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Gordon S. Shephard

PROMEC Unit, Medical Research Council, PO Box 19070, Tygerberg 7505,
South Africa, e-mail: gordon.shephard@mrc.ac.za

FUSARIUM MYCOTOXINS AND HUMAN HEALTH

REVIEW

ABSTRACT

Species within the genus *Fusarium* produce a diverse range of mycotoxins, many of which have significant impacts on human health. Of the five generally recognised major mycotoxins, three (fumonisins, deoxynivalenol (DON) and zearalenone (ZON)) are produced by Fusaria. Apart from DON, other trichothecenes such as T-2 toxin, have received considerable international attention due to their impact on human health. The fumonisins, which occur ubiquitously in maize and its products, have been linked to oesophageal cancer, liver cancer and neural tube defects. DON, a frequent contaminant of maize, wheat and their products, although showing no carcinogenic potential, is immunomodulatory and produces emesis and growth retardation in animals. ZON is a naturally occurring endocrine disrupting chemical. Acute exposure to these mycotoxins has in each case been linked to outbreaks of human disease – gastro-intestinal effects in the case of fumonisins and DON, and precocious pubertal changes in the case of ZON. Concern over their toxicological effects has led to risk assessments by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which has set maximum tolerable daily intakes (TDI) of 2 µg/ kg body weight (bw) for fumonisins and 0.5 µg/kg bw for ZON. The initial TDI set for DON, namely 1 µg/kg bw has recently been updated by JECFA to include both 3 - and 15-acetylDON. Apart from the above mycotoxins, a number of other secondary metabolites (moniliformin, beauvericin and fusaproliferin) are produced by different Fusaria and their effects on human health, either alone or in combination with other mycotoxins, is largely unexplored.

Key words: cancer, deoxynivalenol, Fumonisin, T-2 toxin, trichothecenes zearalenone

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INTRODUCTION

Fungal species within the genus *Fusarium* occur widely, mainly in cereal crops grown in a range of different climatic zones. Many of these species produce a specific mycotoxin or suite of mycotoxins, the ingestion of which, on an acute or chronic basis, has been implicated in a variety of animal and human health problems. Consequently, *Fusarium* mycotoxin contamination is a potential concern for the quality of all the various commercial grains. It has been suggested that there are five agriculturally important mycotoxins whose known or suspected health effects are of a nature to warrant significant attention (Miller, 1998). These are aflatoxin, fumonisin, deoxynivalenol, ochratoxin A and zearalenone. Of these, aflatoxins are produced by *Aspergillus* species, ochratoxin A by both *Aspergillus* and *Penicillium* species, whereas the other three are *Fusarium* mycotoxins. Deoxynivalenol is the most widespread of the trichothecenes, a major group of mycotoxins.

The aim of this review is to highlight the implications for human health caused by consumption of food supplies contaminated with specific *Fusarium* toxins.

FUMONISINS

The fumonisins are mainly produced by *Fusarium verticillioides* (Sacc.) Nirenberg and *F. proliferatum* (Matsushima) Nirenberg and are universal contaminants of maize and maize-based products (Shephard *et al*., 1996). Little data has been produced for their natural occurrence on other cereals and, in some cases, initial reports have failed to be confirmed (Shephard *et al*., 2005). Although at least 28 chemical analogues have been identified (Rheeder *et al*., 2002), the major fumonisins belong to the B series. Fumonisin B_1 (FB_1) is the most abundant (generally about 70% of the total fumonisin contamination) and it normally co-occurs with lesser amounts of fumonisin B_2 (FB_2) and B_3 (FB_3) (Shephard *et al*., 1996).

