Review Article

Mycotoxins in the food chain: human health implications

Wayne L Bryden PhD

School of Animal Studies, University of Queensland, Gatton, QLD 4343 Australia

Mycotoxins are secondary fungal metabolites that can be produced in crops and other food commodities both pre- and post-harvest. When ingested, mycotoxins may cause a mycotoxicosis which can result in an acute or chronic disease episode. Chronic conditions have a much greater impact, numerically, on human health globally. Reduced growth and development, immunosupression and cancer are chronic effects that have a higher incidence following continual exposure to low level mycotoxin ingestion as is experienced in many developing countries. It has been estimated that 25% of the world's crops are affected by mould or fungal growth and as stable, natural contaminants of the food chain, mycotoxin reduction requires a multifaceted approach, including farmers, government agencies, food processors and scientists. This can have a significant impact on the cost of food production. International regulatory standards for mycotoxins in food commodities determines the extent of global trade in contaminated commodities.

Key Words: mycotoxin, mycotoxicosis, food chain, human health, fungi

Introduction

It has been estimated that 25% of the world's crops are affected by mould or fungal growth.[1] Fungal spoilage of crops can have serious economic consequences and commodities may be contaminated with toxic fungal secondary metabolites known as mycotoxins. Human exposure to mycotoxins may result from consumption of plant derived foods that are contaminated with toxins, the carryover of mycotoxins and their metabolites into animal products such as milk, meat and eggs or exposure to air and dust containing toxins.[2,3] Human food can be contaminated with mycotoxins at various stages in the food chain and the three most important genera of mycotoxigenic fungi are *Aspergillus, Fusarium and Penicillium*. The principal classes of mycotoxins produced by these genera are: aflatoxins (*Aspergillus*), ochratoxins (*Aspergillus* and *Penicillium*) and trichothecenes and fumonisins (*Fusarium*). The disease resulting from mycotoxin exposure is a mycotoxicosis.

Deoxynivalenol (DON) is the trichothecene most often encountered in the field.[4] Fumonisins[5] and aflatoxin B_1 are carcinogenic.[6] There is now overwhelming epidemiological evidence[7] that aflatoxin B_1 consumption contributes significantly to the high incidence of human liver cancer in many developing countries[8], especially in individuals infected with hepatitis B or C virus. Ochratoxin A is nephrotoxic and a possible cause of urinary tract tumors and Balkan – endemic nephropathy.[6] There are a number of other mycotoxins that cause disease and these include zearalenone (*Fusarium*), an oestrogenic mycotoxin[9] and ergot alkaloids produced on cereal grains (*Claviceps*) or by endophytic fungi (*Neophytodium*).[10] The mechanism(s) of action of these mycotoxins is generally well characterised.[11]

There has been a major international research effort, aimed at the identification and quantification of mycotoxins and evaluation of their biological effects in humans and animals. The impetus for the effort is the reports of acute mycotoxicoses in humans, the implication of mycotoxins in chronic human disease, especially cancer and the negative economic effects of animal mycotoxicoses and crop losses due to mycotoxin contamination.[12] However, the mycotoxins that are likely to be encountered by human populations differ between countries. This reflects different crops, agronomic practices and climatic conditions which dictate the fungi that are present in a farming system. Two recent books give a good overview of the significance of mycotoxins in different regions of the world[13] and in European countries.[14] This review describes the impact of mycotoxin contamination of the human food chain.

Mycotoxin exposure and detection

A wide range of commodities can be contaminated with mycotoxins (Table 1) both pre- and post-harvest.[3] Aflatoxins are found in maize and peanuts as well as in tree nuts and dried fruits. Ochratoxin A is found mainly in cereals but significant levels of contamination may also occur in wine, coffee, spices and dried fruits. Fumonisins are found mainly in maize and maize based products. Tricothecenes are chiefly associated with grain as is zearalenone. Available evidence suggests that tissue accumulation of mycotoxins or their metabolites is very low and that residues are excreted in a few days.

