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Dietary mycotoxins, co-exposure, and carcinogenesis in humans: short review.

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Abstract

Mycotoxins, toxic secondary metabolites of fungi, affect global agriculture so prolifically that they are virtually ubiquitous at some concentration in the average human diet. Studies of *in vitro* and *in vivo* toxicity are discussed, leading to investigations of co-exposed mycotoxins, as well as carcinogenic effects. Some of the most common and toxicologically significant mycotoxins, such as the aflatoxins, ochratoxins, fumonisins, trichothecenes, and zearalenone, are outlined. The wide variety of pathogenic mechanisms these compounds employ are shown capable of inducing a complex set of interactions. Of particular note are potential synergisms between mycotoxins with regard to carcinogenic attributable risk, indicating an important field for future study.

Keywords: mycotoxins; carcinogenesis; mycotoxin co-exposure; mycotoxin carcinogenicity; colorectal cancer; hepatocellular cancer

Introduction

Fungi have been observed for millennia, and are found to be relatively ubiquitous in nature, with

spores able to travel vast distances across the surface of the planet (Hirst & Stedman 1967). Many important agricultural products, especially those rich in carbohydrates, are attractive colonization sites for fungi. Some toxic secondary metabolites of fungal growth are identified as mycotoxins, and may be found to contaminate agricultural products (Chelkowski 1998).

Many species from the *Alternaria*, *Aspergillus*, *Claviceps*, and *Fusarium* genera, as well as some *Penicillium* species, and several others are known to produce mycotoxins (Zain 2011). Mycotoxins are small organic molecules produced as secondary metabolites of fungal growth, observed as toxic to animals and humans who consume them. Mycotoxicosis is the term used for poisoning associated with exposures to mycotoxins. The symptoms of mycotoxicosis depend on the type of mycotoxin, the concentration and duration of exposure, as well as age, health, and sex of the exposed individual (Bennett & Klich 2003).

Like all toxicological syndromes, mycotoxicoses can be categorized as acute or chronic. Acute toxicity generally has a rapid onset and an obvious toxic response, while chronic toxicity is characterized by low dose exposure over a long time period, resulting in cancers and other generally irreversible effects (Williams et al. 2015). Although the main human and veterinary health burdens of mycotoxin exposure are related to chronic exposure (e.g., cancer, kidney damage, immune suppression), the best-known mycotoxin episodes are manifestations of acute effects (*e.g.*, Turkey X-syndrome, human ergotism, stachybotryotoxicosis in livestock) (Bennett & Klich 2003).

Some of the most frequently encountered mycotoxins ochratoxin A (OTA) and deoxynivalenol (DON), are reported to interfere with mammalian cellular processes including DNA replication and protein synthesis (Bensassi et al. 2009; Pfohl-Leszkowicz & Manderville 2012). Other mycotoxins, particularly aflatoxin B_1 (AFB_1) and its metabolic precursor sterigmatocystin, have been identified as carcinogenic by the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) Monographs Program (International Agency for Research on Cancer 2007). The IARC Monographs identify environmental factors associated by scientific literature with increased risk of carcinogenesis in humans.

As a result of crops affected by fungal infection being eaten, either directly by humans or as feed for livestock, mycotoxins are introduced to the food chain. Mycotoxins are able to resist decomposition or being broken down by mammalian digestion, even by ruminant livestock, allowing

these compounds to persist in meat and even dairy products (Kang'ethe & Lang'a 2009). This gives rise to certain partially metabolized mycotoxins, such as aflatoxin M_1 (AFM_1), present in milk from cows or humans that consumed feed or food contaminated by aflatoxins. Even temperature treatments, such as cooking and freezing, do not inactivate some mycotoxins.

Due to the broad, overlapping habitats of fungal species, it is observed that multiple species may affect a given region (Alkadri et al. 2014; Jackson et al. 2012). Furthermore, one fungal species may produce many different mycotoxins, and the same mycotoxin may also be produced by several different species. Since many species are each capable of producing multiple mycotoxin compounds, and agricultural products from many sources may be aggregated prior to processing *en masse*, there is a very high likelihood of multiple mycotoxins co-occurring in food and feed products (Mngadi et al. 2008). Consequently, in the richly varied modern diet, individuals undergo dietary exposure to a very wide variety of mycotoxins (Abia et al. 2013; Solfrizzo et al. 2014).

