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DOI: 10.2478/aoas-2025-0127

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Received date: 29 May 2025

Accepted date: 30 October 2025

To cite this article: (2026). Stoev S.D. (2026). Risk assessment in compromised food safety due to underestimated hazard of masked mycotoxins or joint mycotoxin exposure and a safe approach to increase food security, Annals of Animal Science, DOI: 10.2478/aoas-2025-0127

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Running title: Risk assessment of joint mycotoxin exposure

Abstract

This review paper elucidates the most prevalent mycotoxins or mycotoxin combinations in feeds or foods and the possible hazard of mycotoxins occurrence for appearance of certain foodborne ailments in animals or humans. Studies on the occurrence of different mycotoxin combinations in various food commodities in different countries are briefly evaluated. The underestimated hazard of masked/modified mycotoxins and multiple mycotoxin exposure of humans or animals is also evaluated in relation to the current mycotoxin regulations. The risk assessment and risk management of such contamination of food commodities is briefly elucidated. Some natural detoxification methods as a safe approach to prevent adverse effects of target mycotoxins or mycotoxins combination are briefly reviewed. Some tips are given for the safe utilization of mycotoxin-contaminated feed/food by using target biological or/and natural supplements and/or mycotoxin binders. Safety and quality control measures throughout the entire food supply chain are proposed to prevent some target foodborne ailments. The real toxic effects of some target combinations of mycotoxins, as occurred in the real practice, are also assessed and some lower limit values are proposed in such cases.

Key words: food safety, foodborne ailments, risk assessment, masked mycotoxins, joint mycotoxin exposure

The mycotoxins are secondary toxic metabolites produced by fungi and can contaminate feeds/foods or raw ingredients, posing a serious hazard to animals or humans worldwide. Mold infestation in cereals occurs in the field or after the harvest and mycotoxin production is often unavoidable, because of some environmental factors, such as raining at harvest time or subsequent poor storage of feeds/foods ingredients. It is well known that multiple mycotoxin contamination of foods/feeds or raw ingredients occurs at a high rate (Stoev, 2023). Among more than 400 different types of known mycotoxins, only a few are the most dangerous for human/animal health, e.g. aflatoxins (AFs) with aflatoxin B1 (AFB1) and aflatoxin M1 (AFM1)

being the most dangerous, ochratoxin A (OTA), fumonisins (FUMs) with fumonisin B1 (FB1) being the most dangerous, ergot alkaloids, deoxynivalenol (DON), nivalenol (NIV), patulin (PAT), zearalenone (ZEA), diacetoxyscirpenol (DAS) and trichothecenes (mainly T-2 and HT-2) (Pereira et al, 2019; Marc, 2022). Some of the same mycotoxins can contaminate animal/chicken products, e.g. eggs, meat, and milk, if the animals/chicks are exposed to them (Vlachou et al, 2022).

Mycotoxin-contaminated feed is responsible for a lot of problems among animals/chickens, e.g. poor feed conversion, reduced body weight gain, various foodborne diseases, reproductive problems, immunosuppression and increased incidence of secondary infections (Stoev, 2015; Zhivkova et al, 2025). The same mycotoxins may have nephrotoxic (OTA and FB1) (**Figure 1**), hepatotoxic (mainly AFB1), neurotoxic (FB1), immunosuppressive (AFB1, OTA and T-2 toxin), carcinogenic (e.g. AFB1, OTA and FB1) (**Figure 2**), genotoxic/teratogenic (AFB1, OTA, T-2) (**Figure 3**) or oestrogenic (ZEA) effects (Kan and Meijer, 2007; Stoev, 2024a,b) (**Table 1**). The intimate mechanism of these toxic effects is often attributed to the apoptotic effect of mycotoxins, which in some particular cases has been shown to be due to activated endoplasmic reticulum stress (ERS) and subsequent excessive ER-phagy (Deng et al, 2023).

It is often reported that feeds/foods or food ingredients contain more than one mycotoxin, but the contamination levels were in compliance with EU regulations as they were below the maximum permitted values. However, such mycotoxin co-contamination could still exert toxic effects on animals or humans even at such low levels, due to additive or synergistic interactions between mycotoxins that are not taken into account (Bulgaru et al, 2025). Therefore, the necessary risk assessment and possible hazard for animals or humans must be carefully updated for such multimycotoxin exposure in order to define appropriate preventive measures in each particular case. The effectiveness of current regulatory measures is important not only to ensure adequate foods/feeds safety, but also to prevent excessive food waste and subsequent food losses. According to FAO, nearly 25% of the world's crops are contaminated with mycotoxins each year, resulting in the subsequent annual loss of nearly 1 billion tons of food or food commodities (Smith et al, 2016). It is important to highlight that many different types of losses attributable to mycotoxins are reported, e.g. losses from animal/human health disorders or death, decreased livestock production, increased costs for veterinary service or medical care, reduced growth of farm animals, research costs, costs for control and preventive measures, costs for mycotoxin detoxification, economic losses due to food or feed waste, etc. (Marc, 2022; Goda et al, 2025).



