CHAPTER 6.

Mycotoxins and human health

Summary

Mycotoxins have been investigated in relation to a wide range of adverse human health effects, but the evidence for all but a small number of associations is limited. Thus, the full impact on human health of the widespread exposure to mycotoxins remains to be defined. The main exception is for aflatoxins; epidemiological, experimental, and mechanistic studies have contributed to establishing aflatoxins as a cause of human liver cancer, with a particularly elevated risk in people chronically infected with hepatitis B virus. In addition, acute aflatoxicosis after exposure to high dietary toxin levels has been demonstrated. The impairment of child growth by aflatoxin exposure early in life remains an important subject of study. More information is also required on the potential immune effects of aflatoxins, especially in vulnerable populations. For fumonisins, studies indicate a possible role in oesophageal cancer and in neural tube defects, although no definitive conclusions can be drawn at present. For deoxynivalenol and other trichothecenes, exposure has been linked to acute poisoning outbreaks in large numbers of subjects. For ochratoxin A and zearalenone, the human health effects remain undefined. The limited tools available to accurately assess human exposure to mycotoxins and the relative paucity of epidemiological studies need to be addressed if the full extent of the adverse effects of these common dietary contaminants is to be understood and adequate public health measures taken. In this respect, newly established biomarkers of exposure at the individual level are proving valuable in improving exposure assessment in epidemiological studies.

1. Introduction

This chapter covers the effects on human health of the major mycotoxins occurring in foods. This chapter also includes information on mechanisms of action of mycotoxins in humans where relevant to the adverse health effects under consideration. No attempt is made at a comprehensive review, but at appropriate points we refer to more extensive accounts.

The major source of human exposure to mycotoxins is consumption of contaminated foods. Exposure is highest when those foods are dietary staples, such as maize, groundnuts, or various other cereals. Exposures to metabolites or parent toxins may also occur by consumption of contaminated milk and milk products. We covered the dietary sources of mycotoxin exposure in some detail in Chapter 1. In this chapter, we also consider

occupational exposures in granaries and other food and feed processing due to mycotoxins contained in dusts from contaminated grains. The specific effects due to particular mycotoxins are discussed in Sections 2–6. Additional, more general information on health problems associated with mycotoxins in grain dusts is covered in Section 7.

The human health effects considered here encompass acute poisoning, cancer, other chronic diseases, and biological effects, including growth impairment and immunomodulation.

One of the major limitations in assessing the effects of mycotoxins on health has been the inability to accurately assess exposure at the individual level. The development of validated biomarkers for aflatoxins has greatly assisted epidemiological studies and allowed an evaluation of aflatoxins in relation to cancer, aflatoxicosis, child growth impairment, and immune effects (see Wild and Gong, 2010). Development of validated biomarkers for fumonisins (Wild and Gong, 2010; Van der Westhuizen *et al*., 2011) and deoxynivalenol (Meky *et al*., 2003; Turner *et al*., 2008a, 2008b, 2008c) also offers promise for future studies of the human health effects of these mycotoxins. However, the biomarker field for mycotoxins also offers a cautionary tale: an unvalidated biomarker for ochratoxin A in plasma or serum has been used to assess dietary exposure to this toxin, but subsequent careful duplicate diet studies have shown that this biomarker does not reflect intake at the individual level (Gilbert *et al*., 2001). Nevertheless, the availability of biomarkers to measure exposure to mycotoxins provides new opportunities for more systematic monitoring of exposure in populations as well as improved etiological studies.

2. Aflatoxins

Aflatoxins are produced in a wide range of commodities by *Aspergillus flavus* and *A. parasiticus*, and occasionally other *Aspergillus* species. The commodities most at risk are maize and groundnuts in tropical areas (see Chapter 1).

2.1 Mechanisms

Until recently, attention on aflatoxins has been focused on their carcinogenic effects. For more detailed information, see the extensive reviews in IARC (2002), WHO (2002), and Wild and Gong (2010). Consideration is usually given to the naturally occurring aflatoxins in the diet – aflatoxins B_1 (AFB_1), B_2 (AFB_2), G_1 (AFG_1), and G_2 (AFG_2) – or to AFB_1 alone, or more rarely to aflatoxins M_1 (AFM_1) and M_2 (AFM_2), the hydroxylation products of AFB_1 and AFB_2, respectively, that occur in milk. This distinction between the type of aflatoxin exposures under consideration is important but is rarely considered, particularly when studying adverse health effects other than cancer.

Given the focus on mutagenicity and carcinogenicity, most studies have been of AFB_1, which, due to the presence of a double bond at the 8,9 position, can be metabolized to the reactive AFB_1-8,9-epoxide, which binds to cellular macromolecules including DNA (for more detail, see Wild and Turner, 2002). The major DNA adduct is AFB_1-N7-guanine, and this pro-mutagenic lesion commonly results in a G → T transversion mutation. AFB_1-N7-guanine can also be detected in the urine and used as an exposure biomarker in epidemiological studies. AFB_2 and AFG_2 are generally considered to be far less biologically active due to the absence of the 8,9 double bond. AFG_1 can be bioactivated to the 8,9-epoxide but is less mutagenic than AFB_1, reflecting the stearic chemistry of the respective epoxides; the AFB_1-8,9-epoxide intercalates more readily into the DNA double helix than does the equivalent AFG_1 molecule, resulting in higher levels of DNA adduct formation for a given dose. Minimal information exists about the importance of the reactive epoxide for the non-mutagenic actions of aflatoxins or indeed about the biological effects of aflatoxins independent of metabolic activation to the 8,9-epoxide. Unlike AFM_2, AFM_1 contains an 8,9 double bond and hence can be bioactivated to the reactive 8,9-epoxide.

A significant observation in terms of aflatoxin carcinogenicity is the association between exposure and a specific mutation in the *TP53* tumour suppressor gene in liver cancer (hepatocellular carcinoma [HCC]). In HCC tumours from patients who are from regions endemic for aflatoxin and who are chronically infected with hepatitis B virus (HBV), a high prevalence exists of a specific missense mutation in the gene, namely an AGG → AGT (Arg → Ser) point mutation at codon 249 (codon 249^{ser}) (IARC, 2002; Hussain *et al*., 2007). This mutation is extremely rare in HCC associated with HBV in areas where aflatoxins are uncommon, but it is as yet unclear whether HBV infection influences occurrence of the mutation in HCC from aflatoxin-endemic areas.

The major human cytochrome P450 (CYP) enzymes involved in aflatoxin metabolism are CYP3A4, 3A5, and 1A2, and the predominant site of bioactivation is the liver, although CYP3A4 expression in the human intestine means that metabolism may also occur in that organ (Wild and Turner, 2002; Kamdem *et al*., 2006; Thelen and Dressman, 2009). The contribution of these enzymes to AFB_1 metabolism in exposed people will depend on both

the affinity and level of expression of the different enzymes; CYP3A4 appears to be the most important in generating the *exo*-8,9-epoxide, and the relative contribution of CYP3A5, which also produces the *exo*-8,9-epoxide, varies by individual (Kamdem *et al*., 2006). In fact, CYP3A5 expression is polymorphic and varies by ethnic group; for example, 40% of African Americans show no expression due to identified genetic polymorphisms. Such polymorphisms may affect sensitivity to the toxic effects of aflatoxins (Wojnowski *et al*., 2004). CYP1A2 leads predominantly to formation of the hydroxylated AFM_1 metabolite and the AFB_1-*endo*-8,9-epoxide, which does not form DNA adducts.

Given the fact that aflatoxin is known to cross the placenta, it is also of interest that CYP3A7, a major CYP in human fetal liver, can activate AFB_1 to the 8,9-epoxide (Kamataki *et al*., 1995; Wild and Turner, 2002). Indeed, aflatoxin adducts have been identified in cord blood (Wild *et al*., 1991; Turner *et al*., 2007), indicating that environmental levels of aflatoxin are bioactivated to the reactive metabolites in utero.

Detoxification of the aflatoxin *exo*- and *endo*-epoxides occurs mainly through glutathione *S*-transferase-mediated conjugation to reduced glutathione (Guengerich *et al*., 1998). The epoxides can also undergo rapid non-enzymatic hydrolysis to AFB_1-8,9-dihydrodiol, which in turn forms a dialdehyde phenolate ion with an opened ring. The dihydrodiol can react with the ε-amino group of lysine in serum albumin to form aflatoxin–albumin adducts, which are often used as exposure biomarkers (Wild and Gong, 2010). In a further metabolic step, aflatoxin aldehyde reductase catalyses the NADPH-dependent reduction of the dialdehyde phenolate ion to a dialcohol (Johnson *et al*., 2008).

An understanding of the metabolism, DNA damage, and induction of mutations in people exposed to aflatoxins in the diet has contributed to the overall assessment of their adverse health effects (Groopman *et al*., 2008; Wild and Gong, 2010). The major health effects linked to aflatoxin exposure are described briefly here.

2.2 Aflatoxicosis

Sporadic historical accounts of human poisoning with aflatoxins were reported, but these early studies were not definitive in assigning causation (Hall and Wild, 1994). In 1974, hepatitis cases due to aflatoxicosis in Western India (Krishnamachari *et al*., 1975) were associated with consumption of maize contaminated with *A. flavus*. Patients exhibited jaundice preceded by fever, vomiting, and anorexia, with subsequent progression to ascites and oedema in lower extremities. In maize from households where cases occurred, the aflatoxin levels were extremely high, 6.25–15.6 mg/kg, and the estimated daily ingestion of aflatoxins was 2–6 mg in adults.

In Kenya in 1981, another outbreak of acute hepatitis was associated with aflatoxin poisoning (Ngindu *et al*., 1982). Patients were diagnosed with jaundice preceded by abdominal discomfort, anorexia, general malaise, and low-grade fever; tachycardia and oedema were also observed. Maize from two affected households contained up to 3.2 mg/kg and 12 mg/kg AFB_1. An additional report came from an incident in Malaysia in 1988, where 13 children died from acute hepatic encephalopathy after consuming noodles (Lye *et al*., 1995).

In 2004, well-documented cases of aflatoxicosis occurred in Kenya, close to the locality of the cases reported in 1981 (Azziz-Baumgartner *et al*., 2005; Lewis *et al*., 2005). These outbreaks resulted in several hundred deaths associated with consumption of maize heavily contaminated with aflatoxin. A case–control study of aflatoxicosis, defined as acute jaundice of unknown origin, found that aflatoxin levels in foods from affected households were much higher than those in foods from unaffected households. Similar differences between cases and controls were found when aflatoxin biomarker levels in blood were examined (Azziz-Baumgartner *et al*., 2005; McCoy *et al*., 2008).

The association of aflatoxin contamination of maize with acute hepatitis and aflatoxicosis is well supported by the evidence, most notably by the observations in Kenya. It is of interest that aflatoxicosis has been reported only in communities where maize is the dietary staple. This reflects both high levels of aflatoxins in maize and high daily intakes (300–500 g) of this staple commodity. In addition, however, the role of co-contaminating mycotoxins, notably fumonisins, has not been assessed, and these may contribute to the acute toxicity observed.

The level of aflatoxin intake associated with aflatoxicosis and death has been estimated (Wild and Gong, 2010). The intake of total aflatoxins estimated to result in a risk of fatality was > 1 mg/day, i.e. > 20 µg/kg body weight (bw)/day in adults. It was considered that aflatoxicosis without fatality may occur with 5–10-fold lower doses. Further estimates suggested that the total intake of AFB_1 associated with half the exposed people dying (i.e. the median lethal dose [LD_{50}]) would be 0.54–1.62 mg/kg bw, a similar magnitude to the LD_{50} value reported for rabbits, cats, dogs, pigs, and baboons (Wild and Gong, 2010). Therefore, daily exposure to staple foods consumed at several hundred

grams per day and contaminated with ≥ 5000 µg/kg of aflatoxins may lead to death in humans. Daily consumption of foods with > 1000 µg/kg may lead to aflatoxicosis.

It is of great concern that these contamination levels in maize that are associated with aflatoxicosis and death are only 10–100 times the levels that occur regularly in many parts of sub-Saharan Africa. Despite the demonstration that heavy contamination of maize with aflatoxins does lead to aflatoxicosis and death, these outbreaks continue to occur. Thus, in affected parts of the world, there is an urgent need for a rapid field test that, as part of a preventive strategy, can detect dangerously high levels (e.g. > 1000 µg/kg) of aflatoxins in cereals and nuts, as well as an emergency response analogous to those in place for outbreaks of infectious diseases.