Corresponding Author: Professor WL Bryden, School of Animal Studies, University of Queensland, Gatton, QLD 4343 Australia
Tel: +61 7 54601257 Fax: +61 7 54601444
Email: w.bryden@uq.edu.au

Table 1. Some human diseases in which mycotoxins have been implicated

Disease	Mycotoxin source	Fungus
Akakabio-byo	Wheat, barley, oats, rice	*Fusarium spp.*
Alimentary toxic aleukia	Cereal grains (toxic bread)	*Fusarium spp.*
Balkan nephropathy	Cereal grains	*Penicillium spp.*
Cardiac beriberi	Rice	*Aspergillus spp., Penicillium spp.*
Celery harvester's disease	Celery (Pink rot)	*Sclerontinia*
Ergotism	Rye, cereal grains	*Claviceps purpurea*
Hepatocarcinoma	Cereal grains, peanuts	*Aspergillus flavus, A. parasiticus*
Kwashiorkor	Cereal grains	*Aspergillus flavus. A. parasiticus*
Neural tube defects	Maize	*Fusarium verticillioides, F.proliferatum*
Oesophageal tumors	Corn	*Fusarium verticilloides, F.proliferatum*
Onyalai	Millet	*Phoma sorghina*
Reye's syndrome	Cereal grains (grain dust)	*Aspergillus*
Stachybotryotoxicosis	Cereal grains, (grain dust)	*Stachybotrys atra*

The hydroxylated metabolite of aflatoxin B_1, aflatoxin M_1 is excreted into milk from 1 to 6% of dietary intake.[15,16] Ochratoxin A has been detected in blood, kidneys, liver and muscle tissue from pigs in several European countries.[17,18] Residues of cyclopiazonic acid (CPA), a co-contaminant with aflatoxin, have been found in meat, milk and eggs.[19] After an extensive review of the literature, Pestka[20] concluded that trace levels of mycotoxins and their metabolites may carry over into the edible tissue (meat) of food producing animals. However, he concluded that to date there is no evidence to suggest that the levels of transmitted mycotoxins pose a threat of acute toxicity.

Ideally determination of exposure and diagnosis of a mycotoxicosis should depend upon the absence of other readily diagnosed diseases and the finding of a mycotoxin in suspect food.[21] It is not enough to have isolated the fungus as one must be able to demonstrate the presence of biologically effective concentrations of the toxin. One difficulty in relying upon chemical analysis of food is that of obtaining a sample representative of the food which was consumed. Another major difficulty is analysis because of the vast array of chemical compounds that are mycotoxins. Detection of many of these compounds requires very sophisticated and expensive laboratory equipment and very skilled analytical chemists.[22] Application of immunological methods to mycotoxin analysis however, has seen the development of immunoassays which are rapid, repeatable and sensitive. Mycotoxins are non-antigenic, but an antibody response can be elicited to the toxin after conjugation to a protein or polypeptide carrier. The availability of antibodies to a number of mycotoxins has allowed the development of enzyme-linked immunosorbent assays (ELISA) for the detection of toxins in food commodities and residual mycotoxins or metabolites in body fluids or tissues.[23] Commercial ELISA kits, which are suitable for field use, have become available for aflatoxins, zearalenone, deoxynivalenol, ochratoxins and fumonisins.

The difficulty of relying on analytical data for determining mycotoxin exposure of human populations is the heterogeneous distribution of mycotoxins in food commodities, the time lag between toxin intake and the development of chronic disease and the inaccuracies of dietary questionnaires for determining food intake data. A more reliable and relevant indicator of individual exposure can be provided by biomarkers which can be determined in urine or blood. Biomarkers include parent compounds and metabolites or macromolecular adducts. An understanding of aflatoxin metabolism has allowed the development of a number of biomarkers, especially the aflatoxin albumen adduct that is measured in serum[24]. This marker has been used extensively to assess human exposure in epidemiological studies. Recently there has been demonstration of a specific mutation in the TP53 gene and this has contributed significantly to the identification of aflatoxin B_1 as a human carcinogen.[24]