The acute ingestion of fumonisins from mouldy maize and sorghum has been linked to an outbreak in the Deccan Plateau in southern India of food-borne disease characterized by borborygmy, abdominal pain and diarrhoea (Bhat *et al*., 1997). Chronic ingestion of fumonisins has been linked as one possible risk factor for the occurrence of oesophageal cancer in areas such as the former Transkei region of South Africa, where fumonisin exposure from contaminated maize is high (Rheeder *et al*.,1992). Similar associations have been reported in maize grown in Linxian County, Henan Province and Cixian County, Hebei Province, China (Zhang *et al*., 1997), maize grown in Huaian County, Jiangsu Province, China (Sun *et al*., 2007), maize grown in Santa Catarina state, southern Brazil (Van der Westhuizen *et al*., 2003) and in polenta produced in northern Italy (Pascale *et al*., 1995). Fumonisins have also been linked as a risk factor

for primary liver cancer in China (Sun *et al*., 2007; Ueno *et al*., 1997). The International Agency for Research on Cancer (IARC) has classified FB_1 as a possible human carcinogen (group 2B) (IARC, 2002).

A cluster of cases of neural tube defects in infants in southern Texas has provided epidemiological evidence that fumonisins may have played a role in these cases in which mothers are presumed to have consumed fumonisin contaminated food (Missmer *et al*., 2006). It is also known that other areas of the world where fumonisin exposure is high, such as former Transkei region in South Africa and regions in northern China, have elevated incidences of neural tube defects (Marasas *et al*., 2004). Support for this association has come from evidence that fumonisins, via their depletion of sphingolipids, interfere with the folate receptor, inhibiting uptake of folate, the cellular deficiency of which is a known cause of NTDs (Stevens and Tang, 1997). Further evidence for these interactions comes from a dose-dependent rise in NTDs in experimental mice, an effect that could be prevented by folate supplementation (Gelineau-van Waes *et al*., 2005).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated fumonisins and have established a provisional maximum tolerable daily intake (PMTDI) of 2 μg/kg body weight/day for FB_1, FB_2 and FB_3, either alone or in combination, based on a no observed effect level (NOEL) of 0.2 mg/kg body weight/day for renal toxicity and a safety factor of 100 (Bolger *et al*., 2001). Based on this criterion, many African communities reliant on subsistence farming of maize, have fumonisin intakes above this internationally recognized value (Shephard *et al*., 2007a). These excessively high exposures are due both to relatively high contamination levels and the culture of a mono-cereal diet in which maize is consumed on average at levels of 400-500 g/per person/day. Investigations of the health implications of these high exposures have been hampered by the lack of an adequate individual biomarker of fumonisin exposure. Fumonisins are potent inhibitors of *de novo* sphingolipid biosynthesis, via their inhibition of the enzyme sphinganine (sphingosine) *N*-acyl transferase (ceramide synthase), which acylates the amino group of the sphingoid base sphinganine (Sa) with a fatty acid moiety to yield dihydroceramide. This intermediate is converted to ceramide and finally to the more complex sphingolipids, such as sphingomyelin and glycosphingolipids, by the addition of the appropriate headgroup (Merrill 1991). The turnover of these complex sphingolipids leads to the formation of the base sphingosine (So). In this biochemical pathway, fumonisin exposure leads to an elevation in sphinganine levels and in the ratio of sphinganine to sphingosine, which can be measured in urine and serum and used as a biomarker of fumonisin exposure (Shephard *et al*., 2007b). This disruption of the sphingolipid biosynthetic pathway has been observed to occur in a dose- and time-dependent manner in cell cultures and animal studies, but has been shown to be insensitive at the exposure levels encountered in subsistence farming communities (Van der Westhuizen *et al*., 2010). More recently, a

urinary biomarker, FB_1 in urine, has been developed for assessing fumonisin exposure in humans (Gong *et al*., 2008).

TRICHOTHECENES

Deoxynivalenol (DON)