2.3 Liver cancer

The International Agency for Research on Cancer (IARC) has classified naturally occurring mixtures of aflatoxins as Group 1, carcinogenic to humans (IARC, 2002) (Table 6.1). Before the 1990s, most studies of aflatoxins and HCC were either ecological correlation studies or case–control studies. The ecological studies did not always consider infection with HBV and hepatitis C virus, had relatively crude estimates of aflatoxin intakes, and had limitations in diagnosis and registration of HCC cases. Despite this, most showed a positive correlation between estimated aflatoxin intakes and HCC rates in a given region (IARC, 1993, 2002).

Prospective cohort studies of improved design, begun in the late 1980s and 1990s in South-East Asia, used biomarkers of exposure to both HBV and aflatoxins. These studies provided strong evidence of a more than multiplicative interaction between these two factors in relation to increased HCC risk (Qian *et al*., 1994; Wang *et al*., 1996; IARC, 2002). In a more recent follow-up of the cohort in Taiwan, China, Wu *et al*. (2009) conducted the largest nested case–control study to date and reported that the combined effect of AFB_1 exposure and HBV infection was more consistent with an additive model than with the multiplicative one observed in the original report of Wang *et al*. (1996). However, after examining the plasma of HCC patients, cirrhosis patients, and controls for the *TP53* gene mutation (codon 249^{ser}; AGG → AGT), Kirk *et al*. (2005) showed that the increased risk associated with the presence of both the 249^{ser} mutation and HBV infection was consistent with a multiplicative effect of exposure to aflatoxin and chronic HBV infection.

The HCC risk from exposure to aflatoxins in the absence of chronic HBV infection is difficult to assess in populations where HBV infection is widespread. A review by Omer *et al*. (2004) reported 1.7–3.4-fold increased risks in individuals exposed to aflatoxins without chronic HBV infection. Wu *et al*. (2009) reported a similar magnitude of increased HCC risk in subjects positive only for aflatoxin exposure biomarkers, but occult HBV infections in some of the individuals in these studies cannot be ruled out.

The overall evidence from epidemiological studies shows a particularly elevated risk of HCC from aflatoxin exposure in individuals chronically infected with HBV and reasonable evidence that an increased risk also exists in individuals exposed to aflatoxins without chronic HBV infection. Given that > 350 million chronic HBV carriers exist worldwide, many living in aflatoxin-endemic areas, the need to reduce aflatoxin exposure remains highly relevant for cancer prevention.

2.4 Cirrhosis

To date, little information exists on the risk of liver cirrhosis in relation to aflatoxin exposure. A case–control study in The Gambia (Kuniholm *et al*., 2008) reported that increasing lifetime groundnut intake (a surrogate for aflatoxin consumption) was associated with a significantly increased risk of cirrhosis, approaching 3-fold with the highest level of consumption. The presence of the codon 249^{ser} mutation associated with aflatoxin was also associated with a similar magnitude of increased risk of cirrhosis. However, further studies are needed before any conclusions can be drawn about aflatoxin and cirrhosis. This is an area that merits more attention, given the large burden of cirrhosis worldwide.

2.5 Immune effects

The immunomodulatory effects of aflatoxins have been considered in experimental studies in cell models and animals as well as in observations of farm animals (IARC, 1993, 2002; WHO, 2002; Williams *et al*., 2004). However, only a few studies have considered the association between aflatoxin exposure and immune parameters in human populations. Two such studies have been reported from The Gambia (Allen *et al*., 1992; Turner *et al*., 2003). The first provided some evidence that children with higher aflatoxin exposure were more likely to have malaria parasitaemia, but no significant associations were observed with experience of malaria infection, antibody titre to asexual stages of *Plasmodium falciparum*, or lymphoproliferative responses. The second study investigated the effect of aflatoxin exposure on cell-mediated immunity (skin test), antibody titres (in response to rabies and pneumococcal vaccines), and salivary immunoglobulin A (IgA). No associations were found between

aflatoxin exposure and either the skin test or antibody titres, but higher aflatoxin exposure was associated with lower salivary IgA, suggesting that aflatoxin exposure could modulate mucosal immunity.

From Ghana, two studies have been reported that compared aflatoxin biomarker levels and subsets of peripheral blood cells in adults (Jiang *et al*., 2005, 2008). In the first, a higher aflatoxin biomarker level was associated with a lower percentage of CD3+ and CD19+ cells (B lymphocyte antigens) expressing the CD69+ activation marker and with lower percentages of CD8+ T cells expressing perforin and granzyme A. In the second study, a higher aflatoxin biomarker level was associated with lower percentages of CD8+ cells expressing perforin and of CD19+ cells expressing CD69+. In addition, HIV-positive individuals with higher aflatoxin biomarker levels had significantly lower percentages of CD4+ T regulatory cells and naive CD4+ T cells compared with HIV-positive individuals with lower aflatoxin biomarker levels.

Overall, the studies of immunomodulation do not permit conclusions to be drawn about the impact of environmental levels of aflatoxin exposure on human immunity and susceptibility to infectious disease. Nevertheless, the data suggest that immune parameters could be affected in populations exposed chronically to aflatoxins. If this were to be proven, the impact would add greatly to the burden of disease related to cancer and aflatoxicosis.

2.6 Child growth impairment

Children are chronically exposed to high levels of aflatoxins in areas where food contamination is endemic. Exposure begins in utero and continues throughout early life, although the breastfeeding period provides some respite from high daily intakes. Studies in several animal species indicate that aflatoxin exposure can severely affect growth and development. However, until recently such effects had not been considered in human populations.

Early studies explored the link between aflatoxin exposure and kwashiorkor (Hendrickse *et al*., 1982), but no firm conclusions could be drawn due to various weaknesses in study design (Hall and Wild, 1994). A study in rural Kenya in the 1980s linked aflatoxin detection in mothers' blood with significantly lower birth weights of female babies (De Vries *et al*., 1989). A more recent study in Kisumu District, Kenya, showed a significantly greater prevalence of wasting (low weight for height) in children fed cereals with high aflatoxin contamination, compared with those whose cereals had lower aflatoxin levels (Okoth and Ohingo, 2004).

A series of studies has been conducted in West African children exposed to aflatoxins early in life. In the first of these, a cross-sectional study of children aged 1–5 years in Benin and Togo, a striking inverse association was found between aflatoxin–albumin adduct level and growth (Gong *et al*., 2002). In a subsequent 8-month longitudinal study, a strong negative correlation was observed between aflatoxin–albumin adduct level and height increase (Gong *et al*., 2004). The highest quartile of aflatoxin–albumin adducts was associated with a mean reduction of 1.7 cm in height increase compared with the lowest quartile. Recently, an association was also found between exposure to aflatoxin in utero and impaired growth during the first year of life in children in The Gambia (Turner *et al*., 2007). This finding suggests that the consumption of aflatoxin-contaminated food during pregnancy may have effects on the child after birth.

In summary, growth faltering in West African children may occur at the time of introduction of solid foods, when high exposure to aflatoxin occurs. The dose–response relationships between aflatoxin biomarker levels and growth effects are also consistent with a causal effect. However, at this time other confounding factors cannot be excluded as explanations for these associations. The mechanisms of action by which aflatoxin may exert an effect on growth are currently unknown, although the possibility of a compromised intestinal integrity, through altered barrier function as a consequence of endothelial cell toxicity or immune suppression, is a valid hypothesis that should be explored further (Wild and Gong, 2010).

In areas where aflatoxin is common, namely sub-Saharan Africa and South Asia, 7.1 million children died under the age of 5 years in 2008. It is estimated that about 50% (3.55 million) of these deaths are related to undernutrition and poor growth (Black *et al*., 2003). If aflatoxin exposure were to be responsible for even a few per cent of these deaths, the total number would be tens of thousands per year.

2.7 Occupational exposures

AFB_1 concentrations of up to 612 µg/kg have been reported in airborne dusts during the handling of contaminated maize and groundnuts (Miller, 1994a; Sorenson, 1999). Most aflatoxin was contained in the < 7 µm and 7–11 µm particle size ranges. In grain dusts, a substantial fraction of the aflatoxin is contained in the spores of *A. flavus* and *A. parasiticus* (Miller, 1994a, 1994b).

Retrospective studies of feed processing workers in Denmark reported elevated risks of HCC, gall bladder cancer, and extrahepatic bile duct cancer in this population exposed occupationally, with a

2-3-fold increased risk after a 10-year latency period. Inhalation exposure to aflatoxin (170 ng/day) was reported to be the most likely explanation. Some evidence of elevated aflatoxin biomarker levels related to the handling of contaminated feeds was also reported (Olsen *et al*., 1988; Autrup *et al*., 1991, 1993). A risk assessment model suggested that exposure to AFB_1 in airborne dust may pose little significant risk during maize harvest and elevator loading/unloading but a relatively high risk during swine feeding and storage bin cleaning (Liao and Chen, 2005).

3. Fumonisins

Fumonisins occur in maize and, much less commonly, other cereals, as a result of infection with *Fusarium verticillioides* and related species (see Chapter 1). An Environmental Health Criteria document for fumonisin B_1 (FB_1) has been published (WHO, 2000a), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established a provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg bw/day for FB_1, FB_2, and FB_3 alone or in combination (WHO, 2001, 2002). This PMTDI is based not on tumorigenicity data but on the no-observed-effect level (NOEL) for nephrotoxicity in rodents of 0.2 mg/kg bw/day, divided by a safety factor of 100 (WHO, 2001).

3.1 Mechanisms

Fumonisins may exert their biological effects through several different mechanisms. FB_1 genotoxicity is somewhat unclear; negative results were obtained from several genotoxicity assays, but other in vitro studies reported that FB_1 induced micronuclei and chromosomal aberrations (Ehrlich *et al*., 2002; IARC, 2002). The DNA damage may be a result of stimulation of oxidative damage and lipid peroxidation (Stockmann-Juvala and Savolainen, 2008). This finding is consistent with increased oxidative DNA damage and malondialdehyde adducts in rat liver and kidney (Domijan *et al*., 2006) and lipid peroxidation (Abel and Gelderblom, 1998) in vivo after FB_1 treatment. Fumonisin-induced carcinogenesis in the liver proceeds through initiation and promotion stages in a manner similar to that for genotoxins and is dependent on the dose and time of exposure (Gelderblom *et al*., 2008a). Nevertheless, no evidence has been found for direct interaction of fumonisin with DNA nor for its metabolism to a reactive metabolite (WHO, 2001; IARC, 2002).

FB_1 disrupts de novo sphingolipid biosynthesis by inhibition of the enzyme ceramide synthase (Merrill *et al*., 2001), resulting in many effects on signalling pathways and cell functions that are dependent on ceramide, sphingoid bases, sphingoid base 1-phosphates, and complex sphingolipids (Dragan *et al*., 2001; Merrill *et al*., 2001). These include effects on apoptosis and mitosis, thus potentially contributing to carcinogenesis through an altered balance of cell death and replication (Stockmann-Juvala and Savolainen, 2008). Disruption of sphingolipid metabolism leads to changes in the sphinganine-to-sphingosine ratio, with increased sphinganine tissue concentrations, which correlate closely with the in vivo toxicity and carcinogenicity of fumonisins (Riley *et al*., 2001). Such changes were demonstrated in rat liver and mouse kidney at carcinogenic doses of FB_1 (Voss *et al*., 2002). Disruption of cholesterol, phospholipid, and fatty acid synthesis and interaction with ceramide have been proposed to play key roles in the differential growth patterns of altered hepatocytes during cancer promotion in the liver (Gelderblom *et al*., 2008b).

The role of fumonisins in immunomodulation has also been highlighted through changes in cytokine levels in vitro and in vivo in animal models (Sharma *et al*., 2000) and effects on antibody vaccine responses in pigs exposed to FB_1 (Taranu *et al*., 2005; Stockmann-Juvala and Savolainen, 2008).

Animal experiments have shown that fumonisins are rapidly excreted unmetabolized from the gut (Shephard *et al*., 1994a, 1994b; Martinez-Larranaga *et al*., 1999). It is not known whether the gut microflora metabolize fumonisins, although hydrolysed FB_1 has been detected in faeces of vervet monkeys (Shephard *et al*., 1994a, 1994b), pigs (Fodor *et al*., 2008), and ruminants (WHO, 2000b). Studies using radiolabelled fumonisins failed to show any metabolism by primary hepatocytes or hepatic esterases and lipases (Cawood *et al*., 1994).