Various mycotoxins were investigated since early last century for individual toxicity, usually in regard to acute pathologies (Schreiner & Reed 1908). However, recent research is indicating complex interactions between chronic co-exposure to multiple mycotoxins possibly having synergistic, or even mitigating effects (Bensassi et al. 2014; Grenier & Oswald 2011). Some of the most common and toxicologically significant mycotoxins, such as the aflatoxins, ochratoxins, fumonisins, trichothecenes, and zearalenone, are outlined below, followed by a description of possible health burdens caused by co-occurrence and co-exposure of multiple mycotoxins, as well as their carcinogenic effects.

Mycotoxins

Aflatoxins

There are six predominant aflatoxins, named AFB_1, aflatoxin B_2 (AFB_2), aflatoxin G_1 (AFG_1), aflatoxin G_2 (AFG_2), AFM_1, and aflatoxin M_2 (AFM_2) (Reddy et al. 2010). In this nomenclature, 'B' and 'G' are used to denote compounds that fluoresce blue or green, respectively, under ultraviolet light. The 'M_1' and 'M_2' compounds are not found on cereal products themselves, but are metabolites expressed in milk of mammals whose diet was contaminated by aflatoxins B_1 and B_2, respectively (Garrido et al. 2003). Finally, the '$_2$' numbered aflatoxins are structural isomers missing one double bond, as compared to the respective '$_1$' numbered molecule, illustrated in **figure 1** below. Among the *Aspergillus* genus, species in the section *Flavi* are most frequently reported producers of AFB_1, while

A. flavus and *A. parasiticus* are commonly used as producers of AFB_1, AFB_2, AFG_1 and AFG_2 for morphological studies (Klich 2007; Varga et al. 2011).

AFB_1 is identified as the most potent naturally occurring carcinogen due to being metabolised in the liver to a reactive epoxide, which may form DNA adducts at some guanine residues (Gouas et al. 2009; Bedard & Massey 2006). The epoxide adduct is reported to catalyze a G → T mutation in the *p53* tumour suppressor protein gene, where it causes a missense mutation effectively inactivating the gene's protein product (Besaratinia et al. 2009). This identified mechanism, as well as previous studies in animal models, has lead the IARC to classify AFB_1, AFB_2, AFG_1, and AFG_2 as Group 1 carcinogens, denoting their explicit carcinogenicity to humans (World Health Organization & International Agency for Research on Cancer 2002). Developing nations, including most of Africa, Latin and South Americas, and Asia are identified as high risk areas for aflatoxin exposure, leading to aflatoxicosis (Williams et al. 2004).

An Italian study using lactating goats illustrated the relatively rapid absorption of AFB_1 and its subsequent metabolism and excretion as AFM_1, with peak concentrations of AFM_1 detected in expressed milk between 3 and 6 hours after oral AFB_1 administration, and non-detection of AFM_1 after 3.5 days post-dosage (Battacone et al. 2012). However, the amount of AFM_1 detected only accounted for less than 0.2% of the original dose, leaving a large majority as either degraded or excreted by other mechanisms. The rates of aflatoxin absorption and degradation were shown to be affected not only by species, but by diet, specifically through varying the roughage component of livestock feed (Upadhaya et al. 2009).

Ochratoxins

Ochratoxin is a mycotoxin that comes in three secondary metabolite forms, A, B, and C, all of which are produced by Penicillium and Aspergillus species contaminating in a wide range of commodities including staple food crops and beverages such as beer and wine (Bayman & Baker 2006). OTA is one of the most commonly encountered mycotoxins, and was reportedly detected in 60% of a healthy Moroccan study population of blood donors (Filali et al. 2002). The structure of OTA is depicted in **figure 2**; the related compound ochratoxin B differs only in having hydrogen in place of the chlorine atom, and ochratoxin C is an ethyl ester form of OTA produced in presence of rumen fluid (Fuchs et al. 1984).