Figure 1. Macroscopic appearance of kidneys with mycotoxic porcine nephropathy (MPN). Different degree of enlargement and mottled or enlarged and pale appearance of kidneys in pigs of 6–8 months of age taken at slaughter time. (Stoev et al, 1998).

Figure 2. Carcinoma in the region of ureters (yellow arrows) of male chick exposed to 5 ppm OTA via the feed, which died at the end of the 20th month of the experiment. Large grey-white neoplastic foci are seen along the ureters and protruded significantly above its surface (Stoev, 2010a).

Figure 3. Malformations in newborn mice whose mothers were exposed to 20 ppm OTA and 6 ppm OTB in the feed given from day 7 up to day 12 of the pregnancy – astomia and anophthalmia (the both fetuses on left), 2 normal fetuses in the centre and spina bifida, e.g. facial cleft and maxillary hypoplasia (the fetus on right) (Stoev, 2022b).

Figure 4. Small grey-white foci on kidney surface in pig fed on diet containing 180 ppb OTA and 1000-3000 ppb penicillic acid (PA) at the end of the 3rd month. Below – normal appearance of kidney from control pig at the same age (Stoev et al, 2001).

Table 1. Target toxicity and susceptibility to major mycotoxins based on animal species, age and sex

Mycotoxins	Organs damaged	Target toxicity	Order of species sensitivity	Age and sex sensitivity
AFB1	Liver, kidneys	Hepatotoxic, nephrotoxic, carcinogenic, teratogenic, immunotoxic	Poultry > rabbits > pigs > ruminants	Young and female animals with increased sensitivity
OTA	Kidneys, liver	Nephrotoxic, hepatotoxic, carcinogenic, teratogenic, immunotoxic	Pigs > poultry > rabbits > ruminants	Male animals with increased sensitivity
DON	Liver, kidney, lymphocytes	Gastrointestinal toxicity, immunotoxic	Pigs > poultry > ruminants	Male and older animals with increased sensitivity
ZEA	Reproductive system (ovaries, testicles, uterus, vulva, vagina, mammary gland), liver, kidneys	Estrogenic	Pigs > dairy cattle > poultry > ruminants	Young prepubertal females with increased sensitivity
FB1 + FB2	Brain, liver, kidneys, small intestine	Neurotoxic, hepatotoxic, nephrotoxic, carcinogenic, teratogenic,	Horses > pigs > poultry > ruminants > fish	Females with increased sensitivity
T-2 + HT-2	Liver, kidneys, lymphocytes	Hepatotoxic, gastrointestinal toxicity, teratogenic, immunotoxic	Poultry > pigs > ruminants	Young animals with increased sensitivity

Nowadays, the EU has introduced maximum permitted values for the most dangerous mycotoxins in human foods or animal feeds (Stoev, 2023), but the same don't take into account the joint mycotoxin exposure and the synergistic effects between some target mycotoxins, which are often found in spontaneously contaminated foods/feeds. In order to ensure more adequate food safety, some additional regulatory measures should be introduced to take into account such synergistic or additive interaction between target mycotoxins. In this regards, the

knowledge of qualified experts in target research areas such as food and health science, human and veterinary medicine, and agriculture, is crucial for the successful implementation of such safety and regulatory measures (Stoev, 2023).

Masked (modified) mycotoxins or mycotoxin derivatives in feeds/foods also pose a great danger in terms of risk assessment and possible hazard for animals or humans, as they are not yet regulated. Modified mycotoxins cannot be easily detected by conventional analytical methods, because such mycotoxins are bound to some other substances in the food, making their detection and quantification in the food difficult. Modified mycotoxins can be also transformed back to their initial (parent) forms during digestion, causing toxic effects characteristic for the parent mycotoxins (Berthiller et al, 2013). Various methods, including Immunoassays, Chromatographic methods, Liquid chromatography tandem Mass spectrometry (LC–MS/MS), Gas chromatography and high-resolution mass spectrometry (GC-MS), and tandem mass spectrometry (MS/MS) are the most widely used techniques for the detection of masked mycotoxins (Fiby et al, 2021; Iqbal, 2021; Singh and Mehta, 2020). Some high- or ultra-performance chromatography systems coupled to mass spectrometry are also widely reported for their valuable application in determining the co-occurrence of multiple mycotoxins, incl. masked mycotoxins, in different food commodities (Battilani et al, 2020). Biosensor technologies, that have been recently developed for mycotoxin detection, use a specific bio-recognition component and a signal processing transducer. The advantage of these methods, compared to traditional food analysis methods, is high selectivity with little or no pre-treatment. These technologies do not require highly trained personnel and are very simple to implement (Ngolong Ngea et al., 2020). Therefore, careful monitoring of food commodities using some target methods is crucial to prevent human exposure to these mycotoxins and to escape any health threat (Stoev, 2015).

The purpose of this review paper is to elucidate the most prevalent mycotoxins in agricultural commodities and the potential hazard to animal/human health. Some useful methods for natural detoxification of mycotoxins will be briefly discussed. The risk assessment and management of the risk of mycotoxin contamination of foods/feeds will be evaluated. The suitability of the current mycotoxin regulations and recommendations with regard to the potential hazard for human/animal health will be briefly discussed. The underestimated hazard of masked/modified mycotoxins and multiple mycotoxin exposure of humans/animals will be elucidated.

