Public Health Impacts of Foodborne Mycotoxins

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Abstract

Mycotoxins are toxic and carcinogenic metabolites produced by fungi that colonize food crops. The most agriculturally important mycotoxins known today are aflatoxins, which cause liver cancer and have also been implicated in child growth impairment and acute toxicoses; fumonisins, which have been associated with esophageal cancer (EC) and neural tube defects (NTDs); deoxynivalenol (DON) and other trichothecenes, which are immunotoxic and cause gastroenteritis; and ochratoxin A (OTA), which has been associated with renal diseases. This review describes the adverse human health impacts associated with these major groups of mycotoxins. First, we provide background on the fungi that produce these different mycotoxins and on the food crops commonly infected. Then, we describe each group of mycotoxins in greater detail, as well as the adverse effects associated with each mycotoxin and the populations worldwide at risk. We conclude with a brief discussion on estimations of global burden of disease caused by dietary mycotoxin exposure.

1. INTRODUCTION

Mycotoxins are secondary metabolites of fungi that cause toxic and carcinogenic outcomes in humans and animals exposed to them. The major foodborne mycotoxins of public health interest are the aflatoxins, fumonisins, trichothecene mycotoxins, and ochratoxin A (OTA). These are produced primarily by fungi of the genera *Aspergillus*, *Fusarium*, and *Penicillium*, which commonly infect food crops. **Table 1** highlights the major mycotoxins that affect human health worldwide, the fungi that produce them, and the agricultural commodities of which they are common contaminants.

This review highlights the known and postulated public health impacts of exposure to dietary mycotoxins. The adverse human health effects range from acute toxicities to cancers to modulation of the immune system. Worldwide, the populations most at risk are from areas with little to no regulatory enforcement or primary prevention strategies to reduce the risk of contamination; as such, these populations consume large amounts of the foods prone to contamination with these mycotoxins (see **Table 1**). This review covers the health effects of the four main groups of mycotoxins listed in **Table 1**, then describes estimates of the global burden of disease associated with certain mycotoxins.

2. AFLATOXINS

The aflatoxins occupy a unique position in the study of environmental toxins and carcinogens, in that extensive elucidation of their toxicology in addition to epidemiology have provided a foundation for quantitative risk assessments based on an understanding of their mechanisms of action. These toxins were discovered in the early 1960s as the causative agent of the turkey X disease epidemic, which resulted in the deaths of thousands of turkey poults, ducklings, and chicks fed a toxic peanut meal (Blount 1961). Subsequent laboratory studies using extracts of groundnut cultures of *Aspergillus flavus* confirmed the existence of a toxic principle capable of inducing acute toxicity characterized by massive liver damage in rats and ducklings (Lancaster et al. 1961, Sargeant et al. 1961). Soon thereafter, purified metabolites with physicochemical properties identical to aflatoxins B_1 and G_1 (AFB_1 and AFG_1) were isolated from mold-contaminated cultures (Nesbitt et al. 1962, Van der Zijden et al. 1962). Final structural elucidation of AFB_1 was accomplished by its total synthesis in 1963 (Asao et al. 1963). Collectively, aflatoxins are a group of approximately

Table 1 Mycotoxins of public health concern, associated fungi, and food/feed crops at risk of contamination

Mycotoxin	Producing fungi	Associated food/feed crops
Aflatoxins	*Aspergillus flavus* *A. parasiticus*	Maize, peanuts, tree nuts, copra, spices, cottonseed
Fumonisins	*Fusarium verticillioides* *F. proliferatum* *A. niger*	Maize
Trichothecene mycotoxins	*F. graminearum* *F. culmorum*	Maize, wheat, barley, oats
Ochratoxin A	*Penicillium verrucosum* *A. ochraceus* *A. carbonarius* *A. niger*	Maize, wheat, barley, oats, dried meats and fruits, coffee, wine

20 chemically related metabolites produced primarily by the foodborne fungi *Aspergillus flavus* and *A. parasiticus*. Aflatoxins contaminate a variety of staple foods, including maize, peanuts, and tree nuts, and cause an array of acute and chronic human health disorders. AFB_1, the most toxic of the aflatoxins, is a potent liver carcinogen, causing hepatocellular carcinoma (HCC) in humans and a wide variety of animal species.

2.1. Hepatocellular Carcinoma

It has been known for decades that aflatoxin exposure causes liver cancer in humans and numerous animal species. The International Agency for Research on Cancer (IARC) has evaluated these compounds on several occasions, the first of which was published in 1972, with Volume 1 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (IARC 1972). Since that time, many experimental and human studies have provided clarifying data and naturally occurring mixes of aflatoxins are now classified as a Group 1 human carcinogen (IARC 1993). Furthermore, concomitant exposure to aflatoxin and the hepatitis B virus (HBV) is common in developing countries and greatly increases HCC risk (Wu F. et al. 2013). Individuals with both exposures have multiplicatively greater risk of developing HCC than those exposed to aflatoxin alone (Wogan et al. 2012).

Collectively, liver cancer, including HCC and cholangiocarcinoma, accounts for 5.7% of all reported cancer cases and is the sixth most common cancer diagnosed worldwide (Parkin et al. 2005). The incidence of HCC varies enormously globally; the burden of this nearly always fatal disease is much higher in developing countries of Asia and sub-Saharan Africa (Groopman et al. 2008, Liu & Wu 2010). There are more than 750,000 new cases each year and more than 300,000 deaths annually in China alone (**http://globocan.iarc.fr**; see also Wang et al. 2002). In contrast to the most common cancers in high-income nations, where more than 90% of cases are diagnosed after age 45, in high-risk regions for liver cancer, onset begins in both men and women by 20 years of age, peaking between 40–49 years of age in men and 50–59 years in women (Chen et al. 2006a, Parkin et al. 2005, Vatanasapt et al. 1995). Gender differences in HCC incidence have also been described; the worldwide annual age-standardized incidence rate among men is 16.0 per 100,000 and 6.0 per 100,000 among women (Ferlay et al. 2010). These epidemiologic findings are consistent with experimental animal data for aflatoxin, which show that male rats have an earlier onset of cancer compared to females (Wogan & Newberne 1967).