Analyses of human faeces has revealed unmetabolized FB_1 and FB_2 (Chelule *et al*., 2000, 2001). The presence of FB_1, FB_2, and FB_3 in human hair has been demonstrated, suggesting that fumonisins are absorbed from the gut after ingestion of contaminated maize (Sewram *et al*., 2003). More recently, FB_1 in urine has been reported in individuals consuming large amounts of maize (Gong *et al*., 2008). Direct evidence therefore exists that human populations are exposed to fumonisins after absorption, although the actual levels and the possible risk this poses still need to be quantified.

Probable daily intake values of fumonisins, determined using a validated dietary assessment tool, showed that intakes of up to 10 times the PMTDI can occur in individuals in a rural, subsistence farming community where maize is the main dietary staple (Burger *et al*., 2010). Drinking home-brewed maize beer further increased the level of exposure. Estimates of daily

fumonisin intake in rural communities in Guatemala (Torres *et al*., 2007) have also shown that total fumonisin intake can potentially be > 10 times the recommended PMTDI.

3.2 Acute poisoning

No confirmed cases have been reported of acute human poisoning due to fumonisin exposure. Part of the difficulty in discerning a specific effect of fumonisins in acute poisoning is their co-occurrence with other mycotoxins, notably aflatoxins and trichothecenes. For example, one poisoning outbreak in India occurred where fumonisin contamination of foods was reported, notably in unleavened bread prepared from mouldy sorghum or maize, and where symptoms were characterized by abdominal pain, borborygmi, and diarrhoea (Bhat *et al*., 1997). However, assays of other mycotoxins potentially present were not reported.

An outbreak of human intoxication related to the consumption of maize gruel prepared from mouldy maize powder occurred in Guangxi Province, China, in 1989 (Li *et al*., 1999). In this case, co-occurrence with trichothecenes was found, and based on an average maize meal intake of 200 g/person (60 kg bw) per day, the total daily dietary intake of deoxynivalenol and FB_1 was 80 µg/kg bw and 2.3 µg/kg bw, respectively.

These incidents highlight the need for comprehensive analyses of mycotoxins in contaminated foods and in biological samples when acute poisoning outbreaks occur.

3.3 Cancer

Ecological studies in the former Transkei region of South Africa showed that both *F. verticillioides* and fumonisin contamination of maize were positively correlated with oesophageal cancer incidence rates (Marasas, 2001; IARC, 2002). Similar correlations have been reported in China (Sun *et al*., 2007). Other reports have associated maize consumption per se with high oesophageal cancer incidence rates but did not consider fumonisin exposure specifically (Franceschi *et al*., 1990). In these studies, other fungi and their mycotoxins were generally also present, and to date no analytical studies have been conducted that specifically link FB_1 to human cancer at any organ site (IARC, 1993, 2002; WHO, 2001).

Based on the disruption of sphingolipid biosynthesis mentioned above, the serum sphinganine-to-sphingosine ratio was used as an exposure biomarker in a nested case–control study of oesophageal cancer in China (Abnet *et al*., 2001), but no association was found between biomarker levels and cancer risk. One study conducted in China did report that the sphinganine-to-sphingosine ratio in urine was significantly increased in males estimated to have consumed > 110 µg/kg bw/day of FB_1 (Qiu and Liu, 2001). However, in all subsequent reports, no association was observed between sphingoid bases or sphinganine-to-sphingosine ratios in the plasma and urine and individual fumonisin exposure, suggesting that these biomarkers are not sufficiently sensitive for monitoring exposure in human populations (Nikièma *et al*., 2004; van der Westhuizen *et al*., 2010; Xu *et al*., 2010).

Many risk factors exist for the development of oesophageal cancer. These differ among geographical regions with respect to demography, ethnicity, genetic susceptibility, cultural practices, and socioeconomic and nutritional status. The use of home-grown maize as one of the main dietary staples, coupled with an underlying poor socioeconomic status, could implicate fumonisins as a contributing factor in the development of oesophageal cancer. However, confounding by other risk factors and the possible interactions of fumonisins with other mycotoxins should be considered in future studies.

Some experimental studies have reported a synergistic interaction between AFB_1 and FB_1 in the development of liver cancer (Carlson *et al*., 2001; Gelderblom *et al*., 2002). Perhaps due to the focus on oesophageal cancer, the role of fumonisins in cancer in other organs has been largely unexplored. However, given the interactions found experimentally, the co-contamination of crops by aflatoxins and fumonisins, and the fact that both toxins occur in populations with a high prevalence of HBV infection, a role for fumonisins in HCC is plausible. Some ecological correlation studies provide support for this hypothesis (Ueno *et al*., 1997; Li *et al*., 2001; Sun *et al*., 2007). The possible interaction between various mycotoxins (fumonisins, aflatoxins, trichothecenes) and the microcystins B (algal toxins) in the development of HCC merits more investigation. Interactions of fumonisins with different dietary constituents could also have an impact on the toxicological effects (Gelderblom *et al*., 2004).

IARC has concluded that there is inadequate evidence in humans for the carcinogenicity of toxins derived from *F. verticillioides* (as *F. moniliforme*), leading to a classification of Group 2B, possibly carcinogenic to humans (IARC, 1993). FB_1 was also classified as Group 2B (IARC, 2002) (Table 6.1).

3.4 Neural tube defects

Animal studies have demonstrated that fumonisin exposure can cause neural tube defects, possibly through the disruption of sphingolipid biosynthesis and consequent depletion of sphingolipids, which are critical for lipid raft functions, specifically folate processing via

the high-affinity folate transporter (Stevens and Tang, 1997; Sadler *et al*., 2002; Gelineau-van Waes *et al*., 2005). Neural tube defects are known to be associated with reduced folate levels, and cell membrane disruption induced by fumonisins could lead to reduced folate absorption through damage to the folate receptors on the membrane (Marasas *et al*., 2004). More recently, elevation in sphingoid base 1-phosphates induced by fumonisins has been implicated in the induction of neural tube defects in mice (Gelineau-van Waes *et al*., 2009).

A possible link between human neural tube defects and fumonisin consumption was suggested when a high rate of neural tube defects was recorded in babies of Mexican American women living in Texas who conceived during 1990–1991 (Hendricks, 1999), soon after the outbreaks of equine leukoencephalomalacia and porcine pulmonary oedema that occurred in 1989–1990 in the USA (Ross *et al*., 1991). In the border region of Texas, exposure to fumonisins may be elevated due to frequent consumption of contaminated maize.

In a case–control study in this region of Texas (Missmer *et al*., 2006), moderate tortilla consumption in the first trimester of pregnancy was associated with an increased risk of neural tube defects compared with low consumption. However, high consumption was not associated with increased risk. A similar result was found using estimates for fumonisin intake from tortillas, whereas an increased sphinganine-to-sphingosine ratio was associated with increased risk, apart from the highest category.

High incidence rates of neural tube defects have been recorded in rural areas of Mpumalanga Province, South Africa, and in the Umzimkulu district of the former Transkei region in Eastern Cape Province, South Africa (Ncayiyana, 1986; Venter *et al*., 1995); in Hebei Province, China (Moore *et al*., 1997; Marasas *et al*., 2004); and in Guatemala (Marasas *et al*., 2004) and Mexico, all areas where large quantities of maize are consumed.

3.5 Occupational exposure

There are no reports of occupational exposure to fumonisin and adverse health effects.

4. Ochratoxin A

Human exposure to ochratoxin A (OTA) occurs principally in Europe and Canada, where it comes from eating foods made from barley and wheat in which *Penicillium verrucosum* has grown. Minor sources include meat, especially pork, from animals fed contaminated grain. In tropical and subtropical countries, OTA consumption is much lower, resulting from contamination due to growth of *Aspergillus carbonarius* and, less commonly, *A. niger* in coffee, cocoa and cocoa products, and dried fruit, and sometimes in cereals, including sorghum, maize, and millet (see Chapter 1).

OTA has been the subject of an Environmental Health Criteria document (WHO, 1990) and JECFA evaluations (WHO, 1991, 2001, 2002, 2007, 2008). JECFA noted that neither a conclusive association between OTA intake and human cancer nor the mechanism by which OTA is carcinogenic in animals has been established. JECFA has confirmed a provisional tolerable weekly intake (PTWI) for OTA of 100 ng/kg bw/week (WHO, 2001, 2008). It is noteworthy that risk assessment indicated that acute toxicity of OTA occurred in animals at lower levels than did long-term effects such as carcinogenicity, so this PTWI is based on acute toxicity.

4.1 Mechanisms

Recent reviews have extensively summarized evidence on the absorption, distribution, metabolism, and mechanisms of action of OTA (Pfohl-Leszkowicz and Manderville, 2007; Marin-Kuan *et al*., 2008; Mally and Dekant, 2009). Wide species differences have been reported in the serum half-life of OTA in vivo. In humans, the elimination of OTA follows a two-phase pattern, a fast excretion followed by a slow clearing, with a calculated plasma half-life of 35 days. Even infrequent exposure (consumption of contaminated food once a week or even once a month) can result in persistent blood levels of OTA (Studer-Rohr *et al*., 2000). Blood samples from healthy people in European countries show OTA levels of 0.1–40 ng/mL (WHO, 2008). The parent molecule is the major compound found in blood, whereas ochratoxin α is the major component detected in urine (Studer-Rohr *et al*., 2000).

OTA is absorbed from the gastrointestinal tract in mammals and becomes strongly bound to plasma proteins (predominantly albumin) in blood, whereby it is distributed to the kidneys, with lower concentrations in liver, muscle, and fat. OTA is metabolized by several different CYP enzymes, depending on the species and tissue involved. In cells expressing human CYP enzymes, the main metabolite was 4(*R*)-hydroxy-OTA formed by CYP1A2, 2B6, 2C9, 2D6, and 2A6, whereas the 4(*S*)-hydroxy-OTA derivative was formed by only CYP2D6 and 2B6 (Pfohl-Leszkowicz and Manderville, 2007). Identified OTA metabolites include not only these two hydroxylated species but also 10-hydroxy-OTA and ochratoxin α, which is formed by hydrolysis of the peptide bond in OTA and thus lacks the phenylalanine moiety and consequently is non-toxic. OTA may also be metabolized

Table 6.1. IARC Monographs evaluations of carcinogenic hazards of mycotoxins to humans

Mycotoxin	Monographs volume (year)	Degree of evidence of carcinogenicity		Overall evaluation of carcinogenicity to humans[a]
		In humans	In animals	
Aflatoxins, naturally occurring mixtures of	56 (1993), 82 (2002)	Sufficient	Sufficient	Group 1
Aflatoxin B_1	56 (1993)	Sufficient	Sufficient	
Aflatoxin B_2	56 (1993)		Limited	
Aflatoxin G_1	56 (1993)		Sufficient	
Aflatoxin G_2	56 (1993)		Inadequate	
Aflatoxin M_1	56 (1993)	Inadequate	Sufficient	Group 2B
Toxins derived from *Fusarium verticillioides*[b]	56 (1993)	Inadequate	Sufficient	Group 2B
Fumonisin B_1	82 (2002)	Inadequate	Sufficient	Group 2B
Fumonisin B_2	56 (1993)		Inadequate	
Fusarin C	56 (1993)		Limited[c]	
Ochratoxin A	56 (1993)	Inadequate	Sufficient	Group 2B
Toxins derived from *Fusarium graminearum, F. culmorum,* and *F. crookwellense*	56 (1993)	Inadequate		Group 3
Deoxynivalenol	56 (1993)		Inadequate[d]	
Nivalenol	56 (1993)		Inadequate	
Zearalenone	56 (1993)		Limited[e]	
Citrinin	40 (1986)	Inadequate	Limited[f]	Group 3
Patulin	40 (1986)	Inadequate	Inadequate	Group 3
Toxins derived from *Fusarium sporotrichioides*	56 (1993)	Inadequate (no data)		Group 3
T-2 toxin	56 (1993)		Limited[g]	

[a] Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans; Group 4, probably not carcinogenic to humans.
[b] Formerly known as *Fusarium moniliforme*. Fumonisin B_1 is also produced by additional *Fusarium* species.
[c] Fusarin C caused marginal increases in incidences of papillomas and carcinomas of the oesophagus and forestomach when given by gavage to mice and rats.
[d] More recent carcinogenicity studies of deoxynivalenol in mice have been negative (Iverson *et al.*, 1995; Lambert *et al.*, 1995) and reinforce the conclusion of the 1993 IARC Working Group that there is inadequate evidence in experimental animals for the carcinogenicity of deoxynivalenol.
[e] Zearalenone caused increased incidences of hepatocellular and pituitary tumours in mice of both sexes when given in the diet, but no carcinogenic effect was seen in rats.
[f] Citrinin caused benign epithelial tumours (clear cell adenomas) of the kidney in male rats in one experiment. Whereas this study (Arai and Hibino, 1983) was unequivocally positive, other studies in other strains of rat at lower doses were negative (IARC, 1986). A single positive study with only benign tumours as findings is considered limited evidence of carcinogenicity by the IARC Monographs criteria.
[g] T-2 toxin caused increased incidences of liver cell tumours and lung tumours in male mice when given in the diet.

by cyclo-oxygenase, lipoxygenase, and epoxygenase, particularly in extrahepatic organs such as the kidney, to yield reactive oxygen species, which in turn may result in oxidative damage.