Compromised food safety due to underestimated hazard of multiple mycotoxin exposure

It is well known that between 75% and 100% of the feed or food samples studied are contaminated with more than one mycotoxin at low levels, which could significantly impair animal or human health (Streit et al, 2012). The frequent co-occurrence of mycotoxins in feeds or foods demonstrates the crucial importance of multi-mycotoxin analytical methods. Multiple mycotoxin contamination in different feeds/foods and foodstuffs represents an important new challenge in terms of food safety, as toxicological information on the toxicity and health consequences of simultaneous intake of several mycotoxins is still very scarce and limited (Stoev, 2008; Stoev et al., 2010a,b; Akinmoladun et al, 2025; Bulgaru et al, 2025). Such an

assessment of adverse health effects is complicated by multiple exposures of farm animals to several mycotoxins in the practice that often have synergistic or additive toxic effects. Also, the susceptibility of animals and humans to each mycotoxin or combination of mycotoxins varies depending on age, species, duration of exposure, intake levels and nutrition. Furthermore, exposure to the toxic effects of several mycotoxins at low concentration with variable rate over long periods of time is expected in a diverse human diet. (Stoev, 2008; Stoev and Denev, 2013).

Screening of maize products intended for animal feeds in UK revealed that all investigated samples (67 n) contained several *Fusarium* mycotoxins simultaneously (up to 12) (Scudamore et al, 1998). FUMs and DON were reported to co-contaminate 75% of the samples. Another investigation by the same authors, made on 330 feed samples, revealed that maize was the most often co-contaminated and nearly 60% of the maize samples studied were positive for more than one mycotoxin, with AFs and FUMs being the most common mycotoxin combination of nearly 28% of samples (Scudamore et al, 1997).

Mycotoxin screening of Brazilian maize revealed that 54% of the samples tested were simultaneously contaminated with AFs and FUMs (Camargos et al, 2001). This is a worrying circumstance, as the country is one of the main producers of maize in the world, and such multiple mycotoxin contamination in Brazilian maize is of international concern. This co-contamination with both mycotoxins requires particular attention, as FB1 has been reported to have a synergistic effect on the development of liver neoplasia provoked by AFB1 (Grenier and Oswald, 2011).

A study of 416 feed samples originating from Southern Europe in years 2005 and 2009 showed that 22% of the same samples contained several mycotoxins (Griessler et al, 2010), as 23% of the samples coming from Spain and 32% of the samples coming from Italy were simultaneously contaminated with two or more mycotoxins, with trichothecenes, ZEA and FUMs being the most often co-occurring mycotoxins.

A similar study of 277 feed samples intended for fattening pigs in Portugal for contamination with ZEA, DON and OTA revealed that 10% of the samples tested contained any two of the same mycotoxins, with ZEA and DON co-occurring most often (Almeida et al, 2011).

Another study of 50 poultry feed samples in Slovakia, investigated for trichothecenes and ZEA, found that 84% of samples contained two or more mycotoxins. Co-contamination with four mycotoxins, e.g. ZEA, DON, HT-2 and T-2, was found most frequently in 32% of investigated samples (Labuda et al, 2005a). A further study of the same researchers on the presence of moniliformin, FB1 and FB2 in poultry feeds in Slovakia showed that 25% of the samples were co-contaminated with all three mycotoxins (Labuda et al, 2005b).

A study on mycotoxin content in diets of dairy cattle from Netherlands, revealed that ZEA and DON were found together in 44% of examined diets, as compound feed and silage were the main sources of mycotoxins (Driehuis et al, 2008).

Another study of 123 barley samples in Spain from the 2007-2008 harvest for AFs, ZEA and OTA, revealed that 31% of the samples were co-contaminated with AFB1 and OTA (Ibáñez-Vea et al, 2012a). Co-contamination with AFB1 and ZEA was seen in 12% of the samples, whereas co-contamination with AFB1, OTA and ZEA was in 27% of the samples. In a study carried out by the same researchers on the occurrence of trichothecenes (types A and B) in the same samples, it was found that 43% of the samples were co-contaminated with three

or more trichothecenes (Ibáñez-Vea et al, 2012b). Finally, the same authors concluded that 96% of the samples investigated in the previous studies were simultaneously co-contaminated by three or more mycotoxins (Ibáñez-Vea et al, 2012c), with the combinations DON, AFB1 and OTA or DON, AFB1, OTA and ZEA being the most common and seen in 29% and 26% of the samples studied, respectively.

A similar study of 82 samples of feed intended for sows, e.g. maize and wheat from different EU countries, conducted in 2008, for the presence of 23 mycotoxins, revealed that 75% of the samples were co-contaminated with two or more mycotoxins (Monbaliu et al, 2010), with the combination DON and FUMs being the most often observed.

