Mycotoxins in the food chain

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ABSTRACT - The paper is the written version of the scientific presentation given on the 17th meeting of the Alps-Adria Scientific Workshop (on 10 April of 2018 in Hnanice, Czech Republic). Mycotoxins are secondary metabolites of fungi, found all around the world as natural contaminants, still unavoidable in the human food chain. This review gives a summary of the occurrence of the most important mycotoxins in Europe, the predicted effect of climate change on their production and the problem of the co-occurrence of these toxins causing multitoxic effects. Experimental results of the research group confirm the complexity of interactions and the fact that interactive effects are hardly predictable.

Keywords: mycotoxins, climate change, multi-toxic effects

INTRODUCTION

Mycotoxins are fungal secondary metabolites found all around the world as natural contaminants. Secondary metabolites are natural products that have a restricted taxonomic distribution, possess no obvious function in cellular growth and are synthesised by cells that have stopped dividing (Weinberg, 1970). These toxic substances pose risk for human and animal health (so they are of feed and food safety concern) and cause significant economic losses. The Food and Agriculture Organization (2007) estimated that 25% of the world's crops are affected by mycotoxins each year (Smith et al., 2016). Though, according to the most recent reports much higher proportion of the global agricultural commodities is contaminated (maybe even above 80%) (according to Kovalsky et al., 2016).

These naturally occurring toxic metabolites are still unavoidable, but the rate and extent of contamination depends on several biological, environmental, technological, and also human factors. The origin of the problem is the infection of the plants with toxin producing moulds. The interaction between the host plant and the mould is very complex and not yet fully understood. The main environmental factors influencing mould proliferation and mycotoxin production are moisture content and

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temperature. Suboptimal conditions around harvesting and storage may increase severity of infection and contamination.

Mycotoxins may be introduced into the food chain via consumption of contaminated food of plant origin, but because of the possibility of the carry over, in case of certain mycotoxins food of animal origin can also be the source of contamination.

The problem is considered as an unavoidable and unpredictable one, even under good agricultural practice, because environmental factors can't be kept under full control. If they are introduced into the food chain it is very difficult to eliminate them, because they are very stable against heat, or chemical treatments.

The analysis of global mycotoxin occurrence is of particular interest because it helps to identify areas of high risk, which may influence global trade. It also helps to study the effect of climatic change, if we have data year after year. The BIOMIN Mycotoxin Survey is the longest running survey using advanced analytical tools. According to the latest survey 94% of the samples examined were positive worldwide. The most frequently occurring mycotoxins were: deoxynivalenol (DON), fumonisin (FUM) and zearalenone (ZEN). In Central Europe the most prevalent mycotoxin is DON, followed by zearalenone and fumonisins, however T-2 toxin is also a frequent contaminant (BIOMIN, 2017). It is also important to note that 76% of the positive samples contained two or more mycotoxins.

The problem of mycotoxins and the diseases caused by them have been existed since ancient times however the causal relationship was unknown. Nowadays we rarely experience acute mycotoxicoses in developed countries still the economic losses may be significant because of the subclinical or chronic exposure to mycotoxins.

Some examples for the challenges of today related to the problem are: predicted effects of climate change, the co-occurrence of mycotoxins, emerging mycotoxins, „masked" (hidden / bound) mycotoxins, prevention and protection, global trading, legislation, etc…

EFFECT OF CLIMATE CHANGE ON THE OCCURRENCE OF MYCOTOXINS

According to the prediction of several competent organisations (Intergovernmental Panel on Climate Change, World Meteorological Organization, etc.) a global warming is taking place. Climate change means:

increase in temperature, variation in precipitation, drought and change in the atmospheric CO_2 concentration (Miraglia et al., 2009).

The agricultural sector is particularly sensitive to these changes, which have direct and indirect consequences on food safety and food security, i.e. on the amount of food available, the quality and nutritional value of food and bacterial and chemical food safety.

It has been suggested that effects will be regional, and not obviously detrimental, but depending on geographical region it can be advantageous as well.

