbent assay.

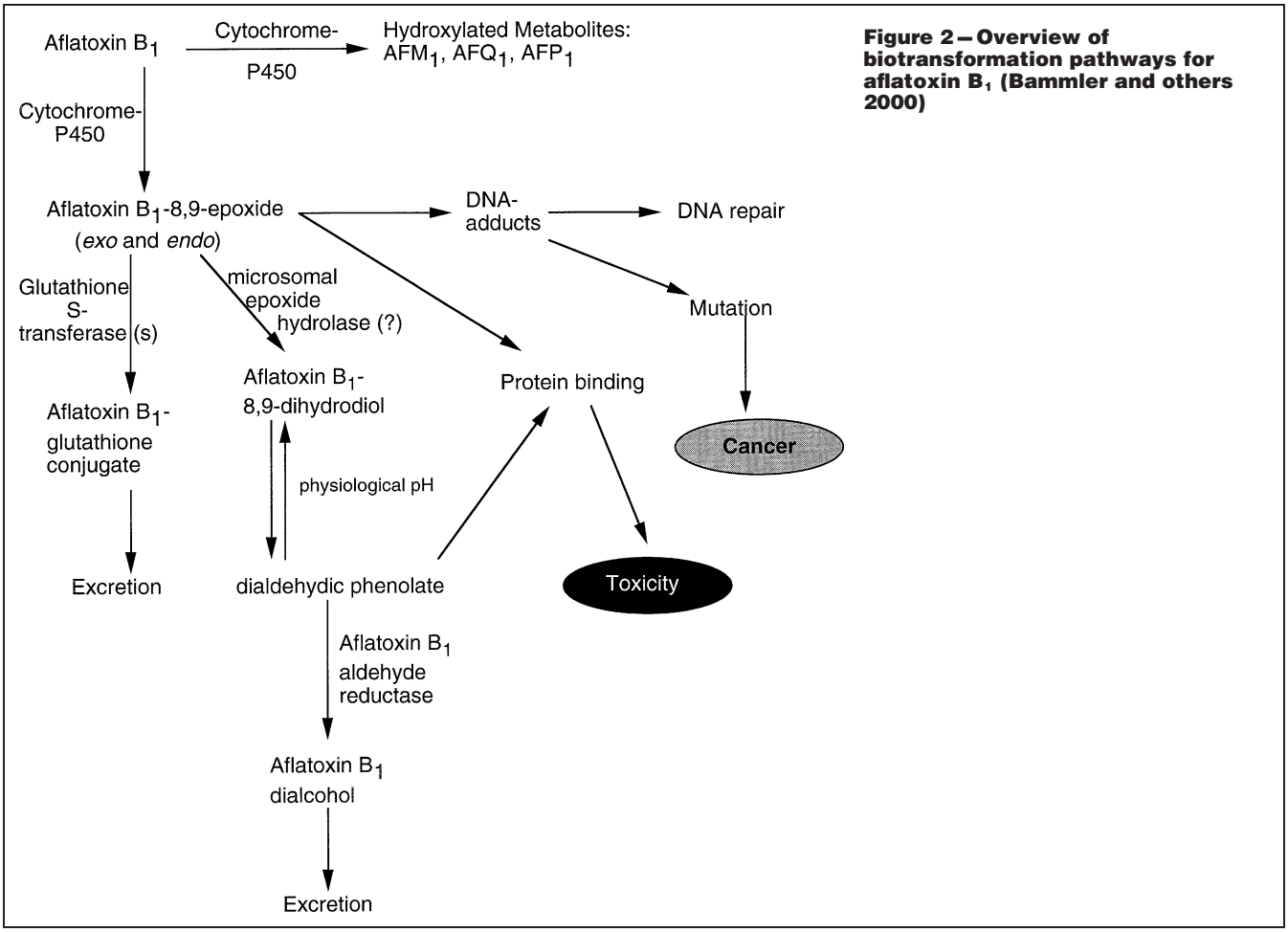

Figure 2—Overview of biotransformation pathways for aflatoxin B_1 (Bammler and others 2000)

macrophage, natural killer cell, and B-cell) immune functions were suppressed or perturbed by this mycotoxin. Immunoglobulin A (IgA) response to some vaccine challenges was suppressed in Gambian children with detectable AFB_1-albumin adducts (a complex formed between the toxin and the biological material, in this case a protein, that may either be repaired or mutate, in which case it could lead to cancer as discussed above) (Turner and others 2003). Decreased human growth was associated with increasing AFB_1-albumin adduct formation in African children (Gong and others 2002). Vitamin A and zinc status were not related to AFB_1 exposure (Gong and others 2004). This suggests that AFB_1 exacerbates protein calorie malnutrition and thereby growth suppression; suppressed immune function is a likely correlate to AFB_1 infection.