In a recent study, 127 samples from 11 provinces in China were investigated for the presence of 15 mycotoxins, with AFB1 (0.56~97.00 µg/kg), DON (9.41~1570.35 µg/kg), FB1 (8.25~1875.77 µg/kg), FB2 (2.74~543.01 µg/kg), OTA (0.62~19.30 µg/kg), and ZEA (1.64~2376.58 µg/kg) being more frequently detected. The authors stated that AFB1 exposure from consumption of Coix seed and malt in China is of high health concern, because AFB1 is a genotoxic carcinogen with no threshold value and there is no provisional maximum tolerable daily intake (PMTDI) value for it. Therefore, there is a different risk at each exposure level of the same mycotoxin. The hazard Index (HI) method showed a range between 113.15-130.73% for malt, indicating a public health concern. The authors pay more attention to the cumulative effects of co-occurred mycotoxins, which impose development of safety management strategies in the future (Zhang Y et al, 2023).

Some other studies have investigated the mycotoxin exposure scenario in the EU adult population (De Santis et al, 2021) using values of urinary biomarkers, that were obtained by modelling the data from two European projects (Battilani et al, 2020; Brera et al, 2015). The primary outcome received was of a public health concern for AFM1, FUMs, NIV, T-2 and HT-2, and a low concern for DON, OTA and CIT. The margin of AFM1-exposure did not meet the reference value considered as a low risk priority. In regard to FUMs and T-2/HT-2, probable daily intake (PDI) values were found to be nearly 10 folds higher than tolerable daily intake (TDI), whereas PDI for NIV was found to be nearly 30 folds higher than the TDI, representing a significant health concern. DON and OTA were reported to be prevalent in the countries of the northern EU regions, whereas ZEA was reported to predominate in the countries of the southern EU regions (De Santis et al, 2021).

A multi-mycotoxin investigation of feed for dairy cattle and poultry in Kenya found that 96% of the samples contained more than one EU-regulated mycotoxin (Kemboi et al, 2020). Among AFs-positive samples, 100% also contained ZEA, 98% FUMs, 92% NIV, and 89% DON, and only a few contained T-2 toxin (6%) and HT-2 toxin (4%). In addition, 25% of the FB1-contaminated samples also contained OTA (Kemboi et al, 2020).

A similar study of 400 feed samples across multiple livestock species in northern Spain (Muñoz-Solano and González-Peñas, 2023) found that 63.5% contained at least two or more mycotoxins. The highest co-contamination rate was seen in poultry feed (70%), followed by sheep feed (63%), cattle feed (62%), and pig feed (59%). A recent study in Romania during 2021-2024 period revealed that six mycotoxins (total aflatoxins-AFs, FUMs, DON, ZEA, T2/HT2 and OTA) were the most frequently encountered in the south area of Romania in poultry, piglets and pig's complete feed. The maximum highest concentrations were reported to be 5.8 ppb for AFs, 4.7 ppm for FUMs, 1.9 ppm for DON, 62.8 ppb for ZEA, 32.1 ppb for

T2/HT2 and 19.7 ppb for OTA, regardless of the type of feed. AFs and ZEA were found to be present in all samples throughout the entire monitored period, and the only mycotoxin that exceeded the guidance value was DON (the recommended level of 0.9 ppm for pig feed was exceeded). It was concluded that sub-chronic and chronic simultaneous exposure to low mycotoxins levels and co-contamination are more common than acute exposure, and such low simultaneous exposure to several mycotoxins can affect animal health over time by lowering the defense capacity, inducing inflammatory reactions and damaging intestinal health, which may have important economic consequences (Bulgaru et al, 2025).

Globally, contamination with multiple mycotoxins still remains a serious problem, as it has been reported that 64% of feed samples worldwide contain at least two different mycotoxins (Gruber-Dorninger et al, 2019).

Despite all these studies, the extent of mycotoxin co-occurrence may still be underestimated, because most of the studies did not screen for the full spectrum of known mycotoxins, and the limitations in analytical techniques may hinder the detection of all contaminants present in the samples studied (Freire and Sant'Ana, 2018).

Although toxicological interactions between mycotoxins pose significant risks to animal health and production, there are currently no international regulations (or some scarce regulations only exist) that address the combined effects of multiple mycotoxins. Although scientific interest in the biological effects of multiple mycotoxin exposure has increased, research in this area is still in its early stages. Therefore, comprehensive monitoring of mycotoxin co-occurrence is crucial, not only to identify the most prevalent mycotoxin combinations, but also to inform regulatory priorities and mitigation strategies aimed at ensuring feed safety (Akinmoladun et al, 2025).

Currently, there is only limited information on the strong synergistic or additive effect between target mycotoxins, e.g.: FB1, OTA, PA, citrinin (CIT) and a new not yet identified nephrotoxic metabolite found simultaneously in feeds from farms with porcine or chicken nephropathy in some countries (Stoev et al., 2010a,b; Miljkovic and Mantle, 2022) or between some couples of mycotoxins such as OTA and PA (Micco et al., 1991; Stoev et al., 1999, 2000, 2001, 2004) or OTA and FB1 (Creppy et al., 2004; Klaric et al., 2007; Stoev et al, 2012), or OTA and CIT (Pfohl-Leszkowicz et al., 2008). It has been suggested that simultaneous exposure to such combinations of mycotoxins, even at low feed levels, is an important circumstance for the development of chronic kidney disease in animals or humans, especially after prolonged mycotoxin exposure. This assumption is based on the circumstance, that the same mycotoxin co-contaminations were seen at high- (PA and FB1) or low and moderate levels (OTA and CIT) in all feeds originated from farms with nephropathy problems in Bulgaria and South Africa (Stoev et al., 2010a,b). In the same studies of feed samples from Bulgaria and South Africa, taken from farms experiencing nephropathy problems, multiple mycotoxin contamination was found, but the contamination levels of OTA were significantly lower than the levels required to provoke kidney damages. Therefore, it is concluded that this nephropathy is provoked by the joint synergistic or additive effects between OTA, FB1 and PA (**Figures 5, Figure 6**).