Mycotoxins and human disease

Mycotoxins have been associated with a number of human diseases, some acute and others chronic and a number of these diseases are listed in Table 1. Although mycotoxins have been implicated in these human illnesses, only rarely has a direct connection been established and much remains to be done to establish the aetiology of many suspect human mycotoxicoses. Beardall and Miller[25] have given a very detailed account of human illnesses that have been associated with mycotoxin ingestion. The many interacting factors in the pathogenesis of a mycotoxicosis (Fig 1) make diagnosis difficult as does confirming mycotoxin exposure. Chronic intake is the most widespread form of mycotoxin exposure and the consequences of this for human health are discussed below. Throughout history there are instances, especially following flood, famine and war, when acute mycotoxicoses have devastated human populations.[26]

Acute disease episodes have occurred recently following high levels of mycotoxin ingestion. Acute liver disease has been reported in India[27], Malaysia[28] and Kenya[29] following aflatoxin consumption. Bhat *et al*[30] reported gastrointestinal pain and diarrhoea in an outbreak of foodbourne disease associated with high fumosin intake in India. Gastrointestinal symptoms including vomiting were apparent in humans after high levels of DON intake

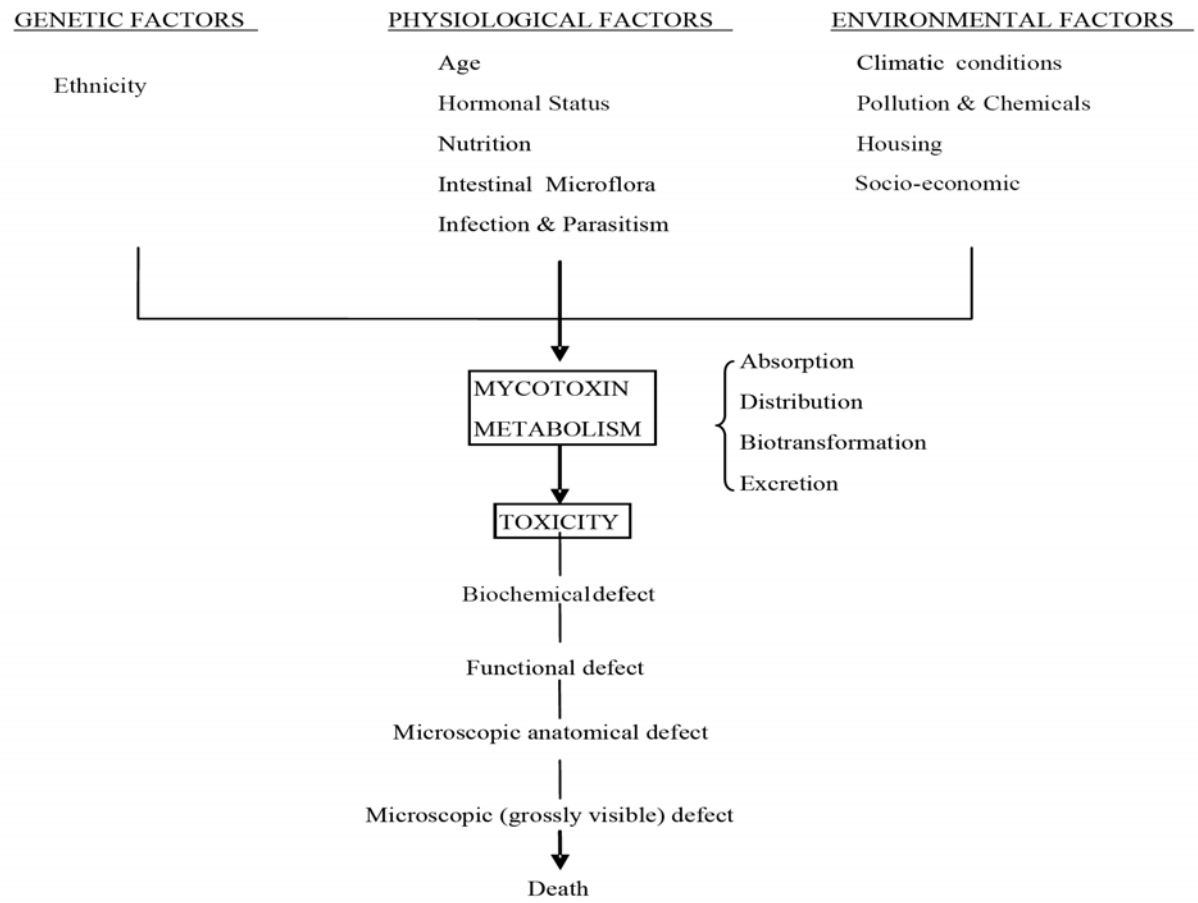

Figure 1. A simplified representation of some general relationships in a mycotoxicosis. Adapted from Bryden[62]

in China.[31] A similar outbreak was observed in India when local villages consumed rain damaged wheat that contained DON and other trichotheces.[32] There have been suggestions that zearalenone caused premature menarche in young girls in South America but these reports have not been substantiated.[9] Since the middle ages there have been episodes of ergotism reported in human populations in Europe and North America.[26] The most recent outbreak of gangrenous ergotism was in Ethiopia in 1978.[33]

Chronic effects of mycotoxins in human populations

In many regions of the world, dietary staples, especially cereal grains contain low levels of mycotoxins. The impact of regular low level intake of mycotoxins on human health is likely to be significant with a number of possible consequences including impaired growth and development, immune dysfunction and the disease consequences of alterations in DNA metabolism.

Growth and development