DON is a type B trichothecene and is a common contaminant of many cereals including wheat, where it is produced by *Fusarium graminearum* Schwabe and *F. culmorum* (W.G. Smith) Saccardo, and maize, where it is produced by *F. graminearum*. The primary toxic effect of trichothecenes including DON is the inhibition of protein synthesis, the potency depending on structural features of the trichothecene moiety. Ingestion of DON by animals can lead to acute gastrointestinal symptoms such as vomiting (emesis) (and hence its common name of vomitoxin), feed refusal and bloody diarrhoea (CAST, 2003). The acute effects of DON in humans are similar to those in animals and involve adverse gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain, headache, dizziness and fever, which can appear 30 minutes after exposure. DON has been implicated in a number of incidents of human intoxication in Asia. In the period 1961 to 1985, about 35 outbreaks of acute food-borne illness were attributed to exposure to DON present in scabby wheat and mouldy maize (Luo, 1988). In the Kashmir valley of India in 1987, an outbreak of illness involving vomiting and dizziness among approximately 50 000 people was attributed to consumption of bread made from rain-damaged wheat that contained several trichothecenes, including DON (Bhat *et al*., 1989). Reports of scabby grain intoxication or red mold toxicosis in India, Japan and Korea involving gastrointestinal symptoms have been associated with ingestion of *Fusarium*-infected grain, particularly *F. graminearum* and hence with *Fusarium* mycotoxins, including DON (Canady *et al*., 2001a). More recently, a number of mycotoxins, including the *Fusarium* toxins fumonisin, DON and T-2 toxin, have been suggested as potential risk factors for induction or persistence of chronic intestinal inflammatory diseases such as celiac disease, Crohn's disease and ulcerative colitis (Maresca and Fantini, 2010).

The interaction of DON with the immune system is complex as it can be both immunostimulatory and immunosuppressive, depending on dose, exposure frequency and timing of the functional immune assay (Pestka, 2008). The dysregulation of serum IgA levels and deposition of IgA immune complexes in the kidney of mice fed DON closely resembles the common human glomerulonephritis, IgA nephropathy. The evaluation of DON by IARC concluded that there was insufficient evidence for the carcinogenicity of DON in experimental animals, a conclusion supported by the two JECFA evaluations described below (IARC, 1993).

JECFA evaluated DON in 2001 and determined a PMTDI of 1 µg/kg body weight/day, based on a NOEL OF 100 µg/kg body weight/day based on absence of biologically significant toxicological changes in a 2-year feeding study in mice and a safety factor of 100 (Canady *et al*., 2001a). Consideration of the WHO GEMS/Food regional diets by this JECFA and some national surveys indicated that this exposure level is approached and surpassed in a number of regional and specific population categories. DON was re-evaluated by JECFA in 2010 (JECFA, 2010). The previous findings of a lack of evidence for carcinogenicity and for the level of the PMTDI were confirmed. In addition, evidence for the natural occurrence of 3-acetyl-DON and 15-acetyl-DON and their rapid hydrolysis to DON in the gut was considered sufficient for the inclusion of the acetyl derivatives in the previously established PMTDI to form a group PMTDI for DON and its acetylated derivatives. In addition, JECFA established an acute reference dose for DON and its acetylated derivatives of 8 µg/kg body weight/day based on a $BMDL_{10}$ of 0.21 mg/kg body weight/day for emesis in pigs and a safety factor of 25.

A human biomarker of exposure to DON has been established by urinary analysis of excreted DON (Turner *et al*., 2008a). This biomarker has been used to indicate a significant reduction in DON exposure in participants of a study in the UK in which wheat intakes were restricted (Turner *et al*., 2008b).

T-2 Toxin

T-2 toxin is a type A trichothecene produced by several *Fusarium* species, the most important being *F. sporotrichioides* Sherb., *F. langsethiae* Torp & Nirenberg and *F. poae* (Peck) Wollenw., which may occur on cereals and grasses in the temperate and cold areas of the world (Marasas and Nelson, 1987a). HT-2 toxin is a hydrolyzed (de-acetylated) naturally occurring analogue of T-2 toxin and is frequently analyzed and evaluated together with T-2 toxin. T-2 toxin is one of the most acutely toxic of the trichothecenes. It is a potent inhibitor of protein, RNA and DNA synthesis and its toxic effects include digestive disorders, haemorrhage in many organs, oral lesions, dermatitis, leucopenia, and blurred and painful vision. It has even been considered as a potential chemical weapon. Its acute effects in humans are most frequently described by a haemorrhagic syndrome, alimentary toxic aleukia (ATA). A similar effect in animals is referred to as mouldy corn toxicosis (Marasas and Nelson, 1987a). It has been reported that ATA occurred in the former USSR during the first half of the twentieth century and caused hundreds of thousands of deaths. In particular, severe outbreaks were experienced during World War II when grain, which was not harvested due to manpower shortages, was left to overwinter in the fields and subsequently consumed in the spring. The main causative agent for ATA is assumed to be T-2 toxin based on subsequent toxigenic studies of the Fusaria implicated in the outbreaks and reproduction of the disease symptoms in animals by pure T-2 toxin. Diacetoxyscirpenol, a group A trichothecene co-

occurring with T-2 toxin and also produced by the same *Fusarium* species, may also have contributed to the outbreaks of ATA, as in pure form it produces similar effects in animals.