OTA has been hypothesized to cause oxidative damage to DNA, leading to mutagenesis and potential carcinogenesis (Zepnik 2001). Recent papers also propose direct genotoxic mechanisms for OTA, describing a pathway that metabolizes OTA into an electrophilic species capable of directly binding to some nucleotide bases (Pfohl-Leszkowicz & Manderville 2012). Consequently, OTA is classified as a possible human carcinogen by IARC, citing sufficient evidence of carcinogenicity in animal models, but insufficient evidence from human studies (World Health Organization & International Agency for Research on Cancer 2002).

OTA is known to bind to blood plasma proteins, delaying its excretion in urine by up to 30 days, a fact greatly relevant to the development of methods for exposure detection (Kumagai 1985). Despite this temporary bioaccumulation, no significant relationship was found between age and plasma OTA levels in a British study population (Gilbert et al. 2001). However, a variable relationship between plasma and urine levels was hypothesized to result from decreased efficiency of OTA metabolic and excretion mechanisms with age.

Fumonisins

Since discovery of this group of mycotoxins in 1988, at least 28 compounds have been identified as fumonisins, with some of the most common forms illustrated in **figure 3** (Voss et al. 2007; Bolger et al. 2001; Tamura et al. 2014). These compounds are predominantly produced on maize and maize products by *F. proliferatum* and *F. verticillioides* (formerly *F. moniliforme*), but have also been reported in cultures of several other *Fusarium* spp., as well as the *Alternaria alternata* f. sp. *lycopersici* natively growing on tomatoes, and *Aspergillus niger* on coffee and grapes (Weidenbörner 2001; Scott 2012). Among the fumonisin compounds, fumonisin B_1 (FB_1) is produced most abundantly, and features most prominently in the literature (Mahmoodi et al. 2012). In an analysis of various foods and feeds from Burkina Faso, FB_1 was detected in over 80% of samples, with FB_2 and FB_3 also found in 69% and 46% of samples, respectively (Warth et al. 2012).

Dietary exposure to fumonisins was reported to have rapid but low absorption, based on oral administration of FB_1 in a rat model, with 3.5% of the dose observed in plasma, peaking in concentration after one hour (Voss et al. 2007). Another study in rats reported observations supporting a hypothesis of FB_1 genotoxicity mediated by oxidative stress mechanisms (Theumer et al. 2010). *Fusaria*-derived toxins such as FB_1 and FB_2 are listed as possible carcinogens in Group 2B of the

IARC classification (World Health Organization & International Agency for Research on Cancer 2002). A recent etiological study also found some positive correlation between prevalence of FB_1 contamination in rice and incidence of esophageal cancer, though this relationship was not seen in other staple foods, such as corn, in the same region of Iran (Alizadeh et al. 2012).

Due to a structural resemblance with ceramide, fumonisins are also reported to disrupt the *de novo* synthesis of ceramide and sphingolipid metabolism, potentially leading to broad impairment of cellular signalling mechanisms (Dutton 1996). FB_1 neurotoxicity was also observed in a carp model (Kovacić et al. 2009). However, formation of fumonisin A_1 (FA_1) through acetylation of the amine site in FB_1 was reported to block these effects (Stockmann-Juvala & Savolainen 2008). Additionally, types of maize processing that involved cooking in alkaline conditions were estimated to mitigate some adverse health effects through hydrolysis of the fumonisins (Voss et al. 2007).

T-2 Toxin and HT-2 Toxin

The T-2 and HT-2 toxins are produced by various *Fusarium* species, particularly *F. sporotrichioides* and *F. poae*, reportedly affecting several major cereal crops including oats, barley, corn, and wheat (Weidner et al. 2013). A European evaluation found oats and oat products contained the highest summed concentrations of these two contaminants (EFSA Panel on Contaminants in the Food Chain 2011).