Numerous animal studies have shown that one of the first effects of mycotoxin ingestion is reduced feed intake and growth.[34] Gong *et al*[35] conducted a cross-sectional epidemiological survey in West Africa in which they determined the aflatoxin exposure of children between 9 months and 5 years of age and examined their growth, development and height against a WHO reference population. The study revealed a very strong association between exposure to aflatoxin in the children and both stunting and being underweight. Both conditions reflect significant malnutrition and exposure of the children to aflatoxin *in utero* and subsequently after birth[35]. The children were also co-exposed to a number of infectious diseases and it is likely that the exposure to disease and aflatoxin would significantly compromise growth and development through reduced food intake and also the repartitioning of nutrients to maintain an upregulated immune system and away from growth and development[36]. There are reports linking kwashiorkor, a disease of malnutrition, to aflatoxin exposure.[37,38] However, it has not been established if the higher occurrence of aflatoxin adducts in children suffering from kwashiorkor is a cause or a consequence of the disease.

Immunosupression

Aflatoxin, trichothecenes, ochratoxin A, sterigmatocystin, rubratoxin, fumonisins, zearalenone, patulin, citrinin, wortmannin, fusarochromanone, gliotoxin and ergot alkaloids have been shown to cause immunosuppression and increase the susceptibility of animals to infectious disease.[3] Substantial evidence exists that mycotoxins can be immunotoxic and exert effects on cellular responses, humoral factors and cytokine mediators of the immune system.[39,40] The effects on immunity and resistance are often difficult to recognise in the field because signs of disease are associated with the infection rather than the toxin that predisposed the individual to infection through decreased resistance and/or reduced vaccine or drug efficacy.[40] Moreover, in animal models, immunosuppressant effects of toxins occurs at lower levels of intake than do the toxin's effects on other parameters of toxicity such as

feed intake and growth rate.

Recent studies in Gambian children[41] and in Ghanaian adults[42] show a strong association between aflatoxin exposure and reduced immunocompetence suggesting that aflatoxin ingestion decreases resistance to infection in human populations. Studies by Pestka and his colleagues[43] have shown that DON can both stimulate and suppress the immune system. This has been demonstrated with the effect of DON on dysregulation of IgA and the development of kidney disease in animal models that closely resembles human glomerulo-nephritris IgA nephropathy.