Some food processing methods have been shown to result in reduction or elimination of aflatoxins. Roasting peanuts resulted in greater reductions of chemically detectable aflatoxins than boiling (Njapau and others 1998). Fermentation of wheat flour dough reduced detectable aflatoxin by approximately 50%, while baking of the dough resulted in lesser reductions ranging from 0 to 25% (Scott 1991). Traditional nonalkaline toasting and boiling processes to produce pinole (a meal of ground corn and beans) from aflatoxin-contaminated corn were reported to significantly reduce chemically detectable aflatoxin (Mendez-Albores and others 2004a). High-temperature (121 °C) alkaline treatment of contaminated corn prior to frying resulted in very low levels of chemically detectable aflatoxin (Camoou-Arriola and Price 1989). Alkaline processing or nixtamalization (the traditional process of cooking corn in lime water to produce nixtamal that is then ground to form masa) of corn also resulted in significant reductions of aflatoxin (Torres and others 2001). Although Cazzaniga and others (2001) reported that extrusion processing (up to 180 °C) of corn did not achieve substantial destruction of aflatoxin, Cheftel (1989) reported significant reductions in detectable aflatoxin during extrusion of rice flours; differences in results may be due to differences in extruder design (Cazzaniga and others 2001). McKenzie and others (1997) reported that treatment with ozone destroyed AFB_1 and G_1 in aqueous model systems; and Prudente and King (2002) reported 92% reduction in contaminated corn, with no reformation of the mycotoxin post-treatment. There are reports of reformation or reactivation of aflatoxins post-process. For example, initial loss of detectable aflatoxin was followed by detection upon acidification of the masa flour. The researchers speculated that this acidification could happen after consumption of nixtamalized aflatoxin-contaminated corn (Mendez-Albores and others 2004b).

Trichothecenes

Approximately 180 trichothecenes are known to exist, but only a few are significant to human health. This Summary focuses on deoxynivalenol (DON), the most prevalent of the trichothecenes in human foods, although related mycotoxins such as 3-acetyl DON, T-2 toxin, and nivalenol also occur with some regularity. The biosynthetic pathway for trichothecene production is known for several *Fusarium* species (Desjardins and others 1993); 11 genes involved in the trichothecene pathway have been cloned (Brown and others 2001). These findings allow researchers to pursue traditional plant breeding and transgenic approaches to mycotoxin control that will be discussed in more detail in a later section of this summary.

Inhibition of protein synthesis is thought to be the fundamental mechanism of trichothecene toxicity. Ehrlich and Daigle (1987) showed that DON and T-2 toxin caused polyribosomal breakdown in mammalian cell lines. 3-acetyl DON had similar lethality to DON *in vivo* because it was converted to DON; however, the addition of a hydroxyl group at the C-4 position, as in nivalenol, decreased lethal dose in mice by 6-fold compared with DON (Thompson and Wannemacher 1986).

More recently, elucidation of DON toxicity mechanisms has focused on differential responses of mRNA and translation products following DON exposure of mice. Cell signaling pathways are activated by 1 mg DON/kg bw, through gene induction and activation of several nitrogen-activated protein kinases. DON (≥100 ng/mL) activates hematopoetic cell kinase and double-stranded RNA-activated protein kinase, which leads to apoptosis (programmed cell death) (Pestka and others 2004). The way in which symptoms relate to these molecular events remains to be clarified. Numerous studies have shown that DON is immunotoxic in animal models. Host resistance assays offer the most definitive assessment of such effects. Male BALB/c mice given 2 ppm DON (in water) 2 wk prior to and concurrent with oral intubation of *Salmonella enteritidis* (3×10^6 CFU) had increased bacterial counts postinfection, indicating that their immune systems were repressed by DON exposure (Hara-Kudo and others 1996). Although human DON exposure may be within the range of doses shown to be immunotoxic in rodents, human exposures and responses to this toxin are ill defined. Meky and others (2003) showed that a small number of urine samples from humans in a high risk region (with greater wheat and corn food intake) had 37 ng DON/mL (14 to 94 ng/mL range), whereas samples from a low-risk region had 12 ng DON/mL (4 to 18 ng/mL range), a significant difference.