For more than 50 years, the relation between aflatoxin exposure and human HCC has been examined using ecologic studies, cross-sectional surveys, and case-control and prospective cohort investigations in high-risk, potentially exposed populations. Early studies in the Philippines (Campbell et al. 1970) demonstrated that an oxidative metabolite of aflatoxin could be detected in urine and thus had the potential to serve as an internal dose marker. Later, Autrup et al. (1983, 1987) reported the presence of AFB_1-DNA adducts in human urine samples in Kenya. Subsequent work conducted in China and Gambia, areas with high HCC incidence, examined both the dietary intake of aflatoxin and the levels of urinary aflatoxin biomarkers (Groopman et al. 1985, 1992a,b). Urinary AFB_1-DNA adducts and aflatoxin M_1 (AFM_1) showed a dose-dependent relationship between aflatoxin intake and excretion. Gan et al. (1988) and Wild et al. (1992) monitored aflatoxin-albumin adducts in serum and observed a significant association between aflatoxin intake and adduct level.

Many case-control studies have explored the relation of aflatoxin exposure and HCC. In an early study, Bulatao-Jayme et al. (1982) compared the dietary intake of aflatoxin in cases of HCC in the Philippines, with intake in age- and sex-matched controls. They found that the mean aflatoxin exposure per day in cases of HCC was 4.5 times higher than in the controls; however, alcohol consumption may have enhanced this effect. Van Rensburg et al. (1985) and Peers & Linsell

(1977) used a similar design for studies in Mozambique and Swaziland, respectively. Again, mean dietary aflatoxin intakes were positively correlated with HCC rates, and the data suggested a dose-dependent increase in liver disease associated with increased aflatoxin intake.

In the Guangxi Zhuang Autonomous Region of China, Yeh et al. (1986, 1989) examined the interaction between HBV infection and dietary aflatoxin exposure dichotomized for heavy and light levels of contamination. Individuals whose sera were positive for the hepatitis B virus surface antigen (HBsAg+) and who experienced heavy aflatoxin exposure had tenfold higher HCC incidences than did people living in areas with light aflatoxin contamination. People who were HBsAg– and highly exposed to aflatoxin had rates of HCC comparable to those of HBsAg+ people consuming diets with light aflatoxin contamination (Yeh et al. 1989). In a case-control study in Taiwan, two biomarkers, aflatoxin-albumin adducts and aflatoxin-DNA adducts in liver tissue samples, were measured (Lunn et al. 1997). The proportion of subjects with detectable levels of aflatoxin-albumin adducts was higher for cases of HCC than for matched controls [odds ratio (OR) 1.5]. A statistically significant association was found between presence of detectable aflatoxin-albumin adducts and HCC risk among men younger than 52 years (multivariate-adjusted OR 5.3).

Another study in Qidong, China, examined 145 men with chronic HBV infection, who were followed for 10 years to determine whether exposure to aflatoxin, concomitant exposure to hepatitis C virus (HCV), or family history of HCC increased the risk of developing HCC (Sun et al. 1999). Eight monthly urine samples collected before the initiation of follow-up were pooled to analyze for AFM_1. AFM_1 was detected in 78 (54%) of the subjects, and the risk of HCC was increased 3.3-fold (95% confidence interval of 1.2–8.7) in those with detectable AFM_1 (above 3.6 ng/L). The attributable risk from aflatoxin exposure, defined as the presence of detectable AFM_1, was 0.553 (0.087, 0.94). The relative risk (RR) of fatal cirrhosis for individuals whose urine contained elevated AFM_1 was 2.8 (0.6, 14.3). Concomitant infection with HCV increased the risk of HCC 5.8-fold (2.0–17), adjusted for age and AFM_1 status. This study shows that aflatoxin exposure detected by the presence of AFM_1 in urine is related, in large part, to HCC risk in men with chronic HBV (Sun et al. 1999).

Two major cohort studies incorporating aflatoxin biomarkers have demonstrated clearly the etiologic role of this carcinogen in HCC. The first study, comprising more than 18,000 men in Shanghai, examined the interaction of HBV and aflatoxin biomarkers as independent and interactive risk factors for HCC. The nested case-control data revealed a statistically significant increase in the RR of 3.4 for those HCC cases in whom a urinary aflatoxin biomarker (AFB_1-N^7gua) was detected. In men whose sera were HBsAg+ but whose urine did not indicate aflatoxin exposure, the RR was 7, whereas in individuals exhibiting both urinary aflatoxin biomarkers and positive HBsAg status, the RR was 59 (Qian et al. 1994, Ross et al. 1992). These results strongly support a causal relationship between the presence of carcinogen and viral-specific biomarkers and the risk of HCC. Most subsequent cohort studies in Taiwan have confirmed the results from the Shanghai investigation. Wang et al. (1996) examined HCC cases and controls nested within a cohort and found that in HBV-infected people there was an adjusted OR of 2.8 for detectable compared to nondetectable aflatoxin-albumin adducts and 5.5 for high compared with low levels of aflatoxin metabolites in urine. In a follow-up study, there was a dose-response relationship between urinary AFM_1 levels and risk of HCC in chronic HBV carriers (Yu et al. 1997). HCC risk was most striking among HBV carriers with detectable AFB_1-N^7-gua in urine.

Furthermore, molecular biological studies on the *p53* tumor suppressor gene, the gene most commonly mutated in many human cancers, have highlighted the relationship between aflatoxin exposure and development of HCC (Greenblatt et al. 1994). Many studies of *p53* mutations in HCC occurring in populations exposed to high levels of dietary aflatoxin have found high frequencies of G:C to T:A transversions, with clustering at codon 249 (Bressac et al. 1991, Hsu et al. 1991).

In contrast, no mutations in codon 249 were found in *p53* in HCC from Japan and other areas where there was little exposure to aflatoxin (Aguilar et al. 1994, Ozturk 1991).

Application of these specific mutations as biomarkers for early detection also offers great promise for HCC prevention (Sidransky & Hollstein 1996). In a seminal study, Kirk et al. (2000) reported for the first time detection of *p53* codon 249 mutations in the plasma of liver tumor patients residing in Gambia; however, the mutational status of their tumors was not determined. They also reported the presence of this mutation in the plasma of a small number of cirrhosis patients. Given the strong relationship between cirrhosis and future development of HCC, the possibility of this mutation serving as an early detection marker should be explored. Jackson et al. (2001) examined 25 HCC tumors for specific *p53* mutations. Analysis of 20 plasma-tumor pairs showed that 11 tumors and 6 plasma samples contained the specific mutation. Furthermore, this group (Jackson et al. 2003) explored the mutation's temporality of detection in plasma before and after clinical diagnosis of HCC in the same patient. This study was facilitated by the availability of longitudinally collected plasma samples from a cohort of 1,638 high-risk individuals in Qidong, who had been followed since 1992. In samples collected prior to HCC diagnosis, 21.7% of the plasma samples had detectable levels of the codon 249 mutation (95% CI: 9.7–41.9%). The codon 249 mutation in *p53* was detected in 44.6% of all plasma samples and approximately 50% of all liver tumor samples following diagnosis of HCC (95% CI: 21.6–70.2%), suggesting a nearly 90% concordance between plasma and *p53* codon 249 mutation outcomes.