Other outbreaks of acute human disease, particularly gastrointestinal effects, have been reported, although frequently the etiological agent is difficult to ascertain as the grain responsible is frequently infected with a number of *Fusarium* species and co-contaminated with a number of trichothecene mycotoxins, including DON (Canady *et al*., 2001a,b). T-2 and HT-2 toxins were evaluated by JECFA on the basis of haematotoxicity (Canady *et al*., 2001b). The committee was unable to find a suitable long term study to set tolerable intakes, but considered a short term study of changes in white and red blood cell counts in pigs to be sufficient to set a group PMTDI for the two toxins at 60 ng/kg body weight/day, based on a lowest observed effect level (LOEL) of 0.029 mg/kg body weight/day. Because no NOEL was available, the safety factor used was 500. Estimates of human intake were not expected to exceed this level.

ZEARALENONE

Zearalenone (ZON) is produced on cereals by *F. graminearum* and *F. culmorum*. It is not acutely toxic, but has strong hormonal properties. In animals, particularly pigs, it can produce an estrogenic syndrome (hyperestrogenism or vulvo-vaginitis) and at low levels it can have anabolic properties. It can be metabolized by mammalian phase I enzymes in which the ketone group is reduced to a hydroxyl to form two stereoisomers, α- and ß-zearalenol. The α-isomer is about 10-fold more estrogenic than the ß-isomer and ZON. The chemically-reduced derivative α-zearalanol (zeranol), which is also more active hormonally than ZON, has been patented and used as an animal growth stimulant, particularly in north America (Marasas and Nelson, 1987b). ZON itself was patented as a human oral contraceptive. Clear evidence of its negative effects from food ingestion has not been obtained, although its involvement with human cervical cancer and premature thelarche has been suggested (Hsieh, 1989). It has been associated with clinical manifestations of hyper-oestrogenism in humans, including an outbreak of precocious pubertal changes (premature thelarche) in young children in Puerto Rico (Saenz de Rodrigues *et al*., 1985) and in south-eastern Hungary (Szuetz *et al*., 1997) and gynecomastia with testicular atrophy in rural males in southern Africa (Campbell, 1991). More recently, evidence has been presented that central precocious puberty in girls from Tuscany, Italy could have been triggered by exposure to ZON and that this may also have caused anabolic growth increase in the exposed individuals (Massart *et al*., 2008).

The JECFA evaluated ZON on the basis of the NOEL for hormonal effects in pigs, the most sensitive species (JECFA, 2000). A PMTDI of 0.5 µg/kg body

weight/day was established and the JECFA recommended that the combined intake of ZON and its metabolites should not exceed this level.

Other Fusarium mycotoxins

Other *Fusarium* mycotoxins such as moniliformin, beauvericin and fusaproliferin also co-occur on many cereals. Of these, moniliformin, which causes acute degenerative lesions in the myocardium, particularly in poultry, is the most important. It has recently been suggested that ingestion of moniliformin is a risk factor for Kashin-Beck disease, a chronic deformative osteoarthrosis, endemic in parts of China (Zhang et al., 2010). However, the implications for human health of these mycotoxins are not clear. Beauvericin itself has found application as a cholesterol lowering agent and a mixture (known as fusafungine) of the group of mycotoxins of which beauvericin is a member (the enniatins) has demonstrated antibiotic properties in successfully relieving the symptoms in patients with upper respiratory tract infections (Feudjio *et al*., 2010).

CONCLUSION

The *Fusarium* mycotoxins discussed in this review represent a diverse range of chemical structures, all of which can have important adverse health effects in humans. Current efforts to reduce *Fusarium* contamination of cereal grains and to reduce mycotoxin contamination of food supplies are of importance due to the health burden produced in many populations by ingestion of these compounds.

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