Several thousand people were affected by gastrointestinal distress in an incident in the Kashmir Valley of India in 1987. Ninety-seven reported feelings of fullness and mild to moderate abdominal pain within 15 min to 1 h after consuming their breakfast or evening snack (consisting of locally produced or homemade wheat bread). Other reported symptoms included throat irritation (63%), diarrhea (39%), vomiting (7%), blood in the stools (5%), and facial rash (2%). Increased incidence of upper respiratory tract infections was reported in children who had consumed the wheat bread for more than a week. Illnesses subsided when consumption of the bread ceased. Samples of flours and wheat in the local markets contained DON (11/17 had toxin levels of 0.346 to 8.38 μg/g), nivalenol (2/19 had levels of 0.03 to 0.1 μg/g), T-2 toxin (4/19 had levels of 0.55 to 4 μg/g), and 3-acetyl DON (4/19 had levels of 0.6 to 2.4 μg/g), but were negative for aflatoxins and ergot alkaloids (Bhat and others 1989). These results provide solid evidence for the potential health implications of fairly low exposure to the toxin and emphasize the need for more work to define human risk from this common foodborne contaminant. The need to define the role of DON in impairment of human immune function is further emphasized given the growing number of epidemics of severe infectious illnesses (for example, HIV) and world population of immune-impaired individuals (young children and the elderly).

Two AOAC® Official Methods—thin layer and gas chromatography (GC) assays—exist for DON quantification (AOAC 2005). High-performance liquid chromatography methods have been peer-reviewed (Trucksess and others 1998), but are not yet approved by AOAC International. Despite the availability of approved methods, variability in sampling and testing procedures presents difficulties for precise determinations. Inexpensive, rapid assays for DON are not standardized or widely available. Development of molecular imprint polymer technology for DON detection (Weiss and others 2003) is promising in that once the polymer matrix is formed, it may be regenerated by solvent washing and used repeatedly, compared with immunoaffinity columns, which cannot be regenerated. Because prevention of DON contamination seems highly unlikely, and detoxification methods, discussed below, are far from practical at this point, DON detection deserves greater attention within the food science community.

The Council for Agricultural Science and Technology (CAST 2003) estimated that the annual US cost due to DON contamination of human food crops is $637 million. The CAST model included 727 samples of wheat and corn foods from data gathered from FDA and private surveys conducted during 1995 to 1997. Food losses were based on samples with >1 μg/g DON. DON contamination was greater than 1 μg/g in 6.9% of corn samples and 12.4% of wheat samples.

Edwards (2004) reviewed the environmental conditions that favor DON accumulation in food crops. Minimal tillage, nitrogen fertilizers, application of azoxystrobin (fungicide) or glyphosate (herbicide), and production of grains where maize had been grown the previous year were the main risk factors associated with increased DON accumulation. Biological and insect control shows promise, in laboratory environments, for reducing DON contamination levels, but little or no progress has been made in the field.

Current food processing techniques do not significantly contribute to DON remediation, either by reduction or detoxification, in human or animal foods. The combination of high pH (10.0) and high heat (100 °C for 60 min and 120 °C for 30 min) treatment of DON in an aqueous buffer solution produced partial to complete destruction (Wolf and Bullerman 1998). Treatment of wheat and corn with approved food additives, such as dry and aqueous sulfite gas and ozone, has also been investigated. Aqueous sodium bisulfite had the greatest reductive effect by reaction with DON to produce acid-stable sulfonate adduct (DON-S); however, this adduct was hydrolyzed to release DON under alkaline conditions. Upon bread baking, the toxin levels increased by 50 to 75% due to alkaline hydrolysis of the DON sulfonate adduct (Young and others 1986). DON levels in corn were reduced by as much as 95% by autoclaving at 121 °C for 1 h with 8.33% aqueous sodium bisulfite. This corn was mixed with a basal diet and fed successfully to pigs, indicating that this treatment may be a viable option depending on the end use of the contaminated grain (Young and others 1987).