OTA competitively inhibits phenylalanine-tRNA ligase, resulting in inhibition of protein synthesis as well as RNA and DNA synthesis. In animals, acute toxic effects of OTA can be inhibited by co-administration of phenylalanine (FAO/WHO/UNEP, 1999).

The formation of DNA adducts by OTA and their potential role in cancer induction has been investigated (Mally and Dekant, 2009; Mantle *et al*., 2010), and hypotheses for the formation include direct adduct formation induced by OTA after metabolic activation via an OTA phenoxy radical and indirect DNA damage resulting from oxygen radical formation as mentioned above (Pfohl-Leszkowicz and Manderville, 2007).

The concentration of OTA-specific transporters in tissues has been proposed to explain the relative species, sex, and target organ sensitivities to OTA toxicity (reviewed in Dietrich *et al*., 2005). Another contributor to selective sensitivity is the extent of albumin binding, which markedly decreases the uptake of OTA by transporters (Bow *et al*., 2006). Mechanisms that account for the toxicity and carcinogenicity of OTA without invoking the production of OTA DNA adducts have also been proposed (reviewed in Mally and Dekant, 2009) and typically involve alterations in expression of genes regulating rates of cell proliferation and cell death. Potential biomarkers of effect in target tissues include the development of unique gene expression profiles specific to alterations of gene expression induced by OTA. Genes include those involved in cellular defence, cell proliferation, and cell death (reviewed in Marin-Kuan *et al*., 2008; Adler *et al*., 2009; Mally and Dekant, 2009) and in oxidative stress (Arbillaga *et al*., 2008; Cavin *et al*., 2009). Changes in urinary metabolite profiles, obtained using GC-MS, LC-MS, and [^{1}H]-NMR, have been used as a metabonomic approach to assess the potential of these changes for development of a predictive model for OTA toxicity (Sieber *et al*., 2009). Although the results were not specific for OTA, they were indicative of kidney damage and general toxicity, and this approach could prove to be of value for discovery of more specific mechanisms unique to OTA.

4.2 Acute toxicity

The kidney is the major target organ for adverse effects from OTA (Pfohl-Leszkowicz and Manderville, 2007; WHO, 2002). Short-term toxicity studies in mice, rats, dogs, and pigs have shown both time- and dose-dependent development of progressive nephropathy. Significant sex and species differences exist, as well as differences due to route of administration. Other toxic effects include cardiac and hepatic lesions in rats, lesions of the gastrointestinal tract and lymphoid tissues in hamsters, myelotoxicity in mice, and kidney lesions in chickens. Pigs appear to be the most sensitive species to the nephrotoxic effects; the lowest-observed-effect level (8 µg/kg bw) was used as the basis for establishing the PTWI.

A great deal of work has been undertaken recently to elucidate the likely mechanisms of toxicity. Degenerative changes in the proximal tubules of the kidney have been the most common effects seen in animal species studied. However, it has not been possible to determine just what acute effects, if any, OTA has on humans (WHO, 2008).

4.3 Cancer

Evidence for the carcinogenicity of OTA is principally from studies in experimental animals. OTA is carcinogenic to laboratory rats and mice, causing HCC in mice and kidney carcinomas in mice and rats. The mechanism of carcinogenic action has not been firmly established.

Reports of increased cancer risk in humans who consumed OTA have been limited to descriptive studies. No analytical epidemiological studies were available to IARC at the time of the evaluation of OTA (IARC, 1993). The descriptive studies generally focused on the co-occurrence of Balkan endemic nephropathy, a fatal chronic renal disease, and higher than expected rates of urinary tract tumours, including tumours of the kidney and urinary bladder, in Bulgaria and other Balkan countries. Available studies have not established that this increased cancer incidence was due to exposure to OTA.

IARC has concluded that there is sufficient evidence that OTA is carcinogenic in experimental animals but inadequate evidence that OTA increases cancer risk in humans. OTA has therefore been classified as Group 2B, possibly carcinogenic to humans (IARC, 1993) (Table 6.1).

4.4 Occupational exposure

OTA is found in the spores of *P. verrucosum* on grains and also *A. carbonarius* as well as some strains of *A. niger* on grapes and coffee beans. Some occupational studies in Europe reported elevated OTA levels in plasma in workers exposed to grain dust (Pfohl-Leszkowicz and Manderville, 2007). From what was inferred to be a massive exposure to OTA from working in a confined space with grain contaminated by

A. ochraceus, a farmer developed acute renal disease after temporary respiratory distress (Di Paolo *et al.*, 1993). Only limited estimates of inhalation exposure to OTA from occupational exposure are available (Mayer *et al.*, 2007).

5. Deoxynivalenol

Deoxynivalenol (DON) is produced in cereals, especially wheat, as the result of growth of *Fusarium graminearum* and related species (see Chapter 1). JECFA has established a PMTDI for DON of 1 µg/kg bw/day on the basis of the NOEL for body weight reduction in mice in a 2-year bioassay and a safety factor of 100 (WHO, 2001, 2011). The NOEL in mice was 100 µg/kg bw/day (Iverson *et al.*, 1995).

5.1 Mechanisms

DON is directly toxic via an epoxide moiety and thus does not require metabolic activation to exert its biological effects. Low-level trichothecene exposure in animal models has been shown to modulate the expression of several cytokines and chemokines that are key regulators of immune function (Pestka, 2008). Exposure to DON causes the upregulation of the mRNAs responsible for production of cytokines, chemokines, and other immune-related proteins and can also induce gene transcription. In addition, DON modulates numerous physiological processes controlled by mitogen-activated protein kinases (MAPKs). These include processes controlling cell growth, differentiation, and apoptosis, which are all crucial for signal transduction in the immune response (Pestka, 2008). Thus, in addition to altered cytokine expression, alterations in MAPK expression are likely to also contribute to the immune dysregulation and toxicity of DON and other trichothecenes. Also associated with MAPK activation by DON is the activation of processes leading to the ribotoxic stress response, which is induced by other translational inhibitors that, like DON, bind to or damage a specific region at the 3′ end of the 28S rRNA. The ribosome plays a key role in the ribotoxic stress response by serving as scaffolding for interactions between various MAPKs (Pestka, 2008).

DON toxicity studies have recently revealed several possible approaches for developing useful biomarkers of its effects. For example, DON exposure in mice results in upregulation of several suppressors of cytokine signalling. These suppressors are known to impair growth hormone signalling (Pass *et al.*, 2009). Impairment of the growth hormone axis precedes the growth retardation in the mouse induced by DON (Amuzie and Pestka, 2010). Oral DON perturbs the growth hormone axis by suppressing two growth-related proteins, IGFALS and IGF1. Thus, reduced expression of these two proteins in conjunction with elevated urinary DON levels could potentially serve as biomarkers of effect.

Detoxification varies by species; metabolism by gut microflora generates a de-epoxy metabolite (DOM-1), and conjugation to glucuronic acid is catalysed by UDP-glucuronyltransferase (reviewed by Pestka and Smolinski, 2005; Wu *et al.*, 2007). In humans, DON-glucuronide has been reported in urine samples in several studies (Turner *et al.*, 2008a, 2008b, 2008c). In contrast, information on DOM-1 is limited. An absence of de-epoxidase activity in a small series of human faecal samples was reported (Sundstøl-Eriksen and Pettersson, 2003), whereas, in apparent contrast, a study in France of farmers exposed to grain handling reported detection of DOM-1 in a proportion of subjects (Turner *et al.*, 2010).

5.2 Acute toxicity

In animals, DON has a wide range of proven toxicities, including feed refusal, decreased weight gain, gastroenteritis, cardiotoxicity, teratogenicity, and immunotoxicity (Rotter *et al.*, 1996; Meky *et al.*, 2001; Pestka *et al.*, 2004; Pestka and Smolinski, 2005; Gray and Pestka, 2007; Amuzie and Pestka, 2010).

DON can cause acute poisoning in humans, where severe gastrointestinal toxicity is the primary symptom. Consumption of cereals contaminated with DON has been associated with numerous poisoning incidents in China between 1961 and 1991 (see Pestka and Smolinski, 2005) and a major outbreak in India (Bhat *et al.*, 1989); in some of these episodes, tens of thousands of individuals were affected. In these outbreaks, symptoms were analogous to those observed in animals, notably a rapid onset, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, and fever. In an episode in the Kashmir valley, DON levels in wheat ranged from 0.4 mg/kg to 8.4 mg/kg (Bhat *et al.*, 1989), and in China DON poisoning was linked to wheat contaminated at DON levels between 0.3 mg/kg and 100 mg/kg (Pestka and Smolinski, 2005). These data suggest that acute toxicity may occur at exposures estimated in the low µg/kg bw/day range.

5.3 Cancer

Minimal data are available on the carcinogenicity of DON in either humans or experimental animals.

A 2-year bioassay in B6C3F1 mice of both sexes fed DON in the diet at concentrations of 0, 1, 5, or 10 mg/kg showed no increase in the incidence of pre-neoplastic or neoplastic lesions in the liver or other tissues (Iverson *et al.*, 1995). DON was also tested for its ability to initiate or promote skin tumours when applied topically

to the skin of female SENCAR mice, with negative results (Lambert *et al*., 1995). No studies have reported on the carcinogenicity of DON in humans. Oesophageal cancer in humans has been anecdotally linked to consumption of grains infected with *Fusarium* species that produce DON and other mycotoxins, but no analytical epidemiological studies link DON to the occurrence of any human cancer (IARC, 1993).

IARC has concluded that there is inadequate evidence in both humans and experimental animals for the carcinogenicity of DON. DON and other toxins derived from *F. graminearum*, *F. culmorum*, and *F. crookwellense* have therefore been categorized as Group 3, not classifiable as to their carcinogenicity to humans (IARC, 1993) (Table 6.1).

5.4 Occupational exposure

Inhalation exposure to DON has been the subject of several health hazard evaluations. Fusarium head blight in wheat resulting from infection by *F. graminearum* or *F. culmorum* begins at the outside of the grain head and moves inward. As a result, most DON is found in the outer layers of the kernel and the chaff (Miller, 1994b; Snijders, 1994). Grain dusts can contain quite high concentrations of DON and sometimes of other mycotoxins, which are not always present in the kernels. For example, other fungi, including *F. sporotrichioides*, can grow on what becomes the chaff so that small amounts of T-2 toxin can be present.

Air samples collected in grain elevators in Canada contained a mean airborne concentration of 37 ng/m^3 DON and a maximum of 2.59 µg/m^3 DON. Airborne dust from the same source contained 0.5–5.8 mg/kg DON, 1 mg/kg T-2 toxin, and low levels of HT-2 toxin (De Mers, 1994). Concentrations of dusts, fungal spores, and DON associated with handing of grain on farms in Finland, including grain drying, milling, and cattle feeding, were similar to those reported from Canada (Lappalainen *et al*., 1996).

Studies of DON concentrations during grain handling in Germany reported a median concentration of 2 ng/m^3 and a maximum of 703 ng/m^3 (Mayer *et al*., 2007). In France, urinary biomarkers for DON (DON, DOM-1) were higher in active farmers, particularly those from larger farms, than in retired farmers, whose exposure was from diet (Turner *et al*., 2010).

Epidemiological studies have been conducted in Norway relating to occupational exposures of male and female farmers to mycotoxins. Norwegian grains (wheat, oats, and barley) are affected mainly by Fusarium head blight, and various trichothecenes and culmorins have been reported as common (Langseth and Elen, 1996; Ghebremeskel and Langseth, 2001). A longitudinal survey of farmers over more than two decades suggested a relationship between grain farming and mid-pregnancy deliveries in the families of farmers, possibly linked to mycotoxins (Kristensen *et al*., 1997). Small increased relative risks were observed in several cancers in female but not male farmers (Kristensen *et al*., 2000).