Carcinogenicity, mutagenicity and teratogenicity

There has been extensive evaluation of the capacity of mycotoxins to interact with DNA and modify its action.[11] Mycotoxins may be carcinogenic (eg. fumonizins), carcinogenic and teratogenic (eg. ochratoxin) or carcinogenic, mutagenic and teratogenic (eg. aflatoxin)[11]. When it was first appreciated some 40 years ago that aflatoxin was a potential carcinogen, it was this finding that gave significant impetus for the research that has subsequently been conducted to define the role of mycotoxins in human and animal disease. Wild and Turner[24] have extensively reviewed the mechanism of toxicity and carcinogenicity of aflatoxins.

There is now a significant body of evidence demonstrating human exposure *in utero* to a number of mycotoxins but the relevance of this exposure to birth defects or impaired embryonic developed has received relatively little attention. Cawdell-Smith *et al*[44] were able to identify some 40 mycotoxins that had been shown to be teratogenic and/or embryotoxic in animal models. However, most of these mycotoxins have only been evaluated in rapid screening assays that did not seek to delineate their potential teratoenicity during early pregnancy. Aflatoxin B1, ochratoxin A, rubratoxin B, T-2 toxin, sterigmatocystin and zearalenone have been shown experimentally to be teratogenic in at least one mammalian species. Recent epidemiological investigations of human populations in Texas, China, Guatemala and southern Africa that rely on foods prepared from maize, which is often contaminated with fumonisins, found a significantly higher incidence of neural tube defects in babies.[45] Interestingly, fumonisins perturb folate metabolism[46] and folate deficiency is a known cause of neural tube defects in human embryos.

Strategies for reducing mycotoxin risk

In addition to the genetic capacity of the fungus, mycotoxin production depends on many factors. Moisture and temperature are two factors that have a crucial effect on fungal proliferation and toxin elaboration. In the preharvest period, crops that have experienced significant stress whether it be from drought or insects can succumb to fungal invasion. Prior to harvest, preventive measures begin with good agronomic practices including cultivating to improve plant vigour, the judicious use of insecticides and fungicides to reduce insect and fungal infestation, irrigation to avoid moisture stress, harvesting at maturity and breeding programmes to improve genetic resistance to fungal attack.[47] During the post-harvest period, control of moisture and temperature of the stored commodity will largely determine the degree of fungal activity[48]. Moisture content depends mostly on water content at harvest and can be modified by drying, aerating, and turning of the grain before or during storage. Apart from methods that modify the fungal environment many compounds are available that will inhibit mould growth. Organic acids, especially propionic acid, form the basis of many commercial antifungal agents used in the animal feed industry.[47] Once formed, mycotoxins are very stable but many processing practices reduce the level of contamination as food commodities are processed prior to packaging for human consumption.[3]

Approaches to detoxification of mycotoxin contaminated grain have included physical, chemical and biological treatments.[3,49] Methods include dehulling, washing, density segregation of contaminated from non-contaminated kernels, food processing practices and treatment with chemicals including sodium bisulfite, ozone, and ammonia. A diverse variety of substances have been investigated as potential mycotoxin-binding agents[50,51] including synthetic cation or anion exchange zeolites, bentonite, hydrated sodium calcium aluminosilicate (HSCAS) and yeast cell wall preparations. HSCAS is a high affinity adsorbent for aflatoxins, capable of forming a very stable complex with the toxin and hence reducing its bioavailability and thereby diminishing the adverse effects and tissue accumulation of the toxin[52] A yeast cell wall-derived glucomannan prepared from *Saccharomyces cerevisiae* has been shown to efficiently adsorb aflatoxins, zearalenone and fumonisins[53] A feed additive that is a stabilised bacterial species of *Eubacterium* can detoxify trichothecenes by removal of the epoxide group *in vivo* and is a novel approach to mycotoxin decontamination.[54]