Finally, recent work has taken advantage of a population-based cancer registry to track primary liver cancer (PLC) mortality in Qidong, China, a region of 1.1 million residents. Using this database, a greater than 50% reduction in HCC mortality rates was found across birth cohorts from the 1960s to the 1980s for Qidongese subjects less than 35 years of age. Prevalence of HBV infection was unchanged given that all were born before universal vaccination of newborns. Randomly selected serum samples from archived cohort collections since the 1980s were analyzed for aflatoxin biomarkers. Median levels of the aflatoxin biomarker decreased from 19.3 pg/mg albumin in 1989 to undetectable (0.5 pg/mg) by 2009. A population-attributable benefit of 59% for reduced PLC mortality was estimated from a government-imposed switch of dietary staple from maize to rice. These data reinforce the role that aflatoxin plays in high risk for HCC, and subsequent decline in HCC risk when aflatoxin exposure is reduced (Chen et al. 2013).

2.2. Acute Aflatoxicosis

Although there has been an extensive focus on the role of aflatoxin exposure in HCC, over the years, numerous cases of acute aflatoxicosis in humans have been reported in regions of some economically developing countries (Shank et al. 1971). The clinical manifestations of aflatoxicosis were vomiting, abdominal pain, pulmonary edema, and fatty infiltration and necrosis of the liver. In the 1970s, consumption of heavily molded corn caused a putative aflatoxin poisoning in western India. There were at least 97 fatalities, which occurred only in households where the contaminated corn was consumed. Histopathology of liver specimens revealed extensive bile duct proliferation, a lesion often noted in experimental animals after acute aflatoxin exposure (Bhat & Krishnamachari 1977, Krishnamachari et al. 1975). An incident of acute aflatoxicosis in Kenya in the early 1980s also was associated with the consumption of maize highly contaminated with aflatoxin (Ngindu et al. 1982). There were 20 hospital admissions with 20% mortality. In a more recent report (Lye et al. 1995), consumption of aflatoxin-contaminated noodles resulted in acute hepatic encephalopathy in children in Malaysia. Up to 3 mg of aflatoxin may have been present in a single serving of noodles.

In 2004, one of the largest documented aflatoxicosis outbreaks occurred in rural Kenya, resulting in 317 cases and 125 deaths. Aflatoxin-contaminated homegrown maize was the major source

of the outbreak. In a survey involving 65 markets and 243 maize vendors, 350 maize products were collected from the most affected districts: 55% of maize products had aflatoxin levels greater than the Kenyan regulatory limit of 20 ppb, 35% had levels greater than 100 ppb, and 7% had levels greater than 1,000 ppb. Makueni, the district with the most aflatoxicosis cases, had significantly higher market maize aflatoxin than did Thika, the study district with the fewest cases (geometric mean aflatoxin = 52.91 ppb versus 7.52 ppb). Maize obtained from local farms in the affected area was significantly more likely to have aflatoxin levels greater than 20 ppb compared with maize bought from other regions of Kenya or other countries [OR = 2.71; (1.12–6.59)]. In addition to the market survey for aflatoxin exposure, this outbreak in 2004 marked the first time that aflatoxin-albumin adducts independently confirmed the exposure in individuals [the Centers for Disease Control and Prevention (CDC) 2004, Azziz-Baumgartner et al. 2005, Lewis et al. 2005, Probst et al. 2007, Strosnider et al. 2006].

2.3. Growth Impairment in Children

Aflatoxin exposure has also been linked with childhood stunting, a condition in which the child's height for his/her age is two standard deviations or more below a WHO growth reference. Stunting is important from a public health perspective, because it is associated with effects such as increased vulnerability to infectious diseases and cognitive impairments that last well beyond childhood (Ricci et al. 2006). Khlangwiset et al. (2011) summarize the epidemiological studies that show an association between child growth impairment and aflatoxin exposure.

The reader is referred to Khlangwiset et al. (2011) for an in-depth explanation of the available epidemiological studies and animal studies supporting the association between aflatoxin exposure and growth impairment. Studies conducted in Togo and Benin in West Africa (Gong et al. 2002, 2004) demonstrated that height and weight for age in children are lower in a dose-dependent fashion for higher aflatoxin exposures and that over an eight-month study period, those children exposed to the most aflatoxin had the smallest height gains. Additionally, two studies in Gambia in West Africa (Turner et al. 2003, 2007) showed that high aflatoxin-albumin adduct levels in maternal blood, cord blood, infant blood, and children's blood are associated with poorer growth indicators.

Aflatoxin contamination levels in flour gathered from households in Kenya were associated with wasting in children (Okoth & Ohingo 2004). A Ghanaian study (Shuaib et al. 2010) showed that mothers' aflatoxin-albumin adduct levels were associated with babies weighing less at birth. In Iran, two studies (Sadeghi et al. 2009, Mahdavi et al. 2010) demonstrated that higher levels of AFM_1 in mothers' breast milk were associated with smaller infant length and weight at birth.

2.4. Aflatoxin and Immunomodulation

Few studies have examined the link between aflatoxin exposure and markers of immune system dysfunction in humans. Jiang et al. (2008) demonstrated that in HIV-positive and HIV-negative individuals in Ghana, higher levels of aflatoxin-albumin adducts were generally associated with lower levels of CD4+ T regulatory cells and naïve CD4+ T cells, as well as lower B-cell counts. Similarly, an earlier Ghanaian study (Jiang et al. 2005) showed fewer of the many cells involved in immune system response among Ghanaian subjects exposed to higher levels of aflatoxin in the diet. A different study showed that Gambian children with higher levels of aflatoxin-albumin adducts had lower levels of secretory IgA in saliva (Turner et al. 2003). Although these studies all indicate a relationship between aflatoxin exposure and impaired markers of human immunity, there is a need for further epidemiological studies in different world regions to increase the body of evidence linking aflatoxin to immunomodulation.