These toxins are common representatives of the type A trichothecenes, a group identified by specific arrangements of ligands around a sesquiterpenoid cyclic ring (Cano-Sancho et al. 2012). As illustrated in **figure 4**, HT-2 is structurally differentiated from T-2 by oxidation of an acetate ligand at C-4.

Exposure to these compounds is associated with diverse pathologies including skin irritation, gastrointestinal issues (nausea, cramping, and vomiting), impaired mitochondrial function, and hypotrophy of the spleen and thymus (Ueno 1984). Recent research has discovered evidence for these toxins crossing the blood-brain barrier *in vitro*, linking them to neurotoxic effects (Weidner et al. 2013). However, the predominant human health effects reported in literature associate these toxins with inhibited protein synthesis and apoptosis in a wide variety of *in vitro* and *ex vitro* cells, as well as *in vivo* organs, including brain, gastrointestinal tract, skin, spleen, and thymus (Li et al. 2011; EFSA Panel on Contaminants in the Food Chain 2011). Though these tricothecenes were not observed to

produce genotoxic or directly mutagenic effects *in vitro*, the aforementioned widespread disruptive effects of exposure may potentially increase susceptibility to other carcinogenic factors (Rocha et al. 2005).

Deoxynivalenol

DON is produced by *F. graminearum* and *F. culmorum* on cereal crops, and is one of the most commonly encountered mycotoxins (Reddy et al. 2010). Acute dietary exposure to DON is characterized in animals by emesis and feed refusal. DON is rapidly metabolized for urinary excretion as glucuronide conjugates within 24hrs of dietary exposure (Lake et al. 1987).

As illustrated in **figure 5**, DON may be identified as a type-B trichothecene by the carbonyl group at C-8. Like all trichothecenes, DON is a strong inhibitor of protein synthesis (Ji et al. 2014). Literature reports DON preventing eukaryotic polypeptide assembly by interfering with activity of the 60S ribosomal subunit (Pestka 2007).

In 2002, an IARC review of available literature listed DON as a Group 3 (not classifiable) human carcinogen due to inadequate evidence of animal carcinogenicity, and lack of investigation in humans (World Health Organization & International Agency for Research on Cancer 2002). However, a more recent *in vivo* mouse study concluded oral exposure to DON was able to induce lung adenocarcinomas, with the carcinogenic effect synergized by co-exposure to sterigmatocystin (Huang et al. 2004). Unfortunately, the results of this study were argued to be invalid by a following review article, citing an inappropriate experimental design that did not represent real-world conditions of human exposure to DON (Ma & Guo 2008). A third study reported observing clear, dose-dependent induction of DNA strand breakage by DON treatment of *in vitro* liver cells (Zhang et al. 2009).

Zearalenone

Zearalenone (ZEN) is another common mycotoxin produced by various *Fusarium* fungi, detected in some 90% of sampled cereal crops that were grown in central European countries such as Austria, France, and Germany (Baliukoniene et al. 2003). ZEN shares a structural similarity with the human sex hormone 17β-estradiol, and therefore also has a similar affinity to and effect on estrogen receptors, resulting in associations with fertility problems in both humans and livestock (Nordic Council of Ministers 1998).

IARC found limited evidence of ZEN carcinogenicity in animal models, classifying it together with DON in Group 3 (World Health Organization & International Agency for Research on Cancer 2002). Due to rapid metabolism, bioaccumulation is understood to be insignificant, though co-exposure with other mycotoxins is estimated to present a probable health risk due to inadequately researched interactions (Speijers & Speijers 2004).

Interestingly, ZEN is frequently reported to have antagonistic effects on the toxicity of some co-exposed mycotoxins. For example, OTA-induced kidney damage in rats was observed to be significantly mitigated in comparison cases where the animals were given both ZEN and OTA (Grenier & Oswald 2011). In another study, ZEN co-exposed with DON was also observed to produce sub-additive or antagonistic effect on levels of some serum immunoglobulins, as compared to individual ZEN or DON exposure cases (Forsell et al. 1986).