Among the main ecological factors influencing the growth and toxin production of moulds, temperature and water activity are determinant. Climate change may affect all ecological factors important in the mycotoxin problem so will influence directly or indirectly mould growth and toxin production. It is important to emphasize that those climatic conditions which favour mould growth are different from those of toxin production. And because those effects which initiate secondary metabolism in fungi are not well classified, the safest way of protection is to prevent mould infection.

Some of the predicted consequences of changing environmental factors are listed below:

Shift in contamination pattern

As a consequence of warm summers, *Fusarium graminearum* has already become dominant in Europe instead of the previously dominant *F. culmorum*. Besides DON and ZEA, *F. graminearum* may produce nivalenol (NIV) as well however there is a big regional difference in NIV production. If a shift in DON/ZEA co-contamination to NIV/ZEA co-contamination can be predicted, depends on the occurrence of the chemotype of *F. graminearum*. According to different studies worldwide, the occurrence of NIV producing *F. graminearum* is different. Only a very few *F. graminearum* isolates have been proved to be NIV producers in the USA (Abramson et al., 2001). On the other hand the presence of significant populations of NIV-producing *F. graminearum* was ascertained (Gale, 2011). In the United Kingdom 71% DON and 25% NIV producing *F. graminearum* chemotypes were isolated and identified (Jennings et al., 2004). According to a survey the occurrence of NIV in Hungary could be linked exclusively with *F. culmorum* (Xu et al., 2008)

According to the scientific opinion of EFSA (2013) the prevalence of *F. graminearum* has already increased in Central Europe, but out of 13164 samples only 783 samples showed co-occurrence of NIV and DON.

Changes in the level of mycotoxin production

Fumonisins are the third most common mycotoxins in Central Europe. They are produced mainly by *F. verticillioides* and *proliferatum.* Because dry weather during grain fill, late-season rains, drought stress and rainfalls following dry periods favour the proliferation of *F. verticillioides*, it can be expected that the foreseen climate change will favour fumonisin production (Miller, 2008).

Several studies support this prediction. E.g. high fumonisin levels and frequent kernel infections by *F. verticillioides* and *F. proliferatum* could be associated with drought stress in Germany (Goertz et al., 2010). A study in Croatia yielded a significant percentage of mycotoxin positive samples in 2011 in which mycotoxins appeared in the frequency order different from that stated for Croatia in 2007. In 2007 DON was the most common mycotoxin in cereals, followed by ZEA and T-2 toxin, whereas FUM was less represented. In 2011 the mean percentage of FUM positive samples was higher than that of T-2 toxin-positive samples, with significantly higher mean FUM concentrations in all analysed cereals (Pleadin et al., 2013).

Previous studies showed that the FUM1 gene, which is a key gene in fumonisin biosynthetic pathway, is affected by environmental stress (Marin et al., 2010). Water stress (drought) might result in increased risk of FUM contamination of maize caused by *F. verticillioides*. This work also suggested that *F. verticillioides* and *F. graminearum* have different regulation patterns of FUM biosynthesis and so their response to changing environmental conditions is also different.

Increase in aflatoxin B1 (AFB1) production

Several studies support the supposition that the biggest problem is expected by the predicted increase in aflatoxin production and the increase of the size of areas affected (EFSA, 2012). Aflatoxin B1 is of special interest, because it is carcinogenic, genotoxic and immunosuppressive. It can cause both acute and chronic toxicity.

A more recently published risk map for AF contamination compared the situation of today and in case of plus 2 and 5 centigrade scenario, respectively (Battilani et al., 2016). The risk has been demonstrated by the aflatoxin hazard

index (AFI), which increases in parallel with temperature. Currently only 20% of the mean AF contamination was predicted to be above the legal level but this rate may increase.