3. FUMONISINS

Fumonisins are produced by the fungi *Fusarium verticillioides*, *F. proliferatum*, *A. niger*, and some related species [the Joint FAO/WHO Expert Committee for Food Additives (JECFA) 2011b]. *F. verticillioides* is an almost-universal inhabitant of maize, and in certain climatic and environmental conditions can cause *Fusarium* ear rot. Fumonisins were first implicated in human disease in 1988, in connection with high human esophageal cancer (EC) rates in the former Transkei region of South Africa. Shortly thereafter, interest in fumonisins increased in the United States after multiple horse and swine deaths associated with moldy maize-based feed (Marasas 2006, Wu & Munkvold 2008). Fumonisin inhibits the enzyme ceramide synthase, which is critical for biosynthesis of sphingolipids that have multiple functions in the body. High fumonisin exposures cause diseases such as leukoencephalomalacia in horses and also pulmonary edema, reduced weight gain, and liver damage in swine (Marasas et al. 1988, Sydenham et al. 1992, Osweiler et al. 1992, Rotter et al. 1996). Additionally, it can cause liver and kidney cancer in rats and liver cancer in mice (Gelderblom et al. 1991). The most common of the fumonisins found in maize is fumonisin B_1 (FB_1); fumonisins B_2 and B_3 (FB_2 and FB_3) are common co-contaminants. In this section, we describe the postulated human health effects of fumonisin exposure.

3.1. Esophageal Cancer

Fumonisin exposure may be a risk factor for EC in humans. This association was first posited in South African populations at unusually high risk for EC who consumed relatively large amounts of fumonisin-contaminated maize (Marasas 2006). Since then, the results of studies in other nations have supported this association. Sun et al. (2007) collected maize samples from three Chinese counties: Huantai (low incidence of both EC and HCC), Huaian, and Fusui (two counties that have among the highest incidences of these cancers). FB_1 was detected in high proportions of the samples from all three counties: 95.7% from Huaian, 83.0% from Fusui, and 83.3% from Huantai. However, average levels of FB_1 among positive samples from each county were different: 2.84 mg/kg in Huaian, 1.27 mg/kg in Fusui, and 0.65 mg/kg in Huantai. Sun et al. posit that FB_1 may contribute to EC and HCC in the high-risk populations. However, this study did not control for possible confounders or cofactors contributing to cancer risk, such as socioeconomic status, agroecological zone, or other mycotoxins such as aflatoxins that may have been present in the maize.

In a different study in the same Chinese counties (Sun et al. 2011), the cancer risks were described differently. In this study, the authors describe Huaian as a county with high EC risk, whereas Fusui is described as a county with high HCC risk. Two mycotoxins, FB_1 and AFB_1, were analyzed in maize samples. Average daily intake of both mycotoxins was estimated on the basis of FB_1 and AFB_1 levels in maize samples from the three counties and consumption patterns of maize in the corresponding populations. Average daily intake of FB_1 was imputed to be 460 μg in Huaian, 138.6 μg in Fusui, and 92.4 μg in Huantai. Average daily intake of AFB_1 was imputed to be 1.723 μg in Huaian, 2.685 μg in Fusui, and 0.397 μg in Huantai. The trend suggests that higher fumonisin exposure is linked with higher EC incidence. However, exact incidences of cancers in each of these counties are unknown; as such, including a broader range of confounders and cofactors would be helpful in understanding whether an independent association between fumonisin exposure and EC truly exists.

In South Africa, differences in fumonisin exposure among communities were linked to differences in EC risk. Shephard et al. (2007) estimated average daily doses of fumonisin in adults in two subsistence farming communities—Bizana and Centane—in Transkei, South Africa, by estimating maize consumption and using previously determined levels of FB_1 and FB_2 in maize from these communities. Adults in Centane, an area with high EC incidence, consumed an average daily

dose of 8.67 ± 0.18 μg/kg bw/day, whereas adults in Bizana, with relatively low EC incidence, consumed an average daily dose of 3.43 ± 0.15 μg/kg bw/day. Average fumonisin exposures in all age groups in these two communities exceeded the JECFA provisional maximum tolerable daily intake (PMTDI) of 2 μg/kg bw/day.

Finally, FB_1 levels were measured in maize samples from two provinces in Iran in 1999: Mazandaran, with high EC incidence, and Isfahan, with low EC incidence (Shephard et al. 2002). Twenty maize samples from farmers' lots in Mazandaran were found to contain a mean FB_1 level of 3.18 (0.68–7.66) mg/kg. Ten maize samples from local retail markets in Isfahan were found to contain a mean FB_1 level of 0.22 (0.01–0.88) mg/kg. FB_1 levels were thus significantly different in sampled maize in these two provinces, with the higher levels corresponding to the population at high EC risk. Due to the limited sample sizes and the limitations of the sampling protocol, conclusions about fumonisin exposure and the link to EC cannot be drawn. However, this study complements others showing associations between higher fumonisin exposures and increased EC risk.

3.2. Neural Tube Defects

Neural tube defects (NTDs) are embryonic defects of the brain and spinal cord resulting from the failure of the neural tube to close in in utero conditions (Missmer et al. 2004). Two common NTDs are spina bifida, in which the fetal spinal column fails to close completely in the first month of development, commonly resulting in nerve damage and partial leg paralysis, and anencephaly, in which a large proportion of the brain does not develop, leading to stillborn birth or death shortly after birth. Maternal folate consumption, especially in the first trimester, is critical to reducing the risk of NTDs in fetuses. Because fumonisins disrupt sphingolipid metabolism and hence folate transport across cell membranes (Marasas et al. 2006), they have been shown to induce NTDs in laboratory mice (Gelineau-van Waes et al. 2005). Thus, it is possible that fumonisin exposure may play a role in NTD incidence in high-risk human populations, for example, populations in which folate consumption is low, maize consumption is high, and climatic and environmental contaminations are favorable for fumonisin accumulation.

One key epidemiological study (Missmer et al. 2004) has shown an association between increasing fumonisin exposures in pregnant women and increasing risks of NTDs in babies near the Texas-Mexico border. Fumonisin exposure was estimated by maternal serum measurements of the sphinganine:sphingosine (Sa/So) ratio, maternal dietary recall of maize tortilla intake, and measurement of fumonisin levels in tortillas in six-month blocks to account for possible seasonality of fumonisin contamination. Although the Sa/So ratio has not been validated as a human biomarker of fumonisin exposure, this study showed a generally increasing dose-response relationship between Sa/So and the adjusted ORs of NTDs in the population in seven dose groups, except at the highest dose (Sa/So > 0.35). The implication is that there is a dose-response relationship between maternal fumonisin exposure and increased risk of NTDs in babies. Similarly, although maternal dietary recall of tortillas consumed in the first trimester did not correlate with ORs for NTD risk, the estimated fumonisin exposure based on tortilla samples did (except, again, at the highest estimated fumonisin dose: more than 650 ng/kg bw/day).