6. Zearalenone

Zearalenone (ZEA) is a non-steroidal estrogenic mycotoxin. It is produced principally by *F. graminearum* and related species, and consequently occurs wherever DON occurs, most notably as a contaminant of maize, wheat, barley, oats, rye, sorghum, millet, and rice. Distribution of ZEA is worldwide (Zinedine *et al*., 2007). Estimates of human exposure from dietary sources are generally in the range of 1–30 ng/kg bw/day (Zinedine *et al*., 2007). JECFA has established a PMTDI for ZEA of 0.5 µg/kg bw/day based on the NOEL for hormonal effects in pigs (WHO, 2001).

6.1 Mechanisms

ZEA is metabolized during absorption by the intestinal tissue in pigs. Metabolism involves reduction of the 6-keto group of ZEA and results in formation of α- and β-zearalenol as well as, upon further reduction, α- and β-zearalanol, all of which can be conjugated in turn to glucuronic acid (WHO, 2001). Few data are available in relation to metabolism in humans. Studies of liver microsomes in vitro have suggested a high rate of α-zearalenol production compared with that of β-zearalenol in pigs and humans, a point of importance because of the greater relative estrogenicity of α-zearalenol compared with ZEA (Fink-Gremmels and Malekinejad, 2007). In other words, the formation of α-zearalenol may be considered a bioactivation step contributing to the estrogenic effects of ZEA.

ZEA and its metabolites can bind to estrogen receptors, resulting in various changes consequent to binding to elements in the nucleus responsive to estrogens. In addition, however, ZEA is a competitive substrate for enzymes involved in steroid synthesis and metabolism and therefore has the potential to act as an endocrine disruptor. ZEA can activate the pregnane X receptor by displacement of a co-repressor and recruitment of co-activators (Ding *et al*., 2006). Thus, ZEA could have widespread effects on gene expression as a result of the modified activity of this nuclear transcription factor.

6.2 Acute toxicity

ZEA is considered to be of relatively low acute toxicity. No reports have appeared of acute poisoning due to ZEA in humans.

6.3 Cancer

ZEA resulted in an increased incidence of liver cell and pituitary tumours in mice, consistent with a hormonal mode of carcinogenic action (IARC, 1993). No carcinogenic effect was seen in rats, however, and overall animal carcinogenicity data for ZEA were considered limited (IARC, 1993). No studies of human carcinogenicity have been reported for ZEA (Table 6.1).

ZEA was measured in endometrial tissue from a small group of women with endometrial adenocarcinomas, endometrial hyperplasia, or normal proliferative endometria (Tomaszewski *et al*., 1998). ZEA in blood samples has also been investigated in some small studies of early onset of puberty in Hungary (Szuets *et al*., 1997) and in Italy (Massart *et al*., 2008). In the study in Italy, there was a suggestion that elevated serum ZEA and α-zearalenol levels were associated with early puberty in 6 of the 17 girls examined from a rural area, but no positive samples were seen in the 15 patients from an urban area.

6.4 Occupational exposure

No studies of occupational exposure of humans have been reported for ZEA.

7. Occupational exposures to grain and groundnut dusts

Grain dusts present an occupational hazard when protection of workers is inadequate, and several health consequences are possible, including the allergic disease hypersensitivity pneumonitis, endotoxicosis, and organic dust toxic syndrome (Rylander and Jacobs, 1994; Sorenson and Lewis, 1996). Endotoxicosis is a result of exposure to bacterial endotoxin, and organic dust toxic syndrome (also called pulmonary mycotoxicosis, toxic organic dust syndrome, or grain fever), as far as is known, is not caused by mycotoxins. Inhalation of silica, allergens, mycotoxins, and triple-helical glucans contained in airborne dusts is a potential health risk, rarely from systemic exposure but from effects on lung biology. Outdoor work is normally not a problem, except when handling the most damaged maize, small grains, and groundnuts. In contrast, handling contaminated grains, especially damaged grains, in any confined space (e.g. grain storage, storage bin cleaning, animal feeding in barns, indoors) carries a more significant risk.

The allergic disease hypersensitivity pneumonitis, also called extrinsic allergic alveolitis or farmer's lung, develops through repeated exposure to allergens. Dust from any mouldy crop, such as straw, maize, small grains, or groundnuts, can cause the condition. Symptoms may include shortness of breath, a dry cough, a sudden general feeling of sickness, fevers and chills, a rapid heart rate, and rapid breathing. The symptoms are serious, and once an allergic reaction begins, the person will always have the potential for symptoms with exposure to the offending fungi. Long-term exposure can cause permanent lung damage, physical disability, or even death (Sorenson and Lewis, 1996; Schenker *et al*., 1998; Girard *et al*., 2009).

The reproductive structures of many fungi are known to contain mycotoxins or low-molecular-weight toxic compounds, often in high concentrations (Sorenson, 1999). Most is known about the fungi that produce toxins important in agriculture. The conidia of *A. flavus*, *A. parasiticus*, *F. graminearum*, and *F. sporotrichioides* contain very high concentrations of toxins, particularly in the case of the species that produce aflatoxins. The spores of the two *Aspergillus* species have been reported to contain 100–1100 µg aflatoxin/g, or approximately 10^{-4} moles (Wicklow and Shotwell, 1983). Several interesting toxins have been found in sclerotia of various *Aspergillus* species, again at higher concentrations than occur either in culture or in affected crops (Gloer *et al*., 1988; Wicklow *et al*., 1988), some of which are thought to be present in conidia along with kojic acid and other *A. flavus* toxins. Spores of *F. graminearum* contained 30 µg/g of T-2 toxin and those of *F. sporotrichioides* 50 µg/g (both approximately 10^{-5} moles). The spores of many species of toxigenic fungi have been demonstrated to contain mixtures of the toxins associated with the species.

The high-molecular-weight toxic compound present in spores and in spore and mycelial fragments from the anamorphic *Trichocomaceae* (i.e. *Penicillium*, *Aspergillus*, and related hyphomycetes) is (1→3)-β-D-glucan in the triple-helical form (Rand *et al*., 2010). In the species tested so far, the concentration is 1–11 pg/spore (Foto *et al*., 2004; Iossifova *et al*., 2008).

Inhalation of intact spores leads to little net exposure because their relatively large size enables entrapment and removal by lung defence mechanisms. However, in outdoor air, exposure is primarily to spore and mycelial fragments (Green *et al*., 2012) and to dusts (particulate matter < 2.5 µm in diameter), which efficiently penetrate deep into the lung (Buczaj, 2008; see Miller *et al*., 2010). Inhalation of toxins affects macrophage function and other aspects of lung biology. Pure compounds tested for effects in macrophages include fumonisin, aflatoxin (Liu *et al*., 2002), T-2 toxin (Sorenson *et al*., 1986), and the aflatoxin precursor sterigmatocystin (Miller *et al*., 2010). DON has been tested for effects in peritoneal macrophages (Ayral *et al*., 1992).

References

Abel S, Gelderblom WC (1998). Oxidative damage and fumonisin B_1-induced toxicity in primary rat hepatocytes and rat liver in vivo. *Toxicology*, 131:121–131. doi:10.1016/S0300-483X(98)00123-1 PMID:9928627

Abnet CC, Borkowf CB, Qiao YL *et al.* (2001). Sphingolipids as biomarkers of fumonisin exposure and risk of esophageal squamous cell carcinoma in China. *Cancer Causes Control*, 12:821–828. doi:10.1023/A:1012228000014 PMID:11714110

Adler M, Müller K, Rached E *et al.* (2009). Modulation of key regulators of mitosis linked to chromosomal instability is an early event in ochratoxin A carcinogenicity. *Carcinogenesis*, 30:711–719. doi:10.1093/carcin/bgp049 PMID:19237604

Allen SJ, Wild CP, Wheeler JG *et al.* (1992). Aflatoxin exposure, malaria and hepatitis B infection in rural Gambian children. *Trans R Soc Trop Med Hyg*, 86:426–430. doi:10.1016/0035-9203(92)90253-9 PMID:1440826

Amuzie CJ, Pestka JJ (2010). Suppression of insulin-like growth factor acid-labile subunit expression–a novel mechanism for deoxynivalenol-induced growth retardation. *Toxicol Sci*, 113:412–421. doi:10.1093/toxsci/kfp225 PMID:19805407

Arai M, Hibino T (1983). Tumorigenicity of citrinin in male F344 rats. *Cancer Lett*, 17:281–287. doi:10.1016/0304-3835(83)90165-9 PMID:6831385

Arbillaga L, Vettorazzi A, Gil AG *et al.* (2008). Gene expression changes induced by ochratoxin A in renal and hepatic tissues of male F344 rat after oral repeated administration. *Toxicol Appl Pharmacol*, 230:197–207. doi:10.1016/j.taap.2008.02.018 PMID:18417182

Autrup JL, Schmidt J, Autrup H, Autrup H (1993). Exposure to aflatoxin B_1 in animal-feed production plant workers. *Environ Health Perspect*, 99:195–197. PMID:8319623

Autrup JL, Schmidt J, Seremet T, Autrup H (1991). Determination of exposure to aflatoxins among Danish workers in animal-feed production through the analysis of aflatoxin B_1 adducts to serum albumin. *Scand J Work Environ Health*, 17:436–440. doi:10.5271/sjweh.1683 PMID:1788537

Ayral AM, Dubech N, Le Bars J, Escoula L (1992). In vitro effect of diacetoxyscirpenol and deoxynivalenol on microbicidal activity of murine peritoneal macrophages. *Mycopathologia*, 120:121–127. doi:10.1007/BF00578297 PMID:1336129

Azziz-Baumgartner E, Lindblade K, Gieseker K *et al.* (2005). Case-control study of an acute aflatoxicosis outbreak, Kenya, 2004. *Environ Health Perspect*, 113:1779–1783. doi:10.1289/ehp.8384 PMID:16330363

Bhat RV, Beedu SR, Ramakrishna Y, Munshi KL (1989). Outbreak of trichothecene mycotoxicosis associated with consumption of mould-damaged wheat production in Kashmir Valley, India. *Lancet*, 1:35–37. doi:10.1016/S0140-6736(89)91684-X PMID:2563012

Bhat RV, Shetty PH, Amruth RP, Sudershan RV (1997). A foodborne disease outbreak due to the consumption of moldy sorghum and maize containing fumonisin mycotoxins. *J Toxicol Clin Toxicol*, 35:249–255. doi:10.3109/15563659709001208 PMID:9140318

Black RE, Morris SS, Bryce J (2003). Where and why are 10 million children dying every year? *Lancet*, 361:2226–2234. doi:10.1016/S0140-6736(03)13779-8 PMID:12842379

Bow DA, Perry JL, Simon JD, Pritchard JB (2006). The impact of plasma protein binding on the renal transport of organic anions. *J Pharmacol Exp Ther*, 316:349–355. doi:10.1124/jpet.105.093070 PMID:16195420

Buczaj A (2008). Studies of the level of farmers' exposure to dust on private farms – based on fraction analyses. *Ann Agric Environ Med*, 15:79–84. PMID:18581983

Burger HM, Lombard MJ, Shephard GS *et al.* (2010). Dietary fumonisin exposure in a rural population of South Africa. *Food Chem Toxicol*, 48:2103–2108. doi:10.1016/j.fct.2010.05.011 PMID:20488220

Carlson DB, Williams DE, Spitsbergen JM *et al.* (2001). Fumonisin B_1 promotes aflatoxin B_1 and *N*-methyl-*N'*-nitro-nitrosoguanidine-initiated liver tumors in rainbow trout. *Toxicol Appl Pharmacol*, 172:29–36. doi:10.1006/taap.2001.9129 PMID:11264020

Cavin C, Delatour T, Marin-Kuan M *et al.* (2009). Ochratoxin A-mediated DNA and protein damage: roles of nitrosative and oxidative stresses. *Toxicol Sci*, 110:84–94. doi:10.1093/toxsci/kfp090 PMID:19414514

Cawood ME, Gelderblom WC, Alberts JF, Snyman SD (1994). Interaction of ^{14}C-labelled fumonisin B mycotoxins with primary rat hepatocyte cultures. *Food Chem Toxicol*, 32:627–632. doi:10.1016/0278-6915(94)90006-X PMID:8045475

Chelule PK, Gqaleni N, Chuturgoon AA, Dutton MF (2000). The determination of fumonisin B_1 in human faeces: a short term marker for assessment of exposure. *Biomarkers*, 5:1–8. doi:10.1080/135475000230497

Chelule PK, Gqaleni N, Dutton MF, Chuturgoon AA (2001). Exposure of rural and urban populations in KwaZulu Natal, South Africa, to fumonisin B_1 in maize. *Environ Health Perspect*, 109:253–256. PMID:11333186

De Mers F (1994). Preliminary assessment of the risk of exposure to trichothecenes produced by *Fusarium graminearum* in grain dust. Ottawa: Occupational Health and Safety Branch, Human Resources and Skills Development Canada.