Co-occurrence and co-exposure of multiple mycotoxins

In a South African study, the co-occurrence of mycotoxin-producing fungi on crops was reported for almost half of contaminated samples (Mngadi et al. 2008). As mentioned before, many species of mycotoxin-producing fungi are known to be capable of producing more than one mycotoxin. A Polish study reported co-occurrence of mycotoxins in over half the rye samples analysed, with the most common combination being DON and ZEN (Błajet-Kosicka et al. 2014). This mycotoxin pair was also detected in a study on several Chinese wheat producing regions (Ji et al. 2014). Further, analysis of a variety of foods and feeds produced in Burkina Faso and Mozambique reported up to 28 different mycotoxins present and quantifiable in a single sample (Warth et al. 2012). Finally, even greater co-occurrence was reported after a recent analysis detecting between 5 and 41 of the previously discussed mycotoxins in individual samples of maize from various agricultural sites in Malawi (Matumba et al. 2014).

Government and industry regulations exist to minimize the concentrations of individual mycotoxins allowed into food and feed products (Zain 2011; The Commission of the European Communities 2006). However, these regulations are based on individual toxicities, and as such, do not take into account the complex dynamics of compounded risk from co-exposure to groups of mycotoxins, for even acute pathologies. Agricultural products are effectively aggregated and heterogeneously distributed for consumer convenience, leading to a highly unpredictable mixture of

possible mycotoxin contamination in food products (Turner et al. 2012). An analysis of 174 cereal-based food products from Belgian supermarkets reported a median of four mycotoxins present in these consumer-available products (De Boevre et al. 2012). Population studies of mycotoxin exposure therefore also frequently report detectable amounts of multiple mycotoxins in blood and urine samples from human populations all over the globe (Abia et al. 2013; Solfrizzo et al. 2014; Shirima et al. 2014; Njumbe-Ediage et al. 2012). Consequently, an important question remains posed by the current literature, to identify the chronic risks associated with repetitive exposure to low levels of multiple mycotoxins (Warth et al. 2013).

Several *in vivo* studies with various species of farm animals co-exposed to pairs of mycotoxins were compared in the literature, illustrating a complex set of possible synergistic, additive, sub-additive, or antagonistic effects on animal health and growth metrics, as compared with single mycotoxin exposures (Grenier & Oswald 2011; Speijers & Speijers 2004; Bensassi et al. 2014). These reports serve to highlight not only the complex and dynamic interaction between co-exposures, but also the great variety of possible co-exposure situations, and the dearth of studies representative of the real-world situation, particularly in humans (Streit et al. 2013).

Mycotoxins and carcinogenesis

Although mycotoxin exposure has been associated with several acute and chronic human health effects, one of the most important health burdens associated with mycotoxin exposure is the development of cancers. The possible causes of carcinogenesis are virtually innumerable, however, exposure to some chemical factors (*e.g.*, (multi-)mycotoxin exposure) is known to be a strong modulator of carcinogenic risk (Cohen & Arnold 2011). In the unfortunate case of such exposures, three stages are identified in the carcinogenic process: initiation, promotion, and progression (Oliveira et al. 2007). For example, AFB_1 is known to be a potent initiator of hepatocellular carcinoma, while fumonisins are reported to be strong tumour promoters after initiation of carcinogenesis by another agent, such as AFB_1 (Riley 1998). Although several cancers might be associated with multi-mycotoxin exposure (*e.g.* liver, colon, rectum, esophageal, breast cancer, etc.), direct evidence is still scarce for most of these cancer types, and multi-mycotoxin exposure may not yet have been investigated for causal relationship. Therefore, only the two most frequently studied cancer types in relation to mycotoxin exposure will be outlined in this review paper, namely colorectal and hepatocellular

carcinoma.

Colorectal carcinoma

Cancers of either the colon or rectum are the fourth most common causes of death by cancer worldwide (World Health Organization 2014). Rates of incidence rank colorectal cancer slightly higher, as the second and third most common site of cancer diagnosis in women and men, respectively (EpiCast Reports 2012). As with all cancers, the risk of incidence increases with age (Howlader et al. 2011). This is largely due to cumulative risk of carcinogenesis over the course of chronic exposure to potential carcinogens. Particularly, since the prevalent vector of human exposure to mycotoxins is through the diet, it is postulated that the colorectal region is itself highly exposed to these compounds, and therefore a prominent target for pathological developments (Pfohl-Leszkowicz et al. 1995; Bouhet & Oswald 2005).