4. DEOXYNIVALENOL AND OTHER TRICHOTHECENE MYCOTOXINS

The genus *Fusarium* produces a diverse family of mycotoxins known as trichothecenes, which are esters of sesquiterpenoid alcohols positioned around a trichothecane tricyclic ring that is characterized by a double bond at C9-C10 and an epoxide at C12-C13 (Pestka 2010b). The most well-known and regulated of the trichothecene mycotoxins is deoxynivalenol (DON), also known

as vomitoxin. Trichothecenes occur in wheat, maize, barley, rye, oats, and rice following fungal infection in the field and/or as part of postharvest spoilage. The worldwide incidence of *Fusarium* cereal infection, with concomitant trichothecene contamination, has increased because of climate change, increased use of no-till farming to prevent soil erosion, use of susceptible high-yielding cereal cultivars, nonoptimal crop rotation, and inadequate fungicide application.

Regional studies have demonstrated that clear geographic differences exist among *Fusarium* chemotypes as well as the substrates on which they are produced (Starkey et al. 2007, Sugita-Konishi & Nakajiima 2010). The Type A trichothecenes, produced by soil fungi and plant pathogens *Fusarium acuminatum*, *F. poae*, and *F. sporotrichiodes*, include T-2 toxin and HT-2 toxin, which are among the most toxic members of this mycotoxin family. The Type B trichothecenes, produced by *F. graminearum* and *F. culmorum*, are less toxic than the aforementioned Type A members, but are found at greater concentrations in cereal grains and foods. The Type B group includes DON and its two acetylated precursors, 3-acetyldeoxynivalenol (ADON) and 15-ADON, as well as nivalenol (NIV) and its acetylated precursor 4-acetyl-NIV [fusarenon X (FX)].

Trichothecenes have significant potential for evoking pathophysiological effects in humans and animals because they interfere with protein synthesis, induce phosphokinase-mediated stress pathways, aberrantly activate proinflammatory gene expression, disrupt gastrointestinal function, interfere with growth hormone action, and cause cell death (Pestka 2010a). Acute exposures to high trichothecene dosages in experimental animals induce anorexia, diarrhea, and vomiting; moreover, at extremely high doses, additional effects can include gastrointestinal hemorrhage, leukocytosis, circulatory shock, reduced cardiac output, and ultimately death. Chronic exposure of animals to moderate doses of trichothecenes impairs food intake, reduces weight gain, disrupts immune function, and can cause developmental effects. Trichothecenes do not accumulate in tissue or cause cancer. Most trichothecene toxicology studies in experimental animals have focused primarily on T-2 toxin and DON. As described below, findings from these investigations have been coupled with a limited number of human epidemiological studies to predict human health effects.

4.1. Alimentary Toxic Aleukia

The human disease alimentary toxic aleukia (ATA) was initially reported in Eastern Siberia 100 years ago in association with the consumption of *Fusarium*-infected cereals, with subsequent outbreaks observed over an ever-expanding area. Principal symptoms of this disease were vomiting, abdominal pain, and diarrhea followed by white blood cell loss (leukopenia), bleeding from the nose and mouth, bone marrow depletion, and fever. From the 1940s to the 1950s, severe ATA outbreaks were associated with eating overwintered wheat, barley, and millet produced in the Orenburg region, with mortality from sepsis in the affected population reaching as much as 60%. Retrospective studies with *Fusarium* species isolated from moldy grains collected during ATA outbreaks suggested that T-2 toxin, HT-2 toxin, and related trichothecenes may have contributed etiologically to this disease (Joffe 1978). Although no epidemiological studies to date have specifically linked trichothecenes to ATA (Beardall & Miller 1994), ATA symptoms are replicable in cats and rodents treated with extracts of infected wheat or T-2 toxin.

ATA is historically important because it resulted from consumption of heavily molded grains by populations faced with starvation in times of famine and war. JECFA (2002) prepared a detailed review of published studies on T-2 and HT-2 toxin toxicity, which we recommend highly. On the basis of the altered leukocyte and erythrocyte counts observed in a three-week dietary study on pigs, JECFA concluded that there was substantial evidence for the immunotoxicity and hematotoxicity of T-2 toxin in multiple species, with a lowest-observed-effect level (LOEL) of 0.029 mg/kg bw/day. This LOEL was divided by a safety factor of 500 to derive a PMTDI of 60 ng/kg bw for

T-2 toxin. JECFA also concluded that because the toxic effects of T-2 toxin and its metabolite HT-2 toxin were not differentiable, it was appropriate to establish a group PMTDI of 60 ng/kg bw/day for T-2 and HT-2 toxins, alone or in combination.

4.2. Acute Gastroenteritis

Human food poisoning with nausea, diarrhea, and vomiting as hallmark symptoms was associated with *Fusarium*-infested food between 1946 and 1963 in Japan and Korea (Yoshizawa 1983). Researchers similarly documented 32 outbreaks of food poisoning in China from 1961 to 1981 that were associated with ingestion of *Fusarium*-infected wheat, barley, or corn (Luo 1994). These and the earlier Japanese investigations were not directly linkable to trichothecenes because of the lack of suitable analytical methods at the time of these outbreaks. However, from 1984 to 1991, 21 more Chinese gastroenteritis outbreaks were linked to moldy cereal consumption; in these instances, suspect foods were verified to contain DON and/or other trichothecenes. The largest outbreak occurred during 1991 in Anhui province, affecting more than 130,000 people. Wheat samples collected during this outbreak were found to contain DON at 2 to 50 ppm (Pestka & Smolinski 2005).

Following a reported human red mold intoxication episode in Puyang, Henan, China, regional wheat samples from the 1998 and 1999 crops were subjected to DON analysis (Li et al. 2002). For the 1998 Puyang crop, DON was found in 97% of the samples with average and maximum concentrations of 2.85 and 14 ppm, respectively, with nearly 70% of the samples exceeding the Chinese tolerance of 1 ppm. NIV and 15-acetyl-DON were also found in 66% of the samples. By contrast, 89% of wheat samples from Zhumadian, a Henan region without a history of red mold poisoning, contained DON at mean and maximum concentrations of 0.22 and 1.24 ppm, respectively, without detectable 15-ADON and NIV. Notably, in 1999, DON levels in samples collected from the Puyang and Zhumadian areas were less than 1 ppm. An outbreak of gastroenteritis in the Kashmir Valley of India occurred that impacted several thousand individuals ingesting foods made from rain-damaged moldy wheat (Bhat et al. 1989). DON in the range of 0.34 to 8.4 ppm was found in nearly half the samples collected four months after the outbreak.