Obviously, the available data on the joint toxic effects of mycotoxins are scarce, and the health risk of such multiple exposure to mycotoxins is often unknown (**Table 2**). Some researchers reviewed over 100 different cases on multi-mycotoxin interactions and revealed

that most of them reported additive or synergistic interactions between co-occurring mycotoxins in term of adverse effects on animal health (Grenier and Oswald, 2011). In this regard, a strong synergistic effect was seen between OTA and PA, mycotoxins produced by the same OTA-producing fungi, when these mycotoxins were given simultaneously to pigs or chickens (Micco et al., 1991; Stoev et al., 1999, 2000, 2001, 2004) (**Figure 4, Figure 5**).

Some mathematical models classifying interaction effects as antagonisms, additive effects, or synergisms (based on a comparison of the observed effect) have been reported. However, the same models are incorrectly based on the assumption that the dose-effect curves of mycotoxins are linear (simple addition of effects, factorial analysis of variance) (Kifer et al, 2020). It has been suggested that more appropriate mathematical models for assessing mycotoxin interactions include Bliss independence criterion, Loewe's additivity law, Response surface, Highest single agent (HSA) model, Combination index and isobologram analysis, Chou-Talalays median effect approach, Code for the identification of synergism numerically efficient (CISNE), MixLow method and some others. According to Kifer et al (2020), the only appropriate approach to assess the nature of the interaction is to correctly estimate the dose-effect curves of each mycotoxin and combination and to apply a well-defined model (based on Bliss or Loewe's theory) with respecting the model's assumptions and fitting the model by a direct estimation of all model parameters from a nonlinear least squares fitting. Also, the authors conclude that none of the proposed models is ideal, because they all have certain advantages and disadvantages (Kifer et al, 2020). On the other hand, the same mathematical models are based on "in vitro" studies, which can often confuse the final conclusion, because some of the synergistic effects such as the synergism between OTA and PA can be observed only "in vivo" (Micco et al, 1991; Stoev et al, 2001).

Table 2. Impact of combined mycotoxins exposure on body weight gain, productivity, organs damages and immune system of different livestock species

Mycotoxin combination	Type of interaction	Livestock species	Effect on health/productivity	Reference
AFB1+DON	synergistic	pigs	immunosuppression	Chaytor et al, 2011
AFB1+DON	synergistic	pigs	weight loss	Harvey et al, 1989
AFB1+DON	synergistic	dairy cattle	milk yield reduction	Kiyothong et al, 2012
AFB1+DON+ZEA	synergistic	dairy cattle	milk yield reduction	Kiyothong et al, 2012
AFB1+DON+ZEA	synergistic	dairy cows	milk yield reduction	Wu et al, 2022
AFB1+DON+ZEA	additive	dairy cows	immunosuppression	Jovaisiene et al, 2016
DON+ZEA	additive	dairy cows	immunosuppression	Danicke et al, 2017
AFB1+OTA+ZEA	synergistic	dairy cows	milk yield reduction	Wu et al, 2022
AFB1+OTA+ZEA	synergistic	dairy goats	milk yield reduction	Huang et al, 2017
AFB1+DON	additive	poultry	weight loss/rejection of feed	Huff et al, 1986
AFB1+T-2	synergistic	poultry	weight loss	Huff et al, 1988
AFB1+OTA	synergistic	sheep	fertility rate, litter number	Mohamed et al, 2019
AFs+OTA	additive	poultry	egg production, weight loss	Verma et al, 2003
AFB1+OTA	synergistic	broilers	liver/kidney damages	Qing et al, 2022
AFB1+OTA	synergistic	rabbits	weight loss/increased mortality	Prabu et al, 2013
AFB1+FB1	synergistic/additive	broilers	immunosuppression/liver damage	Tessari et al, 2006
AFs+FB1	additive	poultry	weight loss	Kubena et al, 1995
AFs+DAS	synergistic	poultry	weight loss	Kubena et al, 1993
AFB1+DAS	synergistic	pigs	weight loss	Harvey et al, 1991
OTA+PA	synergistic	pigs	kidney damage	Stoev et al, 2001
OTA+PA	synergistic	poultry	weight loss/organs damage	Stoev et al, 2004
OTA+T-2	synergistic	broilers	weight loss/organs damage	Kubena et al, 1989a
OTA+T-2	synergistic	pigs	weight loss/organs damage	Harvey et al, 1994
OTA+DAS	additive	chicks	weight loss/organs damage	Kubena et al, 1994
DON+ZEA	synergistic	pigs	weight loss/feed intake reduction	Jia et al, 2020
DON+ZEA	synergistic	pigs	ovarian/embryo damage	Malekinejad et al, 2007
DON+ZEA	synergistic	sows	damage of reproductive system	Doll et al, 2003
DON+ZEA	synergistic	hens	decrease in egg production	Gimeno et al, 2011
DON+T-2	synergistic	chickens	weight loss/oral lesions	Kubena et al, 1989b
FB1+DAS	additive	turkeys	weight loss	Kubena et al, 1997a
FB1+OTA	additive	turkeys	weight loss	Kubena et al, 1997a
FB1+OTA	additive	pigs	kidney/lung/brain damages	Stoev et al, 2012
FB1+T-2	additive	chickens	weight loss, mortality	Kubena et al, 1997b
FB1+DON	less than additive	chickens	weight loss	Kubena et al, 1997b