The foregoing discussion highlights the need to develop strategies that minimise the production of mycotoxins in food commodities both before and after harvest. A knowledge of fungal ecology, toxicgenicity and food and animal production systems is required. Such an interdisciplinary understanding supports the principles of the HACCP (Hazard Analysis and Critical Control Points) approach for mycotoxin management.[55] However, in developing countries, these processes may not be economically feasible in many high risk regions and that is why it is often more prudent to look for other intervention strategies. In many African countries[29] the mycotoxin problem is related to insufficient food and the reliance on a single crop (eg. maize). In these situations, with high daily intake of the cereal, only moderate mycotoxin contamination levels are required to exceed recommended tolerable intake for mycotoxins. It has been demonstrated in animal studies and in some human studies that oltipraz is an effective agent in blocking aflatoxin adduct formation and it is believed that this predominantly reflects induction of aflatoxin detoxifying enzymes.[24] Nevertheless, the multi-phase and long term development of hepatocellular carcinoma (HCC) may limit the effectiveness of chemotherapeutic agents It was the considered view of WHO that because of the interaction of aflatoxin with hepatitis B virus in the development of HCC, the most

cost effective approach to intervention is vaccination against viral infection.[8]

Economic impact

Mycotoxin contamination of the food chain has a major economic impact. However, the insidious nature of many mycotoxicoses make it difficult to estimate incidence and cost.[47] In addition to crop losses and reduced animal productivity, costs are derived from the efforts made by producers and distributors to counteract their initial loss, the cost of improved technologies for production, storage and transport, the cost of analytical testing, especially as detection or regulations become more stringent and the development of sampling plans.[56] There is also a considerable cost to society as a whole, in terms of monitoring; extra handling and distribution costs; increased processing costs and loss of consumer confidence in the safety of food products. It is estimated that in developing countries, the greatest economic impact is associated with human health.[12] Delineating economic impact reflects the complexity of a mycotoxin contamination within the food chain. There is a clear need to protect consumers through regulations but at what cost?

A comprehensive risk and economic analysis of lowering the acceptable levels for fumonisins and aflatoxin in world trade demonstrated that the United States would experience significant economic losses from tighter controls.[57] The developing countries, China and Argentina were more likely to experience greater economic losses than sub-Sahara Africa. The disturbing outcome of this detailed analysis was that tighter controls were unlikely to decrease health risks and may have the opposite effect.[57] In other words, very stringent international trade regulations could lead to the situation where exporting countries, especially developing countries, would retain higher risk commodities which would subsequently be available for their own populations; communities which are already exposed to higher levels of mycotoxins than consumers in developed countries.

Concluding comments

Mycotoxins are a food safety risk globally. International risk assessments have been performed by JECFA[58,59] for aflatoxin B_1, aflatoxin M_1, DON, fumonisins, ochratoxin A, T-2 toxin and HT-2 toxin. These analyses indicate that health risks from mycotoxins are generally orders of magnitude lower in developed countries that for populations from developing regions. The scope of the mycotoxin problem is readily understood when it is appreciated that there are many thousand secondary fungal metabolites[60], the vast majority of which have not been tested for toxicity or associated with disease outbreaks. In developing countries it is likely that consumers will be confronted with a diet that contains a low level of toxin and in many cases, there may be other toxins present. For example, aflatoxins, fumonisins, DON and zearalenone may occur together in the same grain; many fungi produce several mycotoxins simultaneously, especially *Fusarium* species.[61] Co-occurrence of mycotoxins is of special concern, for instance, in the case of fumonisins (a potent cancer promoter) and aflatoxin (a potent human carcinogen) where a complimentary toxicity mechanism of action occurs.[11] In Africa and Asia the co-occurence of these mycotoxins is common and a significant percentage of the population is infected with for Hepatitis B or C which leads to the conclusion that mycotoxins in these regions can have devastating human health effects. Implicit with these conclusions are the existence of syndromes of apparently unknown aetiology and epidemiology that may involve mycotoxins and the difficulty of establishing "no effect" levels for mycotoxins.

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