De Vries HR, Maxwell SM, Hendrickse RG (1989). Foetal and neonatal exposure to aflatoxins. *Acta Paediatr Scand*, 78:373–378. doi:10.1111/j.1651-2227.1989.tb11095.x PMID:2741679

Di Paolo N, Guarnieri A, Loi F *et al.* (1993). Acute renal failure from inhalation of mycotoxins. *Nephron*, 64:621–625. doi:10.1159/000187411 PMID:8366990

Dietrich DR, Heussner AH, O'Brien E (2005). Ochratoxin A: comparative pharmacokinetics and toxicological implications (experimental and domestic animals and humans). *Food Addit Contam*, 22 Suppl 1:45–52. doi:10.1080/02652030500309327 PMID:16332621

Ding X, Lichti K, Staudinger JL (2006). The mycoestrogen zearalenone induces CYP3A through activation of the pregnane X receptor. *Toxicol Sci*, 91:448–455. doi:10.1093/toxsci/kfj163 PMID:16547076

Domijan AM, Zeljezić D, Kopjar N, Peraica M (2006). Standard and Fpg-modified comet assay in kidney cells of ochratoxin A- and fumonisin B_1-treated rats. *Toxicology*, 222:53–59. doi:10.1016/j.tox.2006.01.024 PMID:16497426

Dragan YP, Bidlack WR, Cohen SM *et al.* (2001). Implications of apoptosis for toxicity, carcinogenicity, and risk assessment: fumonisin B_1 as an example. *Toxicol Sci*, 61:6–17. doi:10.1093/toxsci/61.1.6 PMID:11294969

Ehrlich V, Darroudi F, Uhl M *et al.* (2002). Fumonisin B_1 is genotoxic in human derived hepatoma (HepG2) cells. *Mutagenesis*, 17:257–260. doi:10.1093/mutage/17.3.257 PMID:11971998

FAO/WHO/UNEP (1999). *Mycotoxins of Growing Interest: Ochratoxins*. Walker R, ed. Report from the Third Joint FAO/WHO/UNEP International Conference on Mycotoxins, Tunis, Tunisia, 3–6 March 1999. Rome: Food and Agriculture Organization of the United Nations, World Health Organization, United Nations Environment Programme (FAO/WHO/UNEP Report No. MYC-CONF/99/5b). Available at ftp://ftp.fao.org/es/esn/food/myco5b.pdf.

Fink-Gremmels J, Malekinejad H (2007). Clinical effects and biochemical mechanisms associated with exposure to the mycoestrogen zearalenone. *Anim Feed Sci Technol*, 137:326–341. doi:10.1016/j.anifeedsci.2007.06.008

Fodor J, Balogh K, Weber M *et al.* (2008). Absorption, distribution and elimination of fumonisin B_1 metabolites in weaned piglets. *Food Addit Contam Part A*, 25:88–96. doi:10.1080/02652030701546180

Foto M, Plett J, Berghout J, Miller JD (2004). Modification of the *Limulus* amebocyte lysate assay for the analysis of glucan in indoor environments. *Anal Bioanal Chem*, 379:156–162. doi:10.1007/s00216-004-2583-4 PMID:15042272

Franceschi S, Bidoli E, Barón AE, La Vecchia C (1990). Maize and risk of cancers of the oral cavity, pharynx, and esophagus in northeastern Italy. *J Natl Cancer Inst*, 82:1407–1411. doi:10.1093/jnci/82.17.1407 PMID:2388291

Gelderblom WC, Marasas WF, Lebepe-Mazur S *et al.* (2002). Interaction of fumonisin B_1 and aflatoxin B_1 in a short-term carcinogenesis model in rat liver. *Toxicology*, 171:161–173. doi:10.1016/S0300-483X(01)00573-X PMID:11836022

Gelderblom WCA, Marasas WFO, Lebepe-Mazur S *et al.* (2008a). Cancer initiating properties of fumonisin B_1 in a short-term rat liver carcinogenesis assay. *Toxicology*, 250:89–95. doi:10.1016/j.tox.2008.06.004 PMID:18616970

Gelderblom WCA, Rheeder JP, Leggott N *et al.* (2004). Fumonisin contamination of a corn sample associated with the induction of hepatocarcinogenesis in rats-role of dietary deficiencies. *Food Chem Toxicol*, 42:471–479. doi:10.1016/j.fct.2003.10.010 PMID:14871590

Gelderblom WCA, Riedel S, Burger H-M *et al.* (2008b). Carcinogenesis by the fumonisins: mechanisms, risk analyses, and implications. In: Sianta DP, Trucksess MW, Scott PM, Herman EM, eds. *Food Contaminants*: *Mycotoxins and Food Allergens*. Washington, DC: American Chemical Society (ACS Symposium Series, No. 1001), pp. 80–95.

Gelineau-van Waes J, Starr L, Maddox JR *et al.* (2005). Maternal fumonisin exposure and risk for neural tube defects: disruption of sphingolipid metabolism and folate transport in an *in vivo* mouse model. *Birth Defects Res A Clin Mol Teratol*, 73:487–497. doi:10.1002/bdra.20148 PMID:15959874

Gelineau-van Waes J, Voss KA, Stevens VL *et al.* (2009). Maternal fumonisin exposure as a risk factor for neural tube defects. *Adv Food Nutr Res*, 56:145–181. doi:10.1016/S1043-4526(08)00605-0 PMID:19389609

Ghebremeskel M, Langseth W (2001). The occurrence of culmorin and hydroxy-culmorins in cereals. *Mycopathologia*, 152:103–108. doi:10.1023/A:1012479823193 PMID:11761144

Gilbert J, Brereton P, MacDonald S (2001). Assessment of dietary exposure to ochratoxin A in the UK using a duplicate diet approach and analysis of urine and plasma samples. *Food Addit Contam*, 18:1088–1093. doi:10.1080/02652030110070030 PMID:11761119

Girard M, Lacasse Y, Cormier Y (2009). Hypersensitivity pneumonitis. *Allergy*, 64:322–334. doi:10.1111/j.1398-9995.2009.01949.x PMID:19210361

Gloer JB, TePaske MR, Sima JS *et al.* (1988). Antiinsectan aflavinine derivatives from the sclerotia of *Aspergillus flavus*. *J Org Chem*, 53:5457–5460. doi:10.1021/jo00258a011

Gong YY, Cardwell K, Hounsa A *et al.* (2002). Dietary aflatoxin exposure and impaired growth in young children from Benin and Togo: cross sectional study. *BMJ*, 325:20–21. doi:10.1136/bmj.325.7354.20 PMID:12098724

Gong YY, Hounsa A, Egal S *et al.* (2004). Postweaning exposure to aflatoxin results in impaired child growth: a longitudinal study in Benin, West Africa. *Environ Health Perspect*, 112:1334–1338. doi:10.1289/ehp.6954 PMID:15345349

Gong YY, Torres-Sanchez L, Lopez-Carrillo L *et al.* (2008). Association between tortilla consumption and human urinary fumonisin B_1 levels in a Mexican population. *Cancer Epidemiol Biomarkers Prev*, 17:688–694. doi:10.1158/1055-9965.EPI-07-2534 PMID:18349288

Gray JS, Pestka JJ (2007). Transcriptional regulation of deoxynivalenol-induced IL-8 expression in human monocytes. *Toxicol Sci*, 99:502–511. doi:10.1093/toxsci/kfm182 PMID:17636245

Green BJ, Schmechel D, Summerbell RC (2012). Aerosolized fungal fragments. In: Adan O, Samson RA, eds. *Molds, Water, and the Built Environment*. Wageningen, Netherlands: Wageningen Academic Publishers (in press).

Groopman JD, Kensler TW, Wild CP (2008). Protective interventions to prevent aflatoxin-induced carcinogenesis in developing countries. *Annu Rev Public Health*, 29:187–203. doi:10.1146/annurev.publhealth.29.020907.090859 PMID:17914931

Guengerich FP, Johnson WW, Shimada T *et al.* (1998). Activation and detoxication of aflatoxin B_1. *Mutat Res*, 402:121–128. doi:10.1016/S0027-5107(97)00289-3 PMID:9675258

Hall AJ, Wild CP (1994). Epidemiology of aflatoxin-related disease. In: Eaton DL, Groopman JD, eds. *The Toxicology of Aflatoxins: Human Health, Veterinary, and Agricultural Significance*. San Diego: Academic Press, pp. 233–258.

Hendricks K (1999). Fumonisins and neural tube defects in South Texas. *Epidemiology*, 10:198–200. PMID:10069261

Hendrickse RG, Coulter JB, Lamplugh SM *et al.* (1982). Aflatoxins and kwashiorkor: a study in Sudanese children. *Br Med J (Clin Res Ed)*, 285:843–846. doi:10.1136/bmj.285.6345.843 PMID:6811035

Hussain SP, Schwank J, Staib F *et al.* (2007). *TP53* mutations and hepatocellular carcinoma: insights into the etiology and pathogenesis of liver cancer. *Oncogene*, 26:2166–2176. doi:10.1038/sj.onc.1210279 PMID:17401425

IARC (1986). Citrinin. In: *Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation*. Lyon: International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 40), pp. 67–82.

IARC (1993). Aflatoxins B_1, B_2, G_1, G_2, M_1. In: *Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins*. Lyon: International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 56), pp. 245–395.

IARC (2002). Fumonisin B_1. In: *Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*. Lyon: International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 82), pp. 301–366.

Iossifova Y, Reponen T, Daines M *et al.* (2008). Comparison of two analytical methods for detecting (1-3)-β-D-glucan in pure fungal cultures and in home dust samples. *Open Allergy J*, 1:26–34. doi:10.2174/1874838400801010026

Iverson F, Armstrong C, Nera E *et al.* (1995). Chronic feeding study of deoxynivalenol in B6C3F1 male and female mice. *Teratog Carcinog Mutagen*, 15:283–306. doi:10.1002/tcm.1770150606 PMID:8732880

Jiang Y, Jolly PE, Ellis WO *et al.* (2005). Aflatoxin B_1 albumin adduct levels and cellular immune status in Ghanaians. *Int Immunol*, 17:807–814. doi:10.1093/intimm/dxh262 PMID:15944194

Jiang Y, Jolly PE, Preko P *et al.* (2008). Aflatoxin-related immune dysfunction in health and in human immunodeficiency virus disease. *Clin Dev Immunol*, 2008:790309. doi:10.1155/2008/790309 PMID:18695741

Johnson DN, Egner PA, Obrian G *et al.* (2008). Quantification of urinary aflatoxin B_1 dialdehyde metabolites formed by aflatoxin aldehyde reductase using isotope dilution tandem mass spectrometry. *Chem Res Toxicol*, 21:752–760. doi:10.1021/tx700397n PMID:18266327

Kamataki T, Hashimoto H, Shimoji M *et al.* (1995). Expression of CYP3A7, a human fetus-specific cytochrome P450, in cultured cells and in the hepatocytes of p53-knockout mice. *Toxicol Lett*, 82-83:879–882. doi:10.1016/0378-4274(95)03526-5 PMID:8597156

Kamdem LK, Meineke I, Gödtel-Armbrust U *et al.* (2006). Dominant contribution of P450 3A4 to the hepatic carcinogenic activation of aflatoxin B_1. *Chem Res Toxicol*, 19:577–586. doi:10.1021/tx050358e PMID:16608170

Kirk GD, Lesi OA, Mendy M *et al.* (2005). 249(ser) TP53 mutation in plasma DNA, hepatitis B viral infection, and risk of hepatocellular carcinoma. *Oncogene*, 24:5858–5867. doi:10.1038/sj.onc.1208732 PMID:16007211

Krishnamachari KA, Bhat RV, Nagarajan V, Tilak TB (1975). Hepatitis due to aflatoxicosis. An outbreak in Western India. *Lancet*, 1:1061–1063. doi:10.1016/S0140-6736(75)91829-2 PMID:48730