In both climate change scenarios, the most concerned areas with an increase of aflatoxin contamination are: Eastern Europe, Balkan and the Mediterranean regions. On the other hand countries in which maize cultivation is common (Romania, Hungary, France and north-east Italy) show low risk (Figure 1).
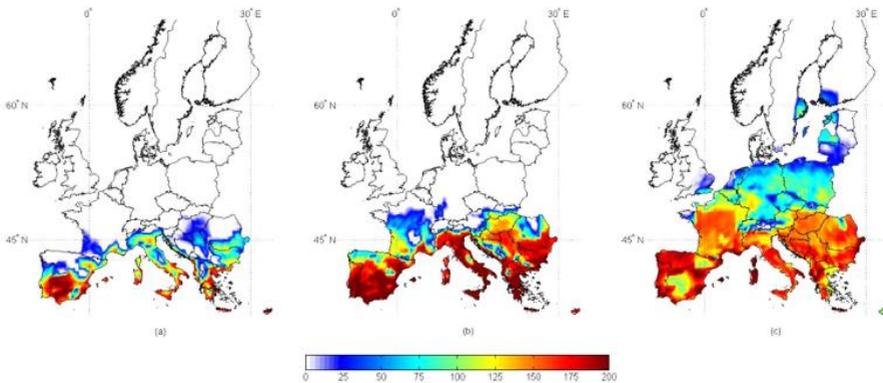

Figure 1. Risk maps for aflatoxin contamination in maize at harvest in 3 different climate scenarios: (a) present, (b) +2 °C, (c) +5 °C. The scale 0–200 refers to the aflatoxin risk index (AFI), higher number indicates increased risk of contamination. (Battilani et. al., 2016)
1. ábra: A kukorica aflatoxin szennyezettségének kockázati térképe három eltérő szcenárió esetén: (a) jelenleg, (b) +2 és (c) +5 °C-os felmelegedés esetén. A 0-200-as skála az aflatoxin indexet (AFI) jelzi, a növekvő érték nagyobb kockázatot jelez. (Battilani és mtsai., 2016)

Changes in biosynthetic pathways

F. graminearum produces DON (as mentioned already earlier as well). Changing water activity (aw) and temperature conditions affect the ratio of DON and its metabolites (15-acetyl-DON and 3-acetyl-DON). According to Leite (2014, in Medina et al., 2017) with decreasing aw the amount of DON decreases, while the amount of its metabolites does not change significantly (Figure 2).
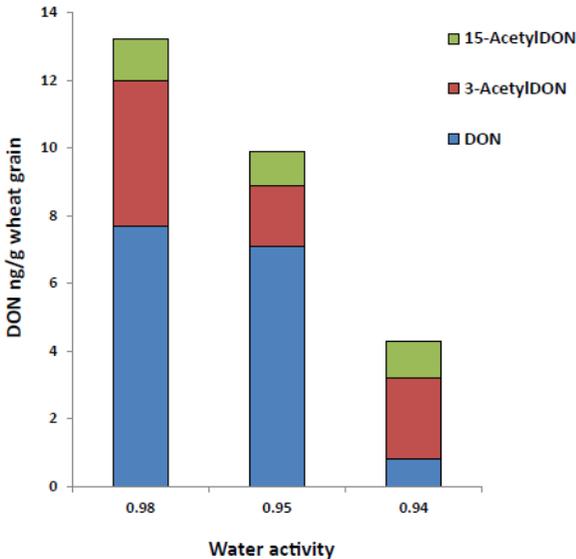
Figure 2. Differential production of DON and its metabolites by *F. graminearum* at different water activity levels (on 25 ºC) (*Leite*, 2014)

2. ábra: A F. graminearum *által termelt DON és metabolitok mennyisége eltérő vízaktivitás hatására (25 ºC-on) (Leite, 2014)*

Also for *F. verticillioides* different temperature and aw resulted in altered ratio of the main fumonisin types, i.e. FB1, 2, 3 and 4 (Medina et al., 2017).

Masked mycotoxins are bound compounds produced in the plants mainly as result of detoxification and resistance mechanism. Because climate change affects plant physiology and also causes significant environmental stress for the plants, alteration in the production of masked mycotoxins can also be forecasted (Medina et al., 2017).

It is also important to investigate if altered environmental factors change biosynthetic pathways, up and down regulations of genes in relation to aw and temperature conditions, so if climate change will result in different secondary metabolite production (new mycotoxins ?) is not yet known.