Removing DON from feed barley by an abrasive dehulling (pearling) process was shown to significantly reduce toxin levels. Naturally contaminated (at various levels) barley was pearled for 15 s to consistently leave 34% of the initial concentration of the toxin and 85% of the grain mass. Longer treatment resulted in significant grain losses, but suitable scale-up remains a hurdle to commercial feasibility (House and others 2003). Grain milling partitioned DON (and zearlenone) to the various kernel fractions (bran > shorts > flour). Zearlenone was reduced below 1 ppm in all of the 27 flour samples; however, 3 of 27 flour samples contained DON levels greater than 1 ppm. FDA advisory information suggests that DON levels above 1 ppm are not acceptable for use in products for human consumption. Reduction effectiveness depended upon the extent of penetration of the fungi into the kernel (Trigo-Stockli and others 1996), thereby limiting the practical implications of this method to control DON levels in milled products. Other methods investigated without success include alkaline processing (Abbas and others 1988) and high temperature (autoclaving) and high pressure processing (extrusion) (Wolf-Hall and others 1999). Ultimately, continued vigilance is necessary to screen potentially contaminated grains and properly dispose of lots with DON levels higher than allowed for specific purposes.

Fumonisins

Fumonisins are produced by the maize pathogens, *Fusarium verticillioides* (formerly *F. moniliforme*) and *F. proliferatum*, and at very low levels by *Alternaria* in black end stem rot in tomatoes (Chen and others 1992), asparagus, and garlic (Seefelder and others 2002). Maize-containing foods are the major fumonisin concern for the food industry. At least 15 related fumonisin compounds have been identified; the fumonisin B (FB) group (Figure 1) is predominant. The *Fusarium* species comprise a very complicated genus. Traditional phenotypic taxonomy based on morphology of the *Fusarium* species can be done by well-trained specialists (Burgess and others 1994); because the morphology of many of the species is very similar and leads to misidentification, this approach has its limitations, however.

The fumonisins are highly water-soluble and unlike all other food mycotoxins because they do not have an aromatic structure or a unique chromophore for easy analytical detection. They are primary amines (carbon group substitution at only 1 of the 3 bonding positions) with 2 tricarballylic groups, which contribute to their water-solubility. Study of metabolic pathways is in progress. Fumonisin synthesis is known to involve acetate precursors and alanine and several of the genes involved in fumonisin synthesis have been identified as a cluster on chromosome 1 in *F. verticillioides* (Desjardins and others 1996).

Fumonisin B_1 (FB_1) is the agent responsible for leukoencephalomalacia (related to necrotic lesions in the cerebrum) in horses and pulmonary edema in swine. Hepatotoxicity (liver damage) and nephrotoxicity (kidney damage) have also been reported in connection with fomonisin intoxication. Equine leukoencephalomalacia was reported in horses in veterinary medical literature in 1902, but the causative agents were not understood until 1990. Several major outbreaks of these diseases were reported in 1989 and 1990 in the United States when the concentration of fumonisins in midwestern maize was quite high. The fumonisins are weakly carcinogenic among different rodent species (Gelderblom and others 1993, Voss and others 1995) and are probable human carcinogens, associated with increased incidence of esophageal cancers in South Africa and China (IARC 1993a,b). Marasas and others (2004) suggested that fumonisin consumption is a risk factor in neural tube and related birth defects. Fumonisins are known to disrupt sphingolipid concentrations and synthesis, which may explain the different etiologies of fumonisin toxicity in livestock, experimental animals, and humans (Merrill and others 1996). Altered plasma sphingosine/sphinganine (blood serum compounds) ratios serve as biomarkers of fumonisin exposure (Riley and others 1993).

Fumonisin content in the US corn was relatively high between 1988 and 1991, but has been low (<0.5 μg/g) in recent years (Figure 3). There are a few reports of high fumonisin levels (up to 150 μg/g) in homegrown corn consumed in China and South Africa. Most commercial foods, however, contain 500 ng/g or less due to low fumonisin levels in corn and ingredient quality control (Shephard and others 1996).

Grain sorting and sizing has not been shown to reduce fumonisin levels in corn. Although corn screenings (small broken pieces of corn kernels) are partly the result of fungal action on the kernels, removal of the screenings did not significantly reduce fumonisin levels (Murphy and others 1993). Because screenings can account for up to 25% of the corn in commerce, this approach for reducing fumonisin levels is not economically viable either. Wet milling of contaminated corn (to produce starch) partitioned fumonisins to all fractions (gluten > fiber > steep water > germ) except the starch fraction. Fraction yields were not different between fumonisin-contaminated corn and the control (Bennett and others 1996). Dry milling of contaminated corn partitioned fumonisin to all fractions, with the bran (pericarp) containing the highest levels (bran > germ > flour > flaking grits) for white, yellow, and blue corn (Katta and others 1997). If levels are reduced sufficiently, the corn may be subjected to decontamination and/or used in lower-risk products (potentially animal feed).