Kristensen P, Andersen A, Irgens LM (2000). Hormone-dependent cancer and adverse reproductive outcomes in farmers' families–effects of climatic conditions favoring fungal growth in grain. *Scand J Work Environ Health*, 26:331–337. doi:10.5271/sjweh.550 PMID:10994799

Kristensen P, Irgens LM, Andersen A *et al.* (1997). Gestational age, birth weight, and perinatal death among births to Norwegian farmers, 1967–1991. *Am J Epidemiol*, 146:329–338. PMID:9270412

Kuniholm MH, Lesi OA, Mendy M *et al.* (2008). Aflatoxin exposure and viral hepatitis in the etiology of liver cirrhosis in The Gambia, West Africa. *Environ Health Perspect*, 116:1553–1557. doi:10.1289/ehp.11661 PMID:19057710

Lambert LA, Hines FA, Eppley RM (1995). Lack of initiation and promotion potential of deoxynivalenol for skin tumorigenesis in Sencar mice. *Food Chem Toxicol*, 33:217–222. doi:10.1016/0278-6915(94)00132-8 PMID:7896232

Langseth W, Elen O (1996). Differences between barley, oats, and wheat in the occurrence of deoxynivalenol and other trichothecenes in Norwegian grain. *J Phytopathol*, 144:113–118. doi:10.1111/j.1439-0434.1996.tb01498.x

Lappalainen S, Nikulin M, Berg S *et al.* (1996). *Fusarium* toxins and fungi associated with handling of grain on eight Finnish farms. *Atmos Environ*, 30:3059–3065. doi:10.1016/1352-2310(95)00449-1

Lewis L, Onsongo M, Njapau H *et al.* (2005). Aflatoxin contamination of commercial maize products during an outbreak of acute aflatoxicosis in eastern and central Kenya. *Environ Health Perspect*, 113:1763–1767. doi:10.1289/ehp.7998 PMID:16330360

Li FQ, Luo XY, Yoshizawa T (1999). Mycotoxins (trichothecenes, zearalenone and fumonisins) in cereals associated with human red-mold intoxications stored since 1989 and 1991 in China. *Nat Toxins*, 7:93–97. doi:10.1002/(SICI)1522-7189(199905/06)7:3<93::AID-NT45>3.0.CO;2-5 PMID:10647510

Li FQ, Yoshizawa T, Kawamura O *et al.* (2001). Aflatoxins and fumonisins in corn from the high-incidence area for human hepatocellular carcinoma in Guangxi, China. *J Agric Food Chem*, 49:4122–4126. doi:10.1021/jf010143k PMID:11513719

Liao CM, Chen SC (2005). A probabilistic modeling approach to assess human inhalation exposure risks to airborne aflatoxin B_1. *Atmos Environ*, 39:6481–6490. doi:10.1016/j.atmosenv.2005.05.054

Liu BH, Yu FY, Chan MH, Yang YL (2002). The effects of mycotoxins, fumonisin B_1 and aflatoxin B_1, on primary swine alveolar macrophages. *Toxicol Appl Pharmacol*, 180:197–204. doi:10.1006/taap.2002.9406 PMID:12009859

Lye MS, Ghazali AA, Mohan J *et al.* (1995). An outbreak of acute hepatic encephalopathy due to severe aflatoxicosis in Malaysia. *Am J Trop Med Hyg*, 53:68–72. PMID:7625536

Mally A, Dekant W (2009). Mycotoxins and the kidney: modes of action for renal tumor formation by ochratoxin A in rodents. *Mol Nutr Food Res*, 53:467–478. doi:10.1002/mnfr.200800149 PMID:19072886

Mantle PG, Faucet-Marquis V, Manderville RA *et al.* (2010). Structures of covalent adducts between DNA and ochratoxin A: a new factor in debate about genotoxicity and human risk assessment. *Chem Res Toxicol*, 23:89–98. doi:10.1021/tx900295a PMID:19928877

Marasas WF (2001). Discovery and occurrence of the fumonisins: a historical perspective. *Environ Health Perspect*, 109 Suppl 2:239–243. PMID:11359691

Marasas WFO, Riley RT, Hendricks KA *et al.* (2004). Fumonisins disrupt sphingolipid metabolism, folate transport, and neural tube development in embryo culture and in vivo: a potential risk factor for human neural tube defects among populations consuming fumonisin-contaminated maize. *J Nutr*, 134:711–716. PMID:15051815

Marin-Kuan M, Cavin C, Delatour T, Schilter B (2008). Ochratoxin A carcinogenicity involves a complex network of epigenetic mechanisms. *Toxicon*, 52:195–202. doi:10.1016/j.toxicon.2008.04.166 PMID:18649906

Martinez-Larranaga MR, Anadon A, Diaz MJ *et al.* (1999). Toxicokinetics and oral bioavailability of fumonisin B1. *Vet Hum Toxicol*, 41:357–362. PMID:10592940

Massart F, Meucci V, Saggese G, Soldani G (2008). High growth rate of girls with precocious puberty exposed to estrogenic mycotoxins. *J Pediatr*, 152:690–695, 695.e1. doi:10.1016/j.jpeds.2007.10.020 PMID:18410776

Mayer S, Curtui V, Usleber E, Gareis M (2007). Airborne mycotoxins in dust from grain elevators. *Mycotoxin Res*, 23:94–100. doi:10.1007/BF02946033

McCoy LF, Scholl PF, Sutcliffe AE *et al.* (2008). Human aflatoxin albumin adducts quantitatively compared by ELISA, HPLC with fluorescence detection, and HPLC with isotope dilution mass spectrometry. *Cancer Epidemiol Biomarkers Prev*, 17:1653–1657. doi:10.1158/1055-9965.EPI-07-2780 PMID:18628416

Meky FA, Hardie LJ, Evans SW, Wild CP (2001). Deoxynivalenol-induced immunomodulation of human lymphocyte proliferation and cytokine production. *Food Chem Toxicol*, 39:827–836. doi:10.1016/S0278-6915(01)00029-1 PMID:11434990

Meky FA, Turner PC, Ashcroft AE *et al.* (2003). Development of a urinary biomarker of human exposure to deoxynivalenol. *Food Chem Toxicol*, 41:265–273. doi:10.1016/S0278-6915(02)00228-4 PMID:12480302

Merrill AH Jr, Sullards MC, Wang E *et al.* (2001). Sphingolipid metabolism: roles in signal transduction and disruption by fumonisins. *Environ Health Perspect*, 109 Suppl 2:283–289. PMID:11359697

Miller JD (1994a). Mycotoxins. In: Rylander R, Pettersen Y, eds. *Handbook of Organic Dusts*. Boca Raton, FL: CRC Press, pp. 87–92.

Miller JD (1994b). Epidemiology of *Fusarium graminearum* diseases of wheat and maize. In: Miller JD, Trenholm HL, eds. *Mycotoxins in Grain: Compounds Other than Aflatoxin*. St Paul, MN: Eagan Press, pp. 19–36.

Miller JD, Sun M, Gilyan A *et al.* (2010). Inflammation-associated gene transcription and expression in mouse lungs induced by low molecular weight compounds from fungi from the built environment. *Chem Biol Interact*, 183:113–124. doi:10.1016/j.cbi.2009.09.023 PMID:19818335

Missmer SA, Suarez L, Felkner M *et al.* (2006). Exposure to fumonisins and the occurrence of neural tube defects along the Texas-Mexico border. *Environ Health Perspect*, 114:237–241. doi:10.1289/ehp.8221 PMID:16451860

Moore CA, Li S, Li Z *et al.* (1997). Elevated rates of severe neural tube defects in a high-prevalence area in northern China. *Am J Med Genet*, 73:113–118. doi:10.1002/(SICI)1096-8628(19971212)73:2<113::AID-AJMG2>3.0.CO;2-V PMID:9409858

Ncayiyana DJ (1986). Neural tube defects among rural blacks in a Transkei district. A preliminary report and analysis. *S Afr Med J*, 69:618–620. PMID:3704839

Ngindu A, Johnson BK, Kenya PR *et al.* (1982). Outbreak of acute hepatitis caused by aflatoxin poisoning in Kenya. *Lancet*, 1:1346–1348. doi:10.1016/S0140-6736(82)92411-4 PMID:6123648

Nikièma PN, Worrillow L, Traoré AS *et al.* (2004). Fumonisin contamination of maize in Burkina Faso, West Africa. *Food Addit Contam*, 21:865–870. doi:10.1080/02652030400004242 PMID:15666980

Okoth SA, Ohingo M (2004). Dietary aflatoxin exposure and impaired growth in young children from Kisumu District, Kenya: Cross sectional study. *Afr J Health Sci*, 11:43–54. PMID:17298116

Olsen JH, Dragsted L, Autrup H (1988). Cancer risk and occupational exposure to aflatoxins in Denmark. *Br J Cancer*, 58:392–396. doi:10.1038/bjc.1988.226 PMID:3179193

Omer RE, Kuijsten A, Kadaru AM *et al.* (2004). Population-attributable risk of dietary aflatoxins and hepatitis B virus infection with respect to hepatocellular carcinoma. *Nutr Cancer*, 48:15–21. doi:10.1207/s15327914nc4801_3 PMID:15203373

Pass C, MacRae VE, Ahmed SF, Farquharson C (2009). Inflammatory cytokines and the GH/IGF-I axis: novel actions on bone growth. *Cell Biochem Funct*, 27:119–127. doi:10.1002/cbf.1551 PMID:19330796

Pestka JJ (2008). Mechanisms of deoxynivalenol-induced gene expression and apoptosis. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 25:1128–1140. doi:10.1080/02652030802056626 PMID:19238623

Pestka JJ, Smolinski AT (2005). Deoxynivalenol: toxicology and potential effects on humans. *J Toxicol Environ Health B Crit Rev*, 8:39–69. doi:10.1080/10937400590889458 PMID:15762554

Pestka JJ, Zhou HR, Moon Y, Chung YJ (2004). Cellular and molecular mechanisms for immune modulation by deoxynivalenol and other trichothecenes: unraveling a paradox. *Toxicol Lett*, 153:61–73. doi:10.1016/j.toxlet.2004.04.023 PMID:15342082

Pfohl-Leszkowicz A, Manderville RA (2007). Ochratoxin A: An overview on toxicity and carcinogenicity in animals and humans. *Mol Nutr Food Res*, 51:61–99. doi:10.1002/mnfr.200600137 PMID:17195275

Qian GS, Ross RK, Yu MC *et al.* (1994). A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. *Cancer Epidemiol Biomarkers Prev*, 3:3–10. PMID:8118382

Qiu MF, Liu XM (2001). Determination of sphinganine, sphingosine and Sa/So ratio in urine of humans exposed to dietary fumonisin B_1. *Food Addit Contam*, 18:263–269. doi:10.1080/02652030117470 PMID:11304035

Rand TG, Sun M, Gilyan A *et al.* (2010). Dectin-1 and inflammation-associated gene transcription and expression in mouse lungs by a toxic (1,3)-β-D glucan. *Arch Toxicol*, 84:205–220. doi:10.1007/s00204-009-0481-4 PMID:19904525

Riley RT, Enongene E, Voss KA *et al.* (2001). Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. *Environ Health Perspect*, 109 Suppl 2:301–308. PMID:11359699

Ross PF, Rice LG, Plattner RD *et al.* (1991). Concentrations of fumonisin B_1 in feeds associated with animal health problems. *Mycopathologia*, 114:129–135. doi:10.1007/BF00437200 PMID:1886638

Rotter BA, Prelusky DB, Pestka JJ (1996). Toxicology of deoxynivalenol (vomitoxin). *J Toxicol Environ Health*, 48:1–34. doi:10.1080/009841096161447 PMID:8637056

Rylander R, Jacobs RR, eds (1994). *Organic Dusts: Exposure, Effects, and Prevention*. Boca Raton, FL: Lewis Publishers.

Sadler TW, Merrill AH Jr, Stevens VL *et al.* (2002). Prevention of fumonisin B_1-induced neural tube defects by folic acid. *Teratology*, 66:169–176. doi:10.1002/tera.10089 PMID:12353213

Schenker MB, Christiani D, Cormier Y *et al.* (1998). Respiratory health hazards in agriculture. *Am J Respir Crit Care Med*, 158:S1–S76. PMID:9817727

Sewram V, Mshicileli N, Shephard GS, Marasas WF (2003). Fumonisin mycotoxins in human hair. *Biomarkers*, 8:110–118. doi:10.1080/1354750031000081002 PMID:12775496

Sharma RP, Riley RT, Voss KA (2000). Cytokine involvement in fumonisin-induced cellular toxicity. In: de Koe WJ, Samson RA, van Egmond HP *et al.*, eds. *Mycotoxins and Phycotoxins in Perspective at the Turn of the Millennium, Proceedings of the Xth International IUPAC Symposium on Mycotoxins and Phycotoxins, Guarujá, Brazil*. Wageningen, Netherlands: Ponsen & Looyen, pp. 223–230.