CO-OCCURRENCE OF MYCOTOXINS

The topic of co-occurrence of mycotoxin and the interactions and combined effects of them has become a hot topic recently. This is indicated by the large number of scientific papers published in this area: Ibanez-Vea et al. (2012), Rodriguez and Naehrer (2012), Serrano et al. (2012), Streit et al. (2012),

Schatzmayr and Streit (2013), Streit et al. (2013), Alkadri et al. (2014), Gerding et al. (2014), Kovalsky et al. (2016), Smith et al. (2016).

Several surveys indicate that humans and animals are generally exposed to more than one mycotoxin.

This is because:

- similar environmental conditions favour proliferation of several different molds;
- most fungi are able to produce more than one mycotoxin simultaneously in separate foodstuffs;
- animal (and also human) diets generally include several different grain sources which contain different mycotoxins. Especially human diet contains a lot of other foodstuffs which can also contain mycotoxins (coffee, beer, fruits, juices etc.);
- transport of feed and food products across the wold due to globalized trade makes the problem more complicated.

In a 3-year survey, between 2010 and 2012, 83 complete feed and feed complement samples were analysed on a total number of 139 mycotoxins and metabolites simultaneously using multi-mycotoxin LC-MS/MS analysis (Streit et al., 2013). Samples contained 7 to 69 metabolites, 66% of the samples was co-contaminated with 16 to 30 compounds (Figure 3).
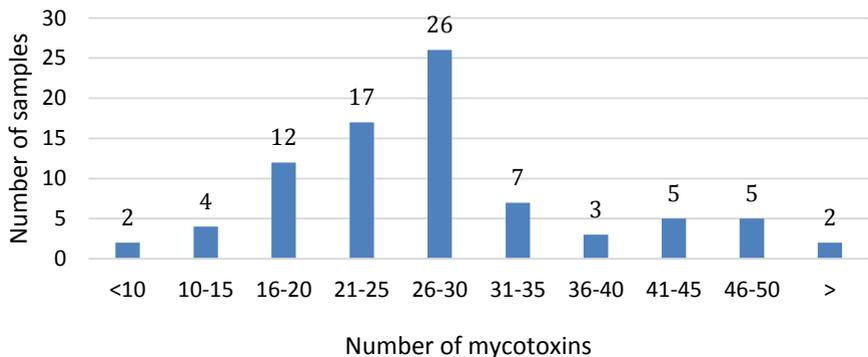

Figure 3. Co-occurrence of mycotoxins between 2010 and 2012 (Streit et al., 2016)

3. ábra: Mikotoxinok együttes előfordulása 2010 és 2012 között (Streit és mtsai., 2016); x tengely: a mikotoxinok száma egy mintában, y tengely: a vizsgált minták száma

The median concentrations of the individual toxins were generally low. Yearly differences were observed regarding concentrations and contamination pattern – presumably due to the different fungal populations on a given year, despite the fact that the cobs were obtained from the same field.

The fact that humans are exposed to more mycotoxins (even if in very low concentrations) has been demonstrated by studies in which exposure was monitored by analysing urine samples.

In a more recent study urine samples of 101 individuals (healthy volunteers) in Germany were analysed by LC-MS/MS for 23 mycotoxins and their urinary metabolites (Gerding et al. 2014). 87% of the samples contained toxic metabolites, and more than half of the positive samples contained two or more compounds. DON and its urinary metabolite (DON-glucuronide) were the most frequent contaminants. The results suggested a low everyday exposure of the investigated German population to mycotoxins. Although 12% of samples exceeded the established TDI (tolerable daily intake) of 1µg/kg body weight set by the Scientific Committee on Food in 2002.

These results also underline the findings according to which multitoxic effects have to be taken into consideration.

The toxicity of combinations of mycotoxins cannot always be predicted based on their individual toxicities, because individual effects may be influenced by interactions, like antagonism, synergism or additive effects.

In 2011 the French INRA group (Grenier and Oswald, 2011) published the results of a meta-analysis of more than 100 publications describing interactions between mycotoxins.

Among the main conclusions of the analysis were:
- the type of interaction varies according to the parameter measured, is influenced by age, sex, nutritional status, duration and route of exposure, levels etc.;
- the co-exposure of more toxins usually leads to greater total effects compared to the total effect of each individual toxin, i.e., *the whole is greater than the sum of its parts' (Aristotle, 384-322 BC).*

This is very important from risk assessment point of view. Risk assessment studies are usually based on the toxicity and occurrence data of individual mycotoxins. It is very important to have reliable data regarding co-occurrence of toxins and their interactions in order to make a better risk assessment, to establish maximum levels and guideline values.