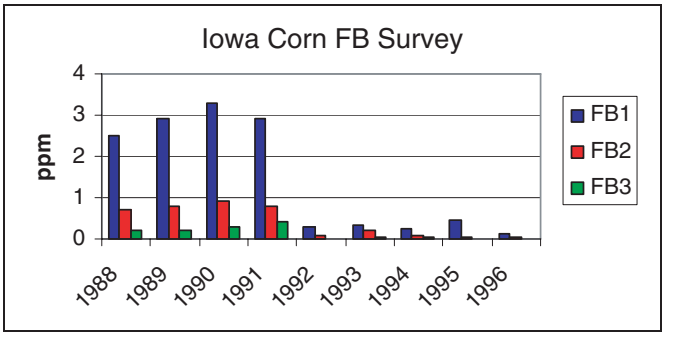

Figure 3—Fumonisin concentrations in ppm (μg/g) in Iowa corn elevator samples during 1988 to 1996

Fermentation of fumonisin-contaminated corn to produce ethanol resulted in reduced ethanol yields and did not significantly degrade the toxin. However, distillation of the ethanol resulted in a fumonisin-free alcohol with fumonisins remaining in the distillers' solids (Bothast and others 1992). Ozonolysis of FB resulted in conversion to 3-keto-FB; however, toxicity was not reduced (McKenzie and others 1997). Ammoniation has also been investigated without success; treatment of FB-containing culture material did not reduce its toxicity to rats (Norred and others 1991).

The effects of a variety of heat/chemical processing operations on fumonisin content have been investigated and the fumonisins have proven extremely stable. Jackson and others (1996) investigated stability of 5 ppm in aqueous model systems at pH 4, 7, and 10. They found that FB was most stable under neutral conditions and least stable at pH 4; however, at temperatures above 175 °C FB content was reduced by over 90% regardless of pH, suggesting that high temperature processing may be effective against FB in some instances. However, gaps remain in our understanding of thermal effects due to reactions of other food ingredients with the putative toxic structural moiety of fumonisin, the primary amine group. The primary amine group is key to detection in chromatographic and immunological analytical methods and can be derivatized with acids and/or react with reducing sugars (Maillard reaction) during heat processing, preventing these forms from being detected. The amine group can readily participate in nonenzymatic browning with a variety of reducing sugars and produces an array of typical Maillard products and FB-glucose and FB-fructose adducts, which have been shown to be noncarcinogenic in rat studies (Lu Z and others 1997, Liu and others 2001, Lu Y and others 2002) and lacking acute toxicity in swine studies (Fernandez-Surumay and others 2005). Fumonisin concentrations are lowered during extrusion processing and the remaining low levels of Maillard reaction products are thought to be detoxified because naturally occurring N-acetyl-fumonisin was shown to be nontoxic (Gelderblom and others 1993), and it is presumed that the fumonisin-glucose adducts are likewise nontoxic (Murphy and others 1996).

Further investigations of heat application to reduce FB levels included baking and frying, both of which were shown to produce some reduction in fumonisin levels. Corn-based batter was baked (to make muffins) at 175 °C and 200 °C for 20 min, reducing FB levels by approximately 15% to 30%, with increasing losses as temperature increased. Losses were greatest at the surface of the muffins, which was attributed to greater heat penetration as the baking temperature was raised (Jackson and others 1997). Frying of masa (to make chips)

at temperatures up to 170 °C for 6 min did not produce significant FB losses; frying at 190 °C for 15 min was required to reduce FB levels by 67% (Jackson and others 1997). A more recent study revealed up to 80% reduction in production of fried corn chips; very little of this reduction was the result of frying, however; reduction was due to nixtamilization and rinsing (Voss and others 2001).

Alkaline processing has been shown to be effective in reducing fumonisin levels and activity. The ester bonds of FB are hydrolyzed to release its tricarballylic groups and yield aminopentol (Hendrich and others 1993). Overall levels of both FB and hydrolyzed fumonisin (HFB) were reduced approximately 50% by the traditional nixtamilization process; however both FB and HFB remained in the masa and cooked tortillas in a 1:1 mol/L ratio, suggesting that the cooking, steeping, and rinsing process was effective in reducing toxin content, but that baking to produce tortillas did not result in further reduction (Palencia and others 2003). Other studies of this process (pilot, commercial, and traditional scale processes) have yielded some variation to these results, but most of all exhibited significant reduction of toxicity. HFB is more bioavailable than fumonisin (Dantzer and others 1999), but less toxic to mice (Howard and others 2002) and rats (Hendrich and others 1993, Voss and others 1998); masa production, therefore, is capable of significantly reducing toxicity of fumonisins.