The HT-29 human colonic cell line was used for *in vitro* studies of DON and FB_1, both of which were observed to induce apoptosis, though by different mechanisms (Schmelz et al. 1998; Ma et al. 2012). DON-induced apoptosis was separately reported to be caused by mitochondrial dysfunction, while treatment with FB_1 resulted in accumulation of endogenous free sphingoid bases, inhibiting growth and inducing apoptosis. A different colonic cell line, HCT-116, was used in an investigation of AFB_1, reporting induction of DNA damage and lesions, as well as inactivation of the ATR/Chk1 pathway that would normally help address an appropriate response to this damage (Gursoy-Yuzugullu et al. 2011). Further investigation of synergistic interactions between co-exposed mycotoxins is especially required in the colorectal context.

Hepatocellular carcinoma

Almost 700,000 individuals were recorded to have died of liver cancer in 2008, increasing to over 750,000 by 2010, making hepatocellular carcinoma the third most deadly form of cancer worldwide (Lozano et al. 2012; Ferlay et al. 2010). A slightly older report estimates the annual global diagnosis rate at over 560,000 individuals in 2000, though such estimates are reported elsewhere to experience growth at a rate of at least 3% annually (Bosch et al. 2004; Howlader et al. 2011).

There is a strong, established link between aflatoxin exposure and development of malignant hepatomas, with a speculated 5% to 28% of cases actually caused by aflatoxins (Gursoy-Yuzugullu et

al. 2011). The associated mechanism, as previously discussed, involves metabolism of AFB_1 in the liver to a highly reactive species capable of forming mutagenic DNA adducts. One well-known mutation results in the inactivation of p53 tumour suppressor gene, enabling initiation of carcinogenesis. Subsequently, a synergistic effect promoting tumour growth in the liver was reported for co-exposure to fumonisins (Carlson et al. 2001). Less pronounced effects were reported by multiple studies on co-exposed OTA also resulting in increased hepatic lipid levels and increased relative weight of the organ (Grenier & Oswald 2011).

Conclusion

Though literally innumerable fungal secondary metabolites exist, a few were identified as particularly harmful by centuries of experience and research. The acute and chronic health effects of exposure to these xenobiotics vary almost as widely as the mechanisms by which various mycotoxins produce these effects. Nevertheless, great efforts of research have helped in characterizing the hazards of mycotoxins. Unfortunately, the rate at which mycotoxins are produced and the ubiquity of their production throughout the world's agricultural industries, coupled with modern food processing and distribution techniques, indicates a deeper understanding of actual exposure is needed. In particular, both co-exposure and chronic exposure are increasingly identified as real-world factors, consequences of which are most relevant to inquiries regarding real-world health effects.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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List of Figures