It was also an interesting conclusion that only a few papers investigated the interactions between *Fusarium* toxins which are of major concern worldwide and their co-occurrence has been supported by several surveys, and the number of studies investigating effect of low doses of toxins, representative of field situation is low.

That was the reason why our research group started series of experiments in which the interaction between low doses of the main *Fusarium* mycotoxins are investigated. In these experiments the following parameters were used for monitoring single and combined effects: body weight, feed consumption, blood clinical chemistry, antioxidant and lipidperoxidation parameters, haematotoxicity, comet assay (for genotoxicity) and histopathology.

Single and combined effect of fumonisin B₁ (FB₁) and T-2 toxin in rabbits

The individual and combined effects of 10 mg/kg FB_1 and 2 mg/kg T-2 toxin (n=12/group) mixed with fungal culture of *Fusarium verticillioides* and *Fusarium sporotrichioides* in feed between 40 and 70 days of age, i.e. for 28 days were investigated in weaned rabbits (Hafner et al., 2016). The T-2 exposure both alone and in combination resulted in 15-18% less final body weight compared to control and FB_1 treatment. There was a significant increase in the concentration of plasma total protein, albumin, fructosamine and creatinine in the group treated with FB_1 compared to the control. The liver and the kidney of most animals treated with T-2 toxin, FB_1 and their combination showed pathological changes, the occurrence of which was more frequent in animals exposed to both toxins. T-2 resulted in depletion of lymphocytes in the spleen. FB_1 and T-2 exerted synergistic effect on the antioxidant/oxidative parameters after 2 weeks of exposure, manifesting in less glutathione and glutathione peroxidase, while more malondialdehyde production. Both toxins caused DNA damage in the lymphocytes, which was more pronounced in the group fed T-2 toxin and T-2 combined with FB_1, without additive or synergistic effects (Table 1).

Interaction between FB₁ and DON + zearalenon in rabbits after 65 days exposure

In this study three, orally administered *Fusarium* toxins were tested on adult Pannon White male rabbits, focusing primarily on their reproduction endpoints (Szabó-Fodor et al., 2015). The four treatments were: control (C, toxin-free diet), F (5 mg/kg FB_1), DZ (1 mg/kg DON + 0.25 mg/kg ZEA), FDZ (5 mg/kg FB_1 + 1 mg/kg DON + 0.25 mg/kg ZEA) for 65 days (n=15/treatment).

Among the mycotoxins studied, additive or less than additive effect was found in case of spermatogenesis and sperm cell morphology, synergism in testosterone production, while FB_1 acted antagonistically against DON+ZEA on genotoxicity. All mycotoxins provoked moderate lipid-peroxidation, based on the changes of glutathione concentration, glutathione peroxidase activity and formation of malondialdehyde and conjugated dienes and trienes, and exerted slight genotoxicity, FB_1 acting antagonistically towards DON+ZEA combination (Table 2).

Table 1.

Type of interaction between 10 mg/kg FB1 and 2 mg/kg T-2 toxin when administered in feed for rabbits

Parameter examined (1)	Type of interaction (2)
feed intake, body weight (3)	antagonism
TP, ALB, CREA (4)	antagonism
GSH, GPx (5)	antagonism
MDA (6)	synergism
liver, kidney (7)	synergism / additive
Na/K ATPase activity (RBC) (8)	antagonism
genotoxicity (comet assay) (9)	antagonism

1. táblázat: Az interakció típusa 10 mg/kg FB1 and 2 mg/kg T-2 takarmánnyal történő bevitele esetén nyulakban; (1) a vizsgált paraméter, (2) az interakció típusa, (3) takarmány-felvétel, testsúly, (4) TP (total protein), össz-fehérje, ALB (albumin), CREA (kreatinin), (5) GSH (glutation), GPx (glutation-peroxidáz), (6) MDA (malondialdehid), (7) máj, vese, (8) RBC (red blood cell) vörösvértest Na/K ATP-áz aktivitása, (9) génkárosító hatás (comet assay)

Table 2.