Co-contamination

In addition to add to the complex nature of mycotoxin contamination, there is also the possibility for multiple toxins to be present in the same plant. Various combinations of the above compounds have been identified, with work by Lopez-Garcia (1998) indicating that their behavior in such cases is altered. Information on co-contamination is limited, thereby elevating the challenge faced throughout the farm-to-fork continuum.

Mycotoxin Control Strategies

The preceding sections contained discussions of potential chemical and physical (processing) measures to control mycotoxin contamination of foods and food products. The following sections expand on this strategy to include good agricultural and manufacturing practices, HACCP, and biological and transgenic controls.

Good agricultural practices (GAPs)/good manufacturing practices (GMPs)

The first line of defense against the introduction of mycotoxins is at the farm level and starts with implementation of good agricultural practices to prevent infection. Preventive strategies should be implemented from pre- through postharvest. Preharvest strategies include maintenance of proper planting/growing conditions (for example, soil testing, field conditioning, crop rotation, irrigation), antifungal chemical treatments (for example, proprionic and acetic acids), and adequate insect and weed prevention. Harvesting strategies include use of functional harvesting equipment, clean and dry collection/transportation equipment, and appropriate harvesting conditions (low moisture and full maturity). Postharvest measures include use of drying as dictated by moisture content of the harvested grain, appropriate storage conditions, and use of transport vehicles that are dry and free of visible fungal growth (CAC 2003, Quillien 2002). While implementation of these precautions go a long way toward reducing mycotoxin contamination of foods, they alone do not solve the problem and should be an integral part of an integrated HACCP-based management system (Lopez-Garcia and others 1999)

HACCP

Inclusion of mycotoxin control in HACCP plans, an important aspect of an overall management approach, should include strategies for prevention, control, and quality from farm-to-fork. In the food industry, postharvest control of mycotoxins has been addressed via HACCP plans, which include use of approved supplier schemes. Implementation at preharvest stages of the food system needs more attention. Such action provides a critical front-line defense to prevent introduction of contaminants into the food and feed supplies. Preharvest HACCP programs have been documented for controlling aflatoxin in corn and coconuts in Southeast Asia, peanuts and peanut products in Africa, nuts in West Africa, and patulin in apple juice and pistachio nuts in South America (FAO/IAEA 2001). Aldred and Magan (2004) outlined a number of HACCP schemes for wheat-based commodities and Lopez-Garcia and others (1999) provided guidance for development of an integrated mycotoxin management program. Table 4 displays the effective use of an HACCP-based postharvest hurdle approach to nearly eliminate aflatoxins from peanuts.

Biological control measures

DON levels have been shown to be reduced in the field and in storage without intervention, as discussed by Karlovsky (1999). Such findings include:

- degradation mechanisms resulting in reduced mycotoxin levels in the field. Limited research on DON has suggested the possibility that the mycotoxin may be metabolized by corn enzymes; and
- decline in DON levels in grains stored at −18 °C to 4 °C and trichothecenes at temperatures greater than 0 °C.

Karlovsky explained that such reductions in mycotoxin levels have proven to be inconsistent and decreased levels of mycotoxin in the field do not substantiate the occurrence of biological degradation.

The potential for using microorganisms to detoxify mycotoxins has shown promise. Exposure of DON to microbes contained in the contents of the large intestines of chickens completely transformed it in vitro to de-epoxy-DON (He and others 1992), which is 24 times less toxic than DON itself (Eriksen 2003). Similar findings were demonstrated with the microflora of cow intestines (Binder and others 1998).

Transgenic approaches

Current research efforts are focusing on methods to prevent infection at the preharvest stage with emphasis on mechanisms by which the affected plants may inhibit growth of molds or destroy mycotoxins that they produce. Traditional grain-breeding strategies to select for preferred genetic traits have been conducted for many years. There has been limited success with this approach to *Fusar-*

Table 4—HACCP-based reduction of aflatoxins postharvest[a,b]

Technology	Aflatoxin level (μg/kg)	% Reduction	% Cumulative reduction
Farmer's stock	217	—	—
Belt separator	140	35	35
Shelling plant[c]	100	29	54
Color sorting[c]	30	70	86
Gravity table[c]	25	16	88
Blanching/color sorting	2.2	91	99.0
Re-color sorting[c]	1.6	27	99.3