The combined toxic effect of mycotoxins may vary depending on their physiological effects or mechanisms of action and could exacerbate oxidative stress, immunosuppression, impaired reproduction and organ damage in different species, leading to reduced growth performance, decreased milk and egg production, compromised carcass quality, and increased mortality rates (Gimeno and Martins, 2011; Akinmoladun et al, 2025). Understanding the cellular mechanism of such interactions is critical for improving risk assessment models, formulating integrated mitigation strategies, and protecting both livestock productivity and human food security.

Obviously, it is of a great necessity to introduce new regulations and permissible limits in the case of combined mycotoxin contamination of foods or feeds, because such combinations of mycotoxins often have synergistic or additive interaction and contribute to a greater hazard to humans and animals. This circumstance also requires a simultaneous analysis for the co-occurrence of target mycotoxins in the feeds/foods and a subsequent assessment of the actual hazard of such co-contamination for animal or human health (Annunziata et al, 2025; Bulgaru et al, 2025). Furthermore, new permissible limits at some critical control points should be introduced by Hazard Analysis and Critical Control Point (HACCP) system in EU and worldwide, taking into account the real interaction of target mycotoxins co-contaminating feeds/foods and food products (Stoev, 2023).

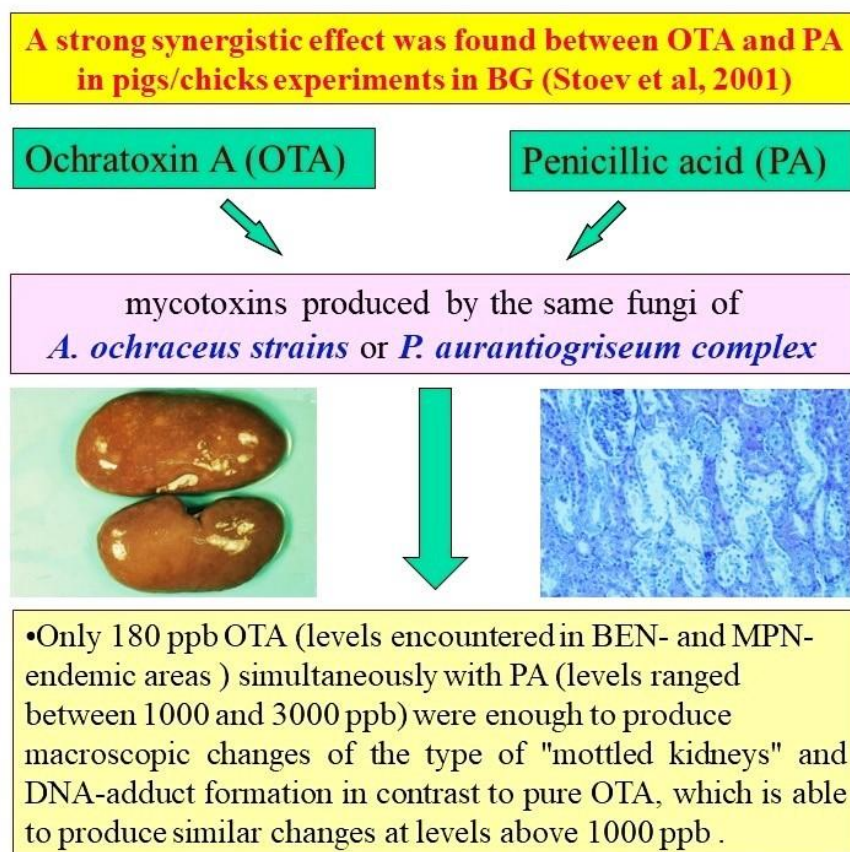


Figure 5. A strong synergistic effect between OTA and PA in pigs and chicks (Stoev et al, 2000, 2001, 2004)