Interaction between 5 ppm FB_1 and 1 ppm DON + 0.25 ppm zearalenon (ZEA) in rabbits after 60 days exposure

Parameter (1)	Type of interaction (2)
feed intake (3)	antagonism (NS)
lipid peroxidation (MDA, GPx, CD, CT) (4)	antagonism
testosterone production (5)	synergism
spermatogenesis (histology) (6)	additive
sperm cell morphology (7)	additive
weight of the spleen (8)	antagonism
genotoxicity (comet assay) (9)	antagonism

NS: not significant

2. táblázat: Az interakció típusa 5 ppm FB_1 és 1 ppm DON + 0,25 ppm zearalenon (ZEA) 60 napos expozícióját követően nyulakban; (1) a vizsgált paraméter, (2) az interakció típusa, (3) takarmány-felvétel, (4) lipid peroxidáció (MDA: malondialdehid, GPx: glutation-peroxidáz, CD: konjugált diének, CT: konjugált triének), (5) tesztoszteron termelés, (6) spermatogenezis (szövettan) (7) spermium morfológia, (8) a lép súlya, (9) génkárosító hatás (comet assay)

Interaction between FB₁, DON and zearalenon (ZEA) in rats after 5 days exposure

To test the complex, acute biochemical effects of combined, naturally co-occuring fusariotoxins, a 5-day rat study was performed. Mycotoxin treatment was invented by intraperitoneal injection: FB_1 (F): 9 µg/animal/day, DON (D): 16.5 µg/animal/day and ZEN (Z): 12.75 µg/animal/day. The binary (FD, FZ, DZ) and ternary (FDZ) mixture of toxins was applied in an additive manner. Bodyweight, feed intake and mortality was not affected by any of the treatments. Plasma aspartate transaminase (AST) activity was the highest in FD, FB_1 and DON toxins acting synergistically on it. In the liver reduced glutathione of the control differed from FZ, DZ and FDZ groups; within the toxin-treated groups F was different from FDZ. The hepatic GPx activity of the control group differed significantly from the FZ, DZ and FDZ, with synergism between Z and D, as well as F and D. None of the toxins alone or in combination exerted strong genotoxicity on lymphocytes, neither on the gross histopathological characteristics (Szabó-Fodor et al., submitted to publication).

In these above briefly described experiments low acute / chronic exposure to these combinations of mycotoxins didn't cause typical diseases, but the alterations indicated that the treatments already exceeded the metabolic and detoxification activity of the body.

From several studies related to interactions it has been concluded that because of the incredibly complicity, mycotoxin toxicology should be investigated from a holistic perspective. Integrated use of multi-omics approach is needed to study the molecular events at a comprehensive level (Dellafiora et al., 2017).

CONCLUSION

It is necessary to highlight the multidisciplinary nature of the mycotoxin problem, and to emphasize the importance of collaboration not only between scientists of the different fields (mycology, biochemistry, plant pathology, analytical chemistry, molecular biology, toxicology, food science, medicine, climatology, etc.), but also between scientists, and people working in the practice, in legislation, finance, authorities, etc..

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ÖSSZEFOGLALÁS - Mikotoxinok az élelmiszerláncban

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A közlemény a 17. Alpok-Adria tudományos konferencián (Hnanice, Csehország, 2018. április 10-én) elhangzott tudományos előadás anyaga. A mikotoxinok a penészgombák mérgező másodlagos anyagcsere termékei, amelyek világszerte előfordulnak, mint természetes környezetszennyező anyagok. Sajnos, ma még nem iktathatók ki az élelmiszerláncból. A közlemény összefoglalja a klímaváltozás miatt várható változásokat a mikotoxinok termelődésében, valamint az egyes mikotoxinok együttes előfordulásából (multi-toxikus expozíció) adódó problémákat. A kutatócsoport saját kísérleti eredményeivel is alátámasztja a multitoxikus hatások bonyolultságát, valamint azt, hogy az együttes hatás nehezen előrejelezhető.

Kulcsszavak: mikotoxin, klímaváltozás, multi-toxikus hatások