[a] Results were obtained from processing of a 40000 kg lot of contaminated peanuts.
[b] From Park and Liang 1993.
[c] Data based on medium-category peanuts only.

ium graminearum and *Aspergillus flavus*. There are hybrids currently in use that limit mycotoxin production; however, the potential to reach unacceptable levels remains. Fumonisin production has received less attention from researchers; however, quantitative trait loci (QTL) have been mapped. Unfortunately, QTL accounted for less than half the variance in *Fusarium* phenotype and despite improved resistance, unacceptable levels are still possible (Munkvold 2003). Traditional methods are plagued by many hurdles, however, including inconsistent, labor-intensive inoculation techniques, lack of single genes and resistant control genotypes, and the financial implications of evaluating results (Munkvold 2003). Duvick (2001) pointed out that visible symptoms of plant mold can be selected for using traditional breeding techniques, but many of the mycotoxin-producing fungi surface with no visible signs.

Genetic modification of mold-susceptible plants holds great promise for controlling this food safety issue. Articles by Karlovsky (1999), Duvick (2001), and Munkvold (2003) review a variety of approaches that are being or have been pursued. One such approach involves increasing production of compounds (for example, antifungal proteins or secondary metabolites, such as hydroxamic acids, phenolics, stilbenes) that reduce infection by the microorganism. This may be accomplished by introducing a novel gene to express the target compound. Another option is to enhance expression of such a compound by the existing gene, thereby capitalizing on the plant's own defense mechanisms. For example, enzymes that catalyze production of antifungals could be targeted for expression. Alternatively, genetic engineering methods to increase production of enzymes that degrade mycotoxins are also being pursued (Duvick 2001, Munkvold 2003). Transgenic maize has been patented for fumonisin-degrading corn for swine consumption (Duvick and Rood 1998). Efforts are also under way to engineer plants to produce compounds that disrupt mycotoxin synthesis. For example, enhanced expression of an α-amylase inhibitor in *Aspergillus* spp. could result in significantly reduced aflatoxin levels (Duvick 2001, Munkvold 2003).

Another avenue for reducing mycotoxin levels would be to reduce insect injury to plant kernels. Insects play an important role in the proliferation of mold growth in the field and in storage.

Resistance developed through the use of several Bt (*Bacillus thermophilus*) genes in corn, wheat, and other cereal grains to minimize insect damage has led to effective reduction in *Fusarium* ear rot (*F. verticillioides* and *F. proliferatum*) mycotoxin levels in grain. Munkvold (2003) cited 19 reports on Bt hybrids, with 12 of these demonstrating reduced mycotoxin production compared to the parent corn. It is important to note, however, that this approach is not a long-term solution for fumonisin production because *Fusarium* spp. can enter the kernels regardless of insect injury. Additionally, reductions of aflatoxin production in the Bt hybrids were not observed.

Bioterrorism

Because a number of mycotoxins, which may be lethal in relatively low doses, may be cultured and grown on a wide variety of grains, the possibility of deliberate mycotoxin contamination of commodities and/or foods should be recognized by the food industry when developing defense plans. The impact of an intentional act of mycotoxin contamination could be severe, with potential public health outcomes involving high mortality and devastating economic consequences stemming from the corresponding impact on the healthcare system, public fear, and avoidance of affected products. Prior to September 11, 2001, there was little concern pertaining to defense against intentional contamination. Because of this, grain storage and delivery systems, as well as food manufacturing plant security systems, deserve attention and crisis plans should be in place to deal with possible biological and chemical terrorism incidents. Where appropriate, these efforts should include mycotoxins.

Risk Assessment

Risk assessment of human health hazards associated with mycotoxins must rely on extrapolation from toxicity data obtained in animal models and human exposure assessments. Exposure assessments are quite sketchy at best, given that there is no publicly accessible ongoing systematic surveillance for human mycotoxin exposures. There are some interesting recent examples of attempts to perform such extrapolations and comparisons. Advances in the statistical estimation of uncertainty make extrapolations increasingly relevant. For example, Eriksen and others (2000) based an extrapolation of zearalenone risk on a no-observed effect level (NOEL) of 40 μg/kg/d in pigs (during a 15-d study), for estrogenic effects. Pigs were the most sensitive species, so although it is not clear to what extent humans and pigs are equivalent in their response, this estimate errs on the side of safety. The NOEL for zearalenone was divided by a safety factor of 80 to derive an acceptable daily intake (ADI) of 0.5 μg/kg for humans. No rationale was given for the choice of safety factor, but, depending on the world region, this ADI is 8 to 31 times greater than estimated human exposures. Since this estimate was done, the term ADI is being replaced by the term reference dose (RfD). Kodell and Gaylor (1999) have provided evidence-based extrapolation factors, combining data across hundreds of studies of toxic effects of nongenotoxic agents and deriving best estimates of major sources of variability in experiments (including interspecies, inter-individual, and duration of toxic exposure). In the example of zearalenone, based on the NOEL in pigs and a combined factor of 46 for inter-individual and interspecies variability (95% confidence estimate), a revised estimate of human RfD would be 0.87 μg zearalenone/kg/d.