In the United States, foods or clinical samples that have been linked to gastroenteritis outbreaks are not routinely analyzed for DON or *F. graminearum* by state or federal public health labs, as is done commonly for food poisoning bacteria and their enterotoxins. In one notable exception, however, the CDC reported 16 gastroenteritis outbreaks in 1,900 school children from seven states who consumed burritos from two manufacturing plants (Steinberg et al. 2006). *Bacillus cereus* and *Staphylococcus aureus* toxins or other possible toxic agents such as metals, alkaloids, biogenic amines and pesticides were not detectable in associated samples. However, DON was detectable in some of these samples at levels below the FDA advisory guideline of 1 ppm. Although the etiology of these outbreaks is unknown, the results are highly consistent with DON-induced gastroenteritis.

The threshold of DON contamination to cause human vomiting is not known. Because mice and rats are incapable of emesis, rodent studies have no value for addressing this issue. However, DON-induced emesis has been demonstrated in pig, dog, cat, and mink (Hughes et al. 1999; Pestka et al. 1987; Wu W. et al. 2013a,b; Young et al. 1983). Because pigs have been used to investigate human intestine function (Nejdfors et al. 2000) and drug-induced emesis (Szelenyi et al. 1994), it is reasonable to suggest that people might be at least as sensitive to DON as pigs. As little as 50 to 100 μg/kg bw are needed for emesis induction in pigs orally gavaged with DON, whereas the no-adverse-effect level (NOAEL) is 25 μg/kg bw.

JECFA (2011b) recognized DON and its acetylated derivatives as a potential cause of acute human illness and established an acute reference dose (ARfD) of 8 μg/kg bw. This ARfD was determined by using 0.21 mg/kg bw/day as the lower limit on the benchmark dose required for

emesis induction in 10% ($BMDL_{10}$) of pigs. JECFA employed an uncertainty factor of 25 to extrapolate an ARfD of 8 μg/kg bw/day.

4.3. Growth Impairment

Another primary concern of public health authorities is the possibility that chronic low dose exposure of children to DON will adversely affect growth. This concern is grounded in risk assessments based on animal studies, as there have been no human epidemiological studies directed toward trichothecene growth effects (Canady et al. 2001, JECFA 2011a, Pestka & Smolinski 2005). In 1983, Canadian researchers set provisional TDIs for DON in children and adults of 1.5 and 3.0 μg/kg bw, respectively (Kuiper-Goodman 1994). In 1998, a Nordic working group suggested a TDI of 1 μg/kg bw (Eriksen & Alexander 1998). The National Institute of Public Health and the Environment in the Netherlands carried out another extensive DON risk assessment in wheat and wheat-containing food products (Pieters et al. 2002). NOAELs were determined on the basis of growth retardation in mice (0.11 mg/kg bw/day) (Iverson et al. 1995), as well as growth effects in swine (0.04–0.06 mg/kg bw/day) (Bergsjo et al. 1992, 1993). The TDI derived from these NOAELs were 1.1 to 3 μg/kg bw, respectively.

On the basis of these studies on growth impairment, JECFA proposed a TDI for DON of 1 μg/kg bw (Canady et al. 2001). Another key consideration is biogeographic differences in *Fusarium* chemotypes (Sugita-Konishi & Nakajiima 2010). DON producers typically predominate in North America, whereas both DON and NIV producers are detected in Japan. Because there have been limited toxicological studies on NIV as compared to DON, assessment for this trichothecene is more challenging. The Scientific Committee on Food (SCF) of the European Commission established a temporary TDI of 0.7 μg NIV/kg bw/day (SCF 2002) on the basis of the LOEL determined previously by Japanese researchers (Ohtsubo et al. 1989, Ryu et al. 1988) and a safety factor of 1,000. The National Institute for Public Health and the Environment in the Netherlands came to a similar conclusion (Pronk et al. 2002). It has been proposed recently that this TDI be reconsidered in light of more recent subacute repeated dose toxicity studies (Gouze et al. 2007, Kubosaki et al. 2008, Takahashi et al. 2008). Even less is known about 3-ADON, 15-ADON, and FX; Pronk et al. (2002) concluded that there was insufficient toxicological data to establish valid TDIs for these trichothecenes. However, recently, JECFA proposed that 3-ADON and 15-ADON be considered equivalently toxic to DON and that a group TDI of 1 μg/kg be used (JECFA 2011a).

4.4. Kashin-Beck Disease

Kashin-Beck disease (KBD) is an endemic and chronic degenerative osteoarthritis, with primary lesions involving the growth plate and subsequent cartilage deterioration, ultimately causing short stature in adults and lifelong disability (Allander 1994). This disease was initially reported in Russia by Kashin then Beck in 1848 and 1906, respectively (Allander 1994), where it was later proposed to be caused by a mycotoxin. Current focus on KBD is in northeastern and southwestern China, where it is endemic, affecting approximately 2.5 million people in 15 provinces (Kang et al. 2013). Disease onset begins in children between the ages of 4 and 13 years, with boys being more susceptible than girls (Zhai et al. 1990). Currently, the causes of KBD are believed to be multifactorial and to include mycotoxin exposure, trace element deficiency, high fulvic acid concentrations in drinking water, and a physically challenging environment. For a historical perspective of this disease, the reader is directed to Allander (1994).

When day-old male broiler chickens were exposed to 2.64 mg/kg T-2 toxin in their diets, the presence of tibial epiphyseal plate lesions were assessed (Nascimento et al. 2001). Notably, the tibias of treated animals exhibited defective maturation, anomalous cartilage vascular invasion, and

retarded cartilage erosion. Similarly, rats gavaged with T-2 toxin presented epiphyseal plate lesions with necrosis of chondrocytes (Yan et al. 2010). These results were comparable to the lesions found when rats were fed food from the KBD endemic region (Yan et al. 2011). The relevance of this latter finding to potential KBD etiology of trichothecenes is questionable, however, because these authors did not explicitly state that they analyzed this food for T-2 toxin or selenium.

Antioxidant capacity and lipid peroxidation were assessed in rats fed a selenium-deficient diet for four weeks then exposed to T-2 toxin for another four weeks (Chen et al. 2012). T-2 toxin-induced oxidative stress in joint tissues could potentially contribute to cartilage damage in KBD. In a subsequent study, rats were fed selenium-deficient or control diets for 4 weeks then exposed to T-2 toxin at 100 or 200 ng/kg bw/day for 4 weeks (Guan et al. 2013). Chondrocyte necrosis in knee joint cartilage with lesions similar to those in human KBD were seen in the selenium-deficient diet groups fed low and high concentrations of T-2 toxin.