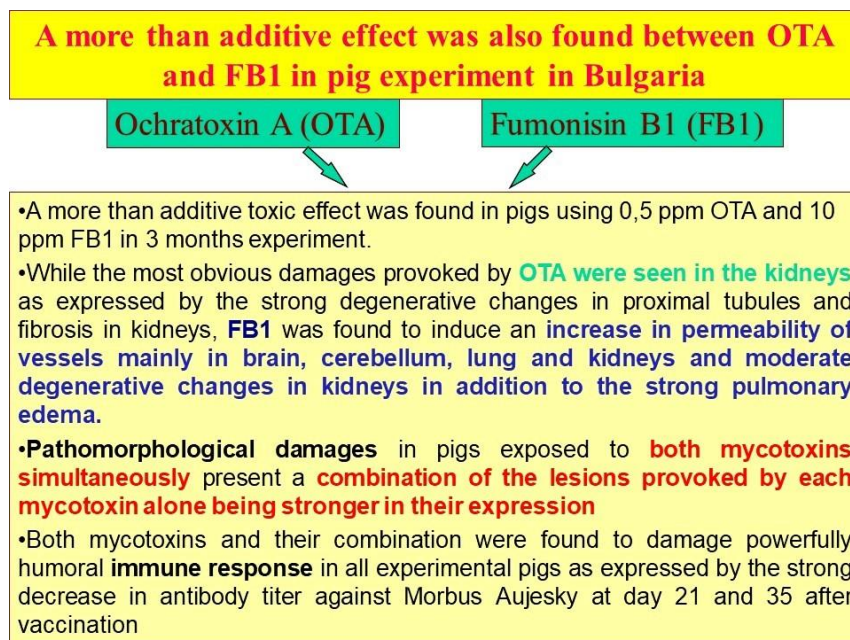


Figure 6. A more than additive effect between OTA and FB1 in pigs (Stoev et al, 2012)

Possible hazard of masked (modified) mycotoxins on human / animal health

Masked (modified) mycotoxins or mycotoxin derivatives in feeds/foods represent another major concern in terms of risk assessment and potential hazard to animals or humans. This happens because the same mycotoxins are hardly detected by conventional analytical methods, which are mainly designed to detect native (parent) mycotoxins. Therefore, the actual contamination levels and the hazard of masked/modified mycotoxins are often underestimated. Regarding mycotoxin contamination, modified mycotoxins represent an emerging problem that poses a potential hazard to human/animal health in terms of food and feed safety. Such plant metabolites (masked mycotoxins) have been found for many mycotoxins, such as DON, T-2 toxin, HT-2 toxin, ZEA, OTA, FUMs and the same can be seen mainly in cereal commodities, such as wheat, barley or corn (Berthiller et al, 2005; 2009, 2013). Unfortunately, toxicological data on such modified mycotoxins are very scarce. Some of them, such as glucoside conjugates of trichothecenes may exert a potential safety threat due to their hydrolyzation to toxic compounds during the digestive process (Dall'Erta et al, 2013). Most of mycotoxins conjugates, such as DON-3G, are found to have lower toxic potential due to reduced absorption in the gastrointestinal system (Nagl et al, 2012, 2014).

Part of the same mycotoxins appeared, because plants are seen to transform mycotoxins into conjugated forms, in order to reduce their toxicity. It is known, that mycotoxins may occur in a modified structure from their parent forms, which is often due to various plant detoxifying capabilities, which are involved in the defense against xenobiotics. Therefore, the chemical structure of mycotoxins is often altered by plants and various modifications are generated by enzymes participated in the detoxification process. Due to the modified chromatographic profiles of these modifications, they cannot usually be detected by conventional analytical methods and are therefore not regulated by legislation (Cirlini et al, 2012). The same

modifications are known as “masked” or “modified” mycotoxins. Usually, masked mycotoxins have lower toxicity compared to their parent compounds, but because of the increased bioavailability during digestion, they still represent a health threat (Berthiller et al., 2013).

In some cases, masked mycotoxins could be a significant part of the total mycotoxins contaminated the feeds, but after ingestion by animal/human, they could turn into the native (parent) mycotoxins after microbial or other kinds of metabolisms (Berthiller et al., 2013). Therefore, it could be assumed that the quantity of mycotoxins in foods and feeds or feedstuffs is actually larger, as the masked mycotoxins have not been measured or taken into consideration (Stoev, 2015).

Among mycotoxins, masked mycotoxins can be divided to extractable conjugated and non-extractable bound forms. The extractable conjugated mycotoxins could be detected when their structure is known, and if analytical standards have been developed. The bound forms of mycotoxins have to be initially separated from the matrix and subsequently subjected to target chemical analysis (Berthiller et al., 2013). The same bound mycotoxins are attached to carbohydrates or proteins by covalence or non-covalence, and cannot be detected by conventional mycotoxin analysis and, therefore, they must be released from the matrix by chemical or enzymatic treatment prior to analysis.