Kuiper-Goodman and others (1996) performed a risk assessment for fumonisins based on human exposure data from Canada and the extant toxicity literature on these mycotoxins. Because fumonisins are almost exclusively found in corn, this is a somewhat simpler case than for most other mycotoxins. Based on 361 corn food samples analyzed over 4 y, human fumonisin intake was estimated to be $<$0.089 μg/kg bw/d. This dose was 1700-fold less than the lowest NOEL obtained from animal studies (a 4.4-y study of 9 vervet monkeys showing a NOEL of 0.15 mg/kg bw/d). The authors concluded that human fumonisin intakes in Canada were very unlikely to pose health risks. A more recent 2-y rodent carcinogenicity study (NTP 2001) confirms this finding, with a NOEL of $>$0.2 mg/kg bw/d with altered sphingosine/sphinganine ratios as a toxic endpoint. The NOEL in this study for cancer (renal carcinogenesis in male rats only) was 0.6 mg/kg bw/d. Kuiper-Goodman (2004) recently reviewed mycotoxin risk assessment and risk management and the efforts of countries to harmonize regulations.

Due to the variation in mycotoxin content of human foods across world regions and seasons, and the continually improving toxicological data sets for mycotoxins, increasingly sophisticated models will be developed to assess human health risk from these foodborne toxins. Progress in the science of risk assessment is allowing a greater level of certainty regarding risk, but toxin interactions and emerging human epidemics of various chronic and infectious diseases will continue to pose major challenges in this field.

Food Safety Implications

Public awareness of issues surrounding mycotoxins is increasing. Karlovsky (1999) provides 3 explanations for this phenomenon. First, analytical chemistry is increasingly able to quantify the pres-

ence of toxins in a growing number of food commodities. Second, new and improved bioassays for toxicological studies on specific targets have surpassed the abilities of less sophisticated methods and allowed identification of negative health effects where previously none had been found. Third, the availability of routine testing methods that are both efficient and affordable has allowed for in-house monitoring, resulting in greater numbers of identified contaminations.

The variability in mycotoxin contamination and the potential for novel mycotoxicoses to emerge make the prospects for ongoing significant human mycotoxicoses likely, especially in low-income countries in which surveillance is less available because of economical and technological constraints. The human health consequences of acute aflatoxicosis alone range from death to exacerbated malnutrition, devastating to the affected populations. In view of ongoing epidemics of immunosuppressive diseases, including HIV infection and chronic protein calorie malnutrition, the additional immunosuppression possible from mycotoxins deserves more attention. Very little is known about the effects of long-term low-level exposure, especially with regard to co-contamination with multiple mycotoxins. Also, due to the heterogeneity of mycotoxin contamination and the potential for sampling regions with elevated toxin levels ("hot spots"), consistent sampling and analysis is difficult (Lopez-Garcia and others 1999). Thus, development of low-tech, inexpensive methods for mycotoxin surveillance is a world health imperative. With several novel approaches being developed, such as molecular imprint polymers (Weiss and others 2003) and immuno- (De Saeger and others 2002) and bio-assays (Widestrand and others 2003), adoption of such methods is within reach. The prevention of mycotoxin contamination of human foods could have a significant effect on public health in low-income countries, and deserves significant attention. The food industry should take the lead in these efforts, because it will lead to improved economic sustainability of the industry, enhanced food safety efforts, enhanced international trade efforts, and improved public health.

Acknowledgments

IFT thanks Tim Phillips, Ph.D., Director, Center for Food Safety, Texas A&M University; Lloyd Bullerman, Ph.D., Professor, University of Nebraska-Lincoln; Charlene Wolf-Hall, Ph.D., Assoc. Professor, North Dakota State University and Eva Binder, Ph.D., CRO Biomin/Romer Groups for reviewing this manuscript.

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