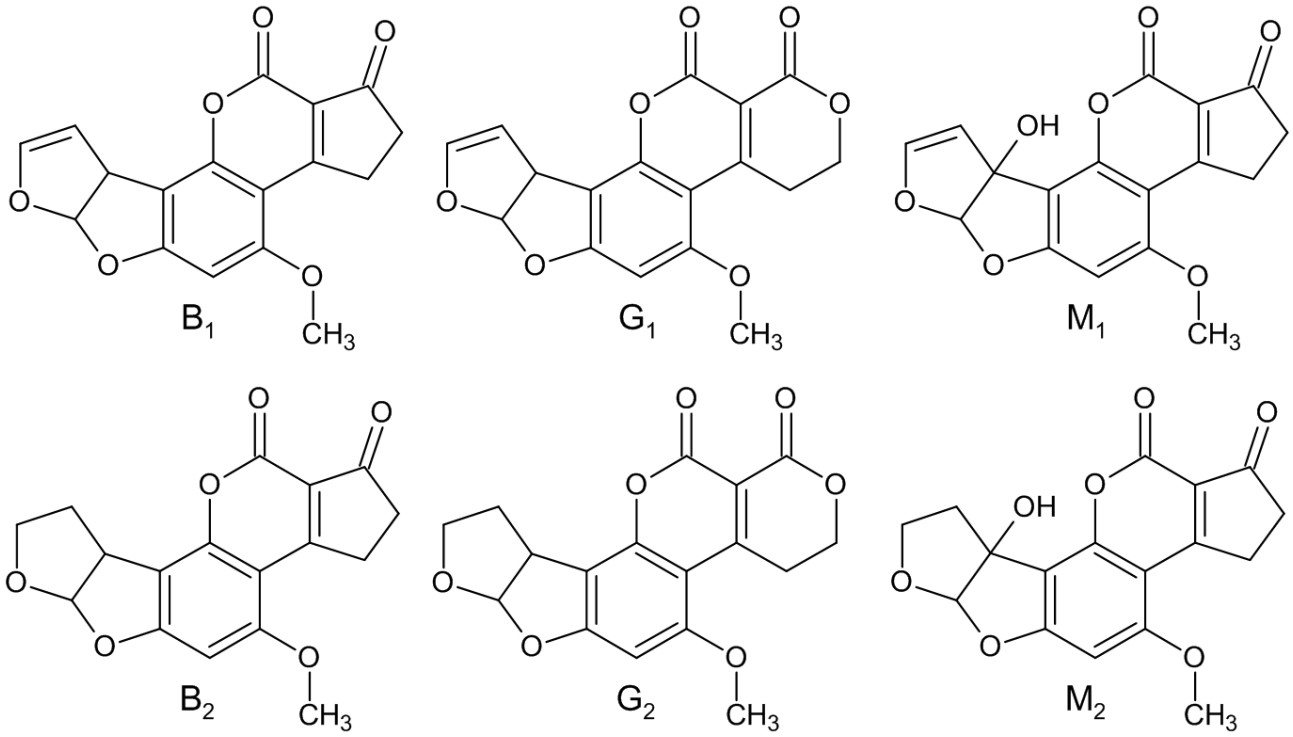


Figure 1: Chemical structures of six different aflatoxins: aflatoxin B_1, aflatoxin B_2, aflatoxin G_1, aflatoxin G_2, aflatoxin M_1, and aflatoxin M_2.

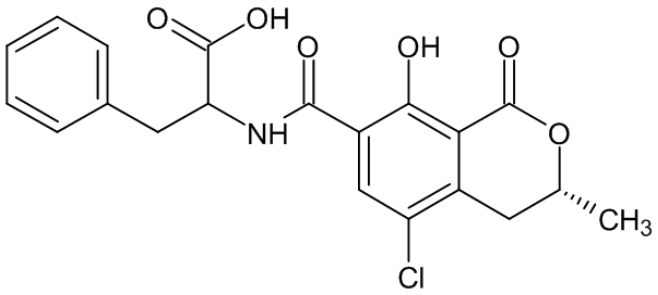
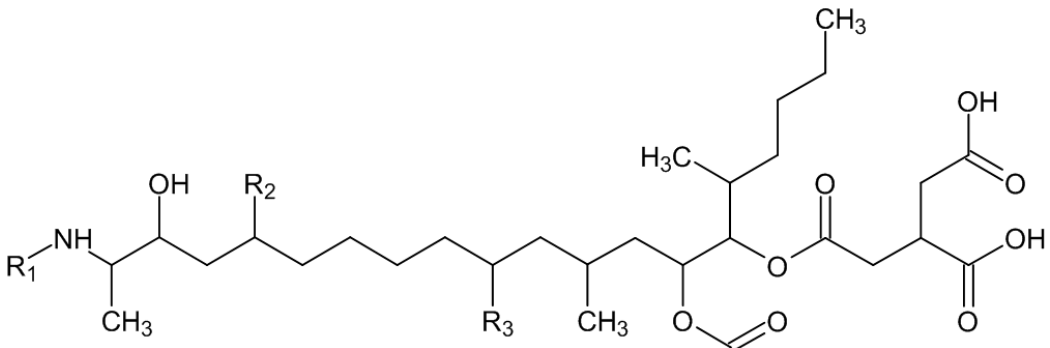


Figure 2: Chemical structure of ochratoxin A.