Mechanisms for the aforementioned in vivo effects of T-2 toxin and selenium have been explored in vitro in human chondrocyte cultures (Chen et al. 2006b). T-2 toxin (1–20 ng/ml) accelerated apoptosis in a concentration-dependent manner, which was linked to an increase in the Bax/Bcl-2 ratio. These effects could be reversed by the addition of selenium. The effects of T-2 toxin have also been studied on aggrecan metabolism in human chondrocytes and cartilage in vitro (Li et al. 2008). The perturbed balance between aggrecan synthesis and degradation in cartilage might be an important step in the initiation of the cartilage degradation. Recently, it was found that DON and NIV could also evoke pro-catabolic changes in cartilage, resulting in the loss of aggrecan and Type II collagen, and other similar effects to T-2 toxin in chondrocyte cultures (Lu et al. 2012). Thus, Type B trichothecenes may act similarly to T-2 toxin in the human chondrocyte model.

There is a critical gap in our knowledge about the extent of human exposure to T-2 and other trichothecenes in regions where KBD is endemic. In a notable exception, a survey was conducted on grains in three rural KBD endemic villages and one non-KBD village in Qinghai Province (Sun et al. 2012). T-2 toxin concentrations in the samples from the three KBD endemic villages were relatively high, with a mean level of 78.1 μg/kg in wheat and 47.5 μg/kg in flour, but was significantly lower in samples from the non-KBD village (12.2 μg/kg). The average selenium contents in wheat and flour from KBD areas were 4.5 and 6.7 μg/kg, respectively—significantly lower than those in samples from the non-KBD village (60.4 μg/kg). These data complement animal studies and suggest that potential associations exist between KBD and both T-2 toxin contamination and selenium deficiency. Although intriguing, these findings must be expanded relative to sampling period and number of samples taken in the endemic and nonendemic areas; additionally, this work should incorporate the use of specific trichothecene biomarkers for exposure in KBD and non-KBD cohorts.

5. OCHRATOXIN A

OTA is produced most commonly by the fungi *Penicillium verrucosum*, *Aspergillus carbonarius*, and *Aspergillus ochraceus*, which can produce OTA across a wide range of temperatures (0–37°C) in multiple agricultural commodities. Hence, OTA can contaminate a wide variety of foods and drinks and can also bioaccumulate in the blood and milk of animals exposed to OTA. Affected commodities include cereal grains and their finished products, nuts, dried fruits, spices, meat, milk, wine, beer, infant formula, and baby foods.

With its limited solubility in water, OTA absorbed from the gastrointestinal tract binds strongly to plasma proteins. This results in reabsorption of OTA in the kidney, and enterohepatic recirculation. Therefore, biotransformation or renal clearance is delayed significantly, resulting in a relatively long half-life of OTA in the body of approximately 35 days (Ringot et al. 2006, Studer-Rohr et al. 2000).

OTA is a potent renal carcinogen in several animal species. Exposure to OTA can induce renal adenomas or carcinomas in 39% of rats at as low as 70 μg/kg bw/day (NTP 1989) and can cause decreased kidney function and enzymatic concentrations at just 8 μg/kg bw/day in female swine (Krogh et al. 1974). Czakai et al. (2011) describe mechanisms of OTA carcinogenicity in rats. Although the kidney is the main target organ for OTA toxicity, adverse effects, including cardiac and hepatic histological abnormalities, lesions of the gastrointestinal tract, and lymphoid tissues in the hamster, have been observed in other organs in animal studies (Hagelberg et al. 1989). Maternal OTA can cross the placenta and accumulate in fetal tissues to induce malformation of the fetus (Fukui et al. 1987). OTA may also be immunotoxic (Bondy & Pestka 2000).

Despite the abundance of adverse effects shown in animal studies, however, there are no documented cases of adverse effects in humans caused by OTA exposure. Several studies in the past examined OTA as the potential cause of Balkan endemic nephropathy (BEN), a chronic, wasting kidney disease associated with a high incidence of urinary tract tumors in Eastern Europeans living near tributaries of the Danube River (Pfohl-Leszkowicz & Manderville 2007). However, there is increasing evidence that the etiologic agent in BEN is more likely to be aristolochic acid; this is based on the type of mutation induced by aristolochic acid, a specific biomarker of aristolochic acid exposure in the kidney tissues of BEN-affected individuals, and similarities to other known cases of aristolochic acid–related disease elsewhere worldwide (Cosyns et al. 1994, Grollman et al. 2007). Recently, it has been asserted that OTA is not a genotoxic carcinogen (Turesky 2005). Regardless, because of sufficient evidence in animal studies, OTA is considered a Group 2B possible human carcinogen (IARC 1993).

Bui-Klimke & Wu (2014) calculated unadjusted ORs from epidemiological studies that correlated OTA exposure (measured by urinary OTA) with various adverse health endpoints. For each adverse health endpoint significantly associated with urinary OTA exposure, a duplicate diet study by Gilbert et al. (2001), which correlated urinary OTA levels with dietary OTA intake, was used to estimate the level of OTA intake necessary to cause nephritic syndrome—the one health endpoint for which there was a statistically significant OR—in all populations. The review of the epidemiological data suggests that, with one exception, there appears to be no statistically significant evidence for human health risks associated with OTA exposure. The one exception concerns an increased risk of nephritic syndrome at very high exposures to OTA, based on case-control studies assessing multiple potential adverse health effects in an Egyptian population (Wafa et al. 1998). However, the sample size of this studied population was very small, and the urinary OTA levels associated with nephritic syndrome were much higher than urinary OTA levels measured in multiple other world regions, with the exception of Sierra Leone (Bui-Klimke & Wu 2014).

Populations in which OTA exposures are extremely high (such as those studied in Egypt and Sierra Leone) may experience a significantly increased risk of nephritic syndrome. However, because this extremely high level of OTA exposure is not expected in most other parts of the world, as evidenced by urinary OTA levels collected in multiple other world regions, the risk of OTA-related nephritic syndrome on a global scale is not expected to be significant.