Shephard GS, Thiel PG, Sydenham EW *et al.* (1994a). Determination of the mycotoxin fumonisin B_1 and identification of its partially hydrolysed metabolites in the faeces of non-human primates. *Food Chem Toxicol*, 32:23–29. doi:10.1016/0278-6915(84)90032-2 PMID:8132161

Shephard GS, Thiel PG, Sydenham EW *et al.* (1994b). Distribution and excretion of a single dose of the mycotoxin fumonisin B_1 in a non-human primate. *Toxicon*, 32:735–741. doi:10.1016/0041-0101(94)90342-5 PMID:7940579

Sieber M, Wagner S, Rached E *et al.* (2009). Metabonomic study of ochratoxin A toxicity in rats after repeated administration: phenotypic anchoring enhances the ability for biomarker discovery. *Chem Res Toxicol*, 22:1221–1231. doi:10.1021/tx800459q PMID:19610676

Snijders CHA (1994). Breeding for resistance to *Fusarium* diseases in wheat and maize. In: Miller JD, Trenholm HL, eds. *Mycotoxins in Grain: Compounds Other than Aflatoxin*. St Paul, MN: Eagan Press, pp. 37–58.

Sorenson WG (1999). Fungal spores: hazardous to health? *Environ Health Perspect*, 107 Suppl 3:469–472. doi:10.1289/ehp.99107s3469 PMID:10423389

Sorenson WG, Gerberick GF, Lewis DM, Castranova V (1986). Toxicity of mycotoxins for the rat pulmonary macrophage in vitro. *Environ Health Perspect*, 66:45–53. doi:10.1289/ehp.866645 PMID:2423320

Sorenson WG, Lewis DM (1996). Organic dust toxic syndrome. In: Howard D, Miller JD, eds. *The Mycota, Vol. VII*. Berlin: Springer-Verlag, pp. 159–172.

Stevens VL, Tang J (1997). Fumonisin B_1-induced sphingolipid depletion inhibits vitamin uptake via the glycosylphosphatidylinositol-anchored folate receptor. *J Biol Chem*, 272:18020–18025. doi:10.1074/jbc.272.29.18020 PMID:9218430

Stockmann-Juvala H, Savolainen K (2008). A review of the toxic effects and mechanisms of action of fumonisin B_1. *Hum Exp Toxicol*, 27:799–809. doi:10.1177/0960327108099525 PMID:19244287

Studer-Rohr I, Schlatter J, Dietrich DR (2000). Kinetic parameters and intraindividual fluctuations of ochratoxin A plasma levels in humans. *Arch Toxicol*, 74:499–510. doi:10.1007/s002040000157 PMID:11131029

Sun G, Wang S, Hu X *et al.* (2007). Fumonisin B1 contamination of home-grown corn in high-risk areas for esophageal and liver cancer in China. *Food Addit Contam*, 24:181–185. doi:10.1080/02652030601013471 PMID:17364919

Sundstøl-Eriksen G, Pettersson H (2003). Lack of de-epoxidation of type B trichothecenes in incubates with human faeces. *Food Addit Contam*, 20:579–582. doi:10.1080/0265203031000102573 PMID:12881132

Szuets P, Mesterhazy A, Falkay G, Bartok T (1997). Early telarche symptoms in children and their relations to zearalenone contamination in foodstuffs. *Cereal Res Commun*, 25:429–436.

Taranu I, Marin DE, Bouhet S *et al.* (2005). Mycotoxin fumonisin B_1 alters the cytokine profile and decreases the vaccinal antibody titer in pigs. *Toxicol Sci*, 84:301–307. doi:10.1093/toxsci/kfi086 PMID:15659571

Thelen K, Dressman JB (2009). Cytochrome P450-mediated metabolism in the human gut wall. *J Pharm Pharmacol*, 61:541–558. doi:10.1211/jpp.61.05.0002 PMID:19405992

Tomaszewski J, Mitурski R, Semczuk A *et al.* (1998). Tissue zearalenone concentration in normal, hyperplastic and neoplastic human endometrium [in Polish]. *Ginekol Pol*, 69:363–366. PMID:9695344

Torres OA, Palencia E, Lopez de Pratdesaba L *et al.* (2007). Estimated fumonisin exposure in Guatemala is greatest in consumers of lowland maize. *J Nutr*, 137:2723–2729. PMID:18029490

Turner PC, Burley VJ, Rothwell JA *et al.* (2008a). Deoxynivalenol: rationale for development and application of a urinary biomarker. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 25:864–871. doi:10.1080/02652030801895040 PMID:18569005

Turner PC, Burley VJ, Rothwell JA *et al.* (2008b). Dietary wheat reduction decreases the level of urinary deoxynivalenol in UK adults. *J Expo Sci Environ Epidemiol*, 18:392–399. doi:10.1038/sj.jes.7500611 PMID:17940556

Turner PC, Collinson AC, Cheung YB *et al.* (2007). Aflatoxin exposure in utero causes growth faltering in Gambian infants. *Int J Epidemiol*, 36:1119–1125. doi:10.1093/ije/dym122 PMID:17576701

Turner PC, Hopton RP, Lecluse Y *et al.* (2010). Determinants of urinary deoxynivalenol and de-epoxy deoxynivalenol in male farmers from Normandy, France. *J Agric Food Chem*, 58:5206–5212. doi:10.1021/jf100892v PMID:20349912

Turner PC, Moore SE, Hall AJ *et al.* (2003). Modification of immune function through exposure to dietary aflatoxin in Gambian children. *Environ Health Perspect*, 111:217–220. doi:10.1289/ehp.5753 PMID:12573908

Turner PC, Rothwell JA, White KLM *et al.* (2008c). Urinary deoxynivalenol is correlated with cereal intake in individuals from the United Kingdom. *Environ Health Perspect*, 116:21–25. doi:10.1289/ehp.10663 PMID:18197294

Ueno Y, Iijima K, Wang SD *et al.* (1997). Fumonisins as a possible contributory risk factor for primary liver cancer: a 3-year study of corn harvested in Haimen, China, by HPLC and ELISA. *Food Chem Toxicol*, 35:1143–1150. doi:10.1016/S0278-6915(97)00113-0 PMID:9449219

Van der Westhuizen L, Shephard GS, Burger HM *et al.* (2011). Fumonisin B_1 as a urinary biomarker of exposure in a maize intervention study among South African subsistence farmers. *Cancer Epidemiol Biomarkers Prev*, 20:483–489. doi:10.1158/1055-9965.EPI-10-1002

van der Westhuizen L, Shephard GS, Rheeder JP, Burger H-M (2010). Individual fumonisin exposure and sphingoid base levels in rural populations consuming maize in South Africa. *Food Chem Toxicol*, 48:1698–1703. doi:10.1016/j.fct.2010.03.047 PMID:20363278

Venter PA, Christianson AL, Hutamo CM *et al*. (1995). Congenital anomalies in rural black South African neonates–a silent epidemic? *S Afr Med J*, 85:15–20. PMID:7784908

Voss KA, Howard PC, Riley RT *et al*. (2002). Carcinogenicity and mechanism of action of fumonisin B_1: a mycotoxin produced by *Fusarium moniliforme* (= *F. verticillioides*). *Cancer Detect Prev*, 26:1–9. doi:10.1016/S0361-090X(02)00011-9 PMID:12088196

Wang LY, Hatch M, Chen CJ *et al*. (1996). Aflatoxin exposure and risk of hepatocellular carcinoma in Taiwan. *Int J Cancer*, 67:620–625. doi:10.1002/(SICI)1097-0215(19960904)67:5<620::AID-IJC5>3.0.CO;2-W PMID:8782648

WHO (1990). *Environmental Health Criteria 105: Selected Mycotoxins: Ochratoxins, Trichothecenes, Ergot*. Geneva: United Nations Environment Programme, International Labour Organization, World Health Organization.

WHO (1991). *Evaluation of Certain Food Additives and Contaminants: Thirty-seventh Report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva: World Health Organization (WHO Technical Report Series, No. 806).

WHO (2000a). *Environmental Health Criteria 219: Fumonisin B_1*. Marasas WFO, Miller JD, Riley RT, Visconti A, eds. Geneva: United Nations Environment Programme, International Labour Organization, World Health Organization. Available at http://libdoc.who.int/ehc/WHO_EHC_219.pdf.

WHO (2000b). *Evaluation of Certain Food Additives and Contaminants: Fifty-third Report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva: World Health Organization (WHO Technical Report Series, No. 896).

WHO (2001). *Safety Evaluation of Certain Mycotoxins in Food: Prepared by the Fifty-sixth Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. Geneva: World Health Organization (WHO Food Additives Series, No. 47).

WHO (2002). *Evaluation of Certain Mycotoxins in Food: Fifty-sixth Report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva: World Health Organization (WHO Technical Report Series, No. 906).

WHO (2007). *Evaluation of Certain Food Additives and Contaminants: Sixty-eighth Report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva: World Health Organization (WHO Technical Report Series, No. 947).

WHO (2008). *Safety Evaluation of Certain Food Additives and Contaminants: Prepared by the Sixty-eighth Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. Geneva: World Health Organization (WHO Food Additives Series, No. 59).

WHO (2011). *Safety Evaluation of Certain Contaminants in Food: Prepared by the Seventy-second Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. Geneva: World Health Organization (WHO Food Additives Series, No. 63).

Wicklow DT, Dowd PF, Tepaske MR, Gloer JB (1988). Sclerotial metabolites of *Aspergillus flavus* toxic to a detritivorous maize insect (*Carpophilus hemipterus*, Nitidulidae). *Trans Br Mycol Soc*, 91:433–438. doi:10.1016/S0007-1536(88)80119-0

Wicklow DT, Shotwell OL (1983). Intrafungal distribution of aflatoxins among conidia and sclerotia of *Aspergillus flavus* and *Aspergillus parasiticus*. *Can J Microbiol*, 29:1–5. doi:10.1139/m83-001 PMID:6403210

Wild CP, Gong YY (2010). Mycotoxins and human disease: a largely ignored global health issue. *Carcinogenesis*, 31:71–82. doi:10.1093/carcin/bgp264 PMID:19875698

Wild CP, Rasheed FN, Jawla MF *et al*. (1991). In-utero exposure to aflatoxin in West Africa. *Lancet*, 337:1602. doi:10.1016/0140-6736(91)93295-K PMID:1675725

Wild CP, Turner PC (2002). The toxicology of aflatoxins as a basis for public health decisions. *Mutagenesis*, 17:471–481. doi:10.1093/mutage/17.6.471 PMID:12435844

Williams JH, Phillips TD, Jolly PE *et al*. (2004). Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences, and interventions. *Am J Clin Nutr*, 80:1106–1122. PMID:15531656

Wojnowski L, Turner PC, Pedersen B *et al*. (2004). Increased levels of aflatoxin-albumin adducts are associated with CYP3A5 polymorphisms in The Gambia, West Africa. *Pharmacogenetics*, 14:691–700. doi:10.1097/00008571-200410000-00007 PMID:15454734

Wu HC, Wang Q, Yang HI *et al*. (2009). Aflatoxin B_1 exposure, hepatitis B virus infection, and hepatocellular carcinoma in Taiwan. *Cancer Epidemiol Biomarkers Prev*, 18:846–853. doi:10.1158/1055-9965.EPI-08-0697 PMID:19273485

Wu X, Murphy P, Cunnick J, Hendrich S (2007). Synthesis and characterization of deoxynivalenol glucuronide: its comparative immunotoxicity with deoxynivalenol. *Food Chem Toxicol*, 45:1846–1855. doi:10.1016/j.fct.2007.03.018 PMID:17507135

Xu L, Cai Q, Tang L *et al*. (2010). Evaluation of fumonisin biomarkers in a cross-sectional study with two high-risk populations in China. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 27:1161–1169. doi:10.1080/19440049.2010.481638 PMID:20589550

Zinedine A, Soriano JM, Moltó JC, Mañes J (2007). Review on the toxicity, occurrence, metabolism, detoxification, regulations and intake of zearalenone: an oestrogenic mycotoxin. *Food Chem Toxicol*, 45:1–18. doi:10.1016/j.fct.2006.07.030 PMID:17045381