	R_1	R_2	R_3
FB_1	H	OH	OH
FB_2	H	OH	H
FB_3	H	H	OH
FB_4	H	H	H
FA_1	CH_3CO	OH	OH
FA_2	CH_3CO	OH	H
FA_3	CH_3CO	H	OH

Figure 3: Chemical structure and ligands identifying some common fumonisins (Bolger et al. 2001; Tamura et al. 2014).

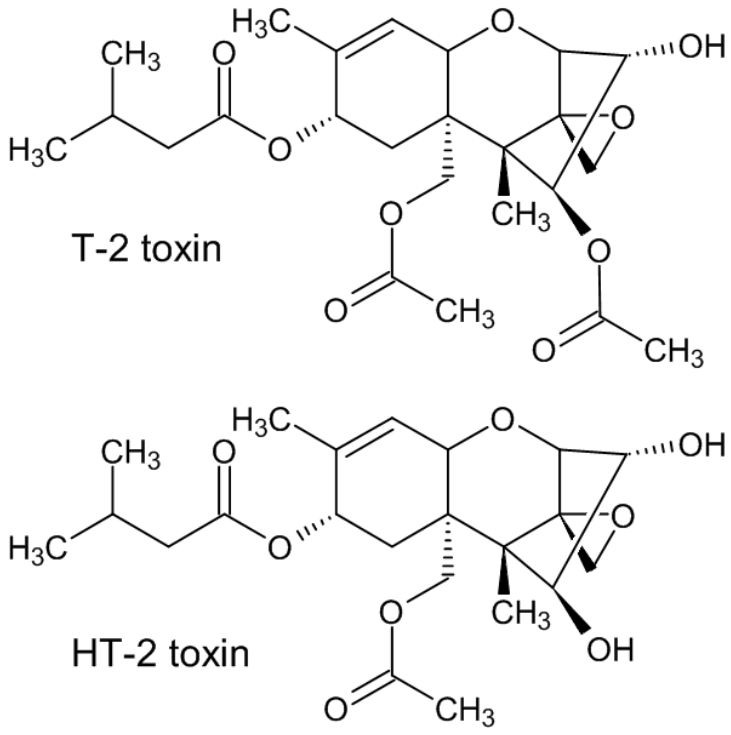


Figure 4: Chemical structures of T-2 toxin and HT-2 toxin.

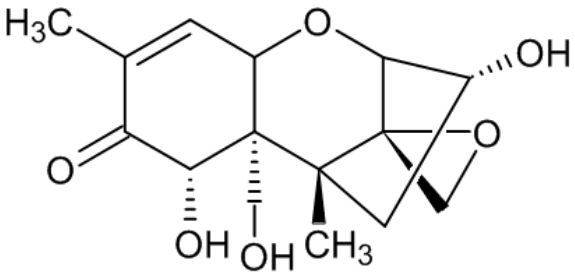


Figure 5: Chemical structure of deoxynivalenol.

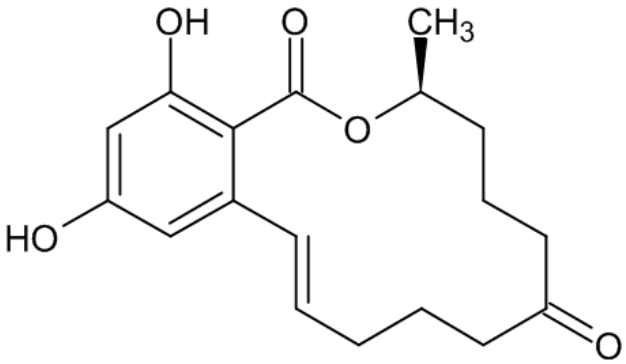


Figure 6: Chemical structure of zearalenone.