6. GLOBAL BURDEN OF MYCOTOXIN-RELATED DISEASES

Work on estimating the burden of aflatoxin-related chronic disease has been summarized by Wu (2013). Two separate analyses have been conducted to estimate the global burden of liver cancer attributable to aflatoxin. Liu & Wu (2010) used a quantitative cancer risk assessment approach, using dose-response data for the relationship between aflatoxin and liver cancer risk in populations of HBV-negative and HBV-positive individuals (JECFA 1998, Henry et al. 1999), and multiplying the corresponding cancer potency factors by aflatoxin exposure data for multiple

nations worldwide. In their analysis, which included approximately 5 billion individuals around the world (summing populations across nations for which aflatoxin data were available), they estimated that 25,200 to 155,000 liver cancer cases annually could be attributed to aflatoxin exposure.

In a follow-up study, Liu et al. (2012) used a different approach to estimate global burden of cancer caused by aflatoxin, estimating population-attributable risk from a systematic review and meta-analysis of 17 epidemiological studies on aflatoxin, HBV, and liver cancer in Africa and Asia. It was estimated that approximately 23% (21–24%) of all HCC cases annually could be attributable to aflatoxin, for a total of approximately 172,000 cases per year. Because liver cancer is the third leading cause of cancer deaths worldwide, and mortality rapidly follows diagnosis, the contribution of aflatoxin to this deadly cancer is significant.

At the moment, because of the relatively small number of epidemiological studies undertaken and the limited nature of dose-response relationships, it is not possible to conduct a quantitative risk assessment definitively linking an aflatoxin dose with a particular risk of stunting in a population. Further studies to explore the relationship between aflatoxin and childhood stunting are currently underway.

Little if any work has been done in estimating the burden of human disease caused by exposure to the other dietary mycotoxins. In part, this is because of a lack of certainty about the link between particular human diseases and exposure to the mycotoxins in question. Additionally, there are uncertainties regarding human exposures to these mycotoxins in different parts of the world and the accuracy of measuring exposure. Biomarkers of fumonisin, DON, and OTA exposure have been developed and are in various stages of validation (Turner et al. 2012).

7. SUMMARY

Mycotoxins are among the most important food contaminants to control in order to protect public health around the world. Their associated diseases range from cancers to acute toxicities to developmental effects. Typically, health effects associated with mycotoxin exposures disproportionately affect populations in low-income nations where dietary staples are frequently contaminated and control measures are scarce.

Because aflatoxin is one of the most important risk factors for one of the deadliest cancers worldwide—liver cancer—its eradication in the food supply is critical. It is responsible for up to 172,000 liver cancer cases per year, most of which would result in mortality within several months of diagnosis (Wu 2013). Recent studies indicate that reduction of aflatoxin exposure in a Chinese population can lead to significant decreases in age-standardized rates of liver cancer mortality (Chen et al. 2013). Possibly even more critical from a global public health standpoint is the link between aflatoxin exposure and childhood stunting, which can lead to a variety of adverse health conditions that last well beyond childhood. However, at the moment there is insufficient evidence for a quantitative risk assessment to evaluate doses of aflatoxin that lead to particular levels of risk in children's populations.

For other agriculturally important mycotoxins—fumonisins, trichothecenes, and OTA—the weight of evidence linking exposure to specific human health effects is relatively more limited. Suggestive evidence exists for the role of fumonisins in EC and NTDs; however, the role may be contributory rather than causal. Trichothecenes have been implicated in acute toxicities and gastrointestinal disorders, and other more long-term adverse effects may be caused by trichothecene exposures. With OTA, impacts to human populations are limited; however, animal studies suggest possible contributions to toxic effects.

The potential for decreased food security, should such foods become less available to a growing human world population, must counterbalance the assessment of human health risks and removal

of mycotoxin-contaminated foods from the human food supply. Further studies are needed to improve our ability to assess the true risks from the diverse range of human mycotoxin exposures. Use of these basic data with translational studies will enhance our understanding of the potential of mycotoxins to adversely affect human health. Over the long-term, this will enable validation and/or refinement of existing risk assessments and regulatory standards for these mycotoxins, thus assuring human safety simultaneously with maximizing availability of essential food commodities.

A variety of methods exist by which to mitigate the risks associated with mycotoxins in the diet. Two articles that review the wide range of mycotoxin control strategies are Kabak et al. (2006) and Khlangwiset & Wu (2010). Specifically, the latter divides interventions into preharvest, postharvest, dietary, and clinical methods of reducing the risks of aflatoxin to human health, either through direct reduction of aflatoxin levels in crops or reducing their adverse effects in the human body. Preharvest interventions include good agricultural practices, conventional or transgenic breeding to resist drought, insect pest damage or fungal infection, and biocontrol (use of atoxigenic strains of fungi to competitively exclude toxigenic strains). Postharvest interventions focus largely on proper sorting, drying, and storage of food crops to reduce the risk of fungal growth and subsequent mycotoxin accumulation. Dietary interventions include the addition of dietary chemopreventive agents or toxin-adsorbing agents into the diet, or increasing dietary diversity where possible. A clinical intervention to reduce the adverse effects of aflatoxin is vaccination against HBV, to prevent the synergism of aflatoxin exposure and chronic HBV infection in greatly increasing liver cancer risk. Wu & Khlangwiset (2010) describe a framework by which to evaluate the feasibility of each of these mycotoxin risk-reduction interventions in resource-poor settings, with a focus on sub-Saharan Africa.

Some of the important research questions that remain regarding these toxins concern the entire life cycle of the production and effects of mycotoxins. Below, we offer some possible related research directions.

FUTURE ISSUES

1. Why do these fungi produce these toxins? Understanding the functions of these toxins for the fungi may shed light on solutions to prevent production of mycotoxins.
2. Does mycotoxin exposure in human populations have interactive effects with nutrients or other dietary or environmental factors to compound health risks, such as growth impairment, in vulnerable populations? Because multiple dietary and environmental risk factors are present together in low-income settings worldwide, mycotoxin exposure may cause even greater damage to human health than previously supposed when evaluated separately. Conversely, reducing mycotoxin exposure in high-risk populations may result in even greater health benefits than may have been previously supposed.
3. How can growers, food handlers, and consumers be encouraged to adopt interventions that reduce the risk of mycotoxins in their foodstuffs? Despite efforts to develop effective methods of reducing mycotoxins and their adverse effects in humans, these methods will not have the intended benefits unless they are adopted by the populations at highest risk of mycotoxin exposure. There may be a wide variety of reasons that populations do not adopt these interventions: They are cost prohibitive, they cannot be easily delivered to the places they are needed, their necessity is not obvious, etc. These factors need to be understood so that adoption of useful technologies and methods to reduce mycotoxin risk can be achieved and global public health improved.

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