Masked mycotoxins can be transformed into their parent forms by using various forms of hydrolysis with carefully selected conditions (Sewram et al., 2003; Dall'Asta et al., 2009). This must be done in advance in order to use the known conventional analytical methods. However, the method of hydrolysis is different for each masked mycotoxin and no single hydrolysis method suitable for all masked mycotoxins has been elaborated. Usually, masked mycotoxins have lower toxicity when compared to their parent forms, but rarely they can have higher toxicity when their bioavailability is longer (Berthiller et al., 2013). Unfortunately, the scarce toxicokinetic and toxicodynamic investigations available in the literature don't allow an adequate assessment of the risk and potential hazard of masked mycotoxins, in contrast to their parent forms. Therefore, it is almost impossible to perform a proper risk assessment of contamination levels of masked mycotoxins in feeds or foods, due to the scarce data on their levels of exposure in different animals or humans and the lack of sufficient data on their actual toxic properties. Regarding the toxicity of masked mycotoxins, it must be taken into account, that these mycotoxins can be transformed in the gastro-intestinal tract of humans and animals, releasing their parent forms of toxins, thus increasing exposure to the same mycotoxins and posing an increased threat to human health. Therefore, it is of crucial importance to understand the fate of masked mycotoxins during food processing or digestion in order to estimate their possible involvement in the real toxicity on animals or humans. Nowadays, there is only scarce information on the occurrence of masked mycotoxins in feeds or foods, as well as on their transformation and stability or their release into the food chain. Furthermore, masked mycotoxins can easily escape the conventional detection methods due to the biotransformation of their structures.

Masked mycotoxins, that are not detected by conventional analytical methods, could explain why naturally DON-contaminated feedstuffs usually exerts a stronger toxic effect compared to feedstuffs artificially contaminated with pure DON (Dersjant-Li et al., 2003; Trenholm et al., 1994). The same conjugates (masked mycotoxins) could be produced by the fungi themselves (3-ADON, 15-ADON) or elaborated as a part of the defense mechanism of

infected plants (ZEA-4-Glucoside, DON-3-Glucoside) (Berthiller et al, 2009). The same masked mycotoxins may exert toxic effects themselves or may undergo conversion into their parent forms during digestive process and further increase the toxicity of mycotoxin-contaminated feeds (Garais et al, 1990; Vendl et al, 2009). Such conjugates are usually not detectable when tested for parent toxins.

Therefore, the effect of the gut microbiota on “masked mycotoxins” is of major concern, because of bioactivation of some masked mycotoxins. *In vitro* studies with DON-3glucoside revealed that human fecal microbiota is capable to hydrolyze DON-3glucoside (Dall’Erta et al, 2013). A recent study revealed that *Butyrivibrio fibrisolvens*, *Roseburia intestinalis*, and *Eubacterium rectale* hydrolyze DON-3- β -glucoside, HT-2- β -glucoside, and NIV-3- β -glucoside (Daud et al, 2020). Some other toxicokinetic studies in rats and pigs confirmed that the largest part of DON-3glucoside is excreted as DON (Broekaert et al, 2017; Gratz et al, 2018). Some additional toxicokinetic studies with different conjugated forms of ZEA confirmed the intestinal hydrolysis of these compounds in pigs (Catteuw et al, 2019). Therefore, in addition to the beneficial effect of the microbiota on the toxicokinetics of mycotoxins, a negative effect was also found in the form of hydrolysis of masked (conjugated) mycotoxins. Such hydrolysis is often associated with gastric acidity or digestive enzymes, and contributed to the release of parent mycotoxins (non-conjugated forms) in gastrointestinal tract and the subsequent increase in the overall toxicity of contaminated foods/feeds.

The presence of modified forms of mycotoxins in foods and feeds may pose a non-negligible additional risk to human or animal health and is an important emerging issue in health risk assessment (Lorenz et al, 2019). Therefore, European Food Safety Authority (EFSA) considered it appropriate to assume that many modified mycotoxins exhibit the same toxicity as their parent compounds and may substantially contribute to the overall exposure (EFSA, 2014, 2017a,b, 2018). In this regard, EFSA extended the TDI for ZEA of 0.25 $\mu\text{g/kg bw}$ to a group-TDI covering ZEA and its modified forms (EFSA, 2017a). Unfortunately, nowadays, realistic estimates of human dietary exposure to ZEA or DON and their modified forms, based on food consumption and occurrence data, are hampered by the lack of commercially available analytical standards and certified reference materials, in addition to the lack of validated analytical methods for the simultaneous quantification of the same mycotoxins and their modified forms (Lorenz et al, 2019).

Such a wide range of masked mycotoxins may co-appear as contaminants in addition to parent compounds in foods or feeds. The assessment of the actual hazard of the co-occurrence of some mycotoxins together with their masked forms in feedstuffs and food products represents a new big challenge for monitoring authorities and their regulatory bodies, which should be undertaken in order to protect the human and animal health and to evaluate human health hazard for the final consumers (Stoev, 2015).

On the other hand, the guidance values of mycotoxins for feedstuffs or cereals should be elaborated for the less tolerant animal species, but unfortunately the same are often done for the most tolerant ones. Therefore, such values should be considered as upper guidance value, and the lower guidance values should be applied by the manufacturers for cereals and feeds intended for more sensitive animals or poultry (EC Recommendations 2006/576/EC).

Natural methods of mycotoxins detoxification and/or elimination

Mycotoxin binder or adsorbent against mycotoxicoses

A promising strategy for decreasing mycotoxin exposure is to significantly reduce bioavailability of some mycotoxins by incorporating various mycotoxin-adsorbing agents into the feeds, which can decrease mycotoxin absorption. During the recent years, much attention is given to the way of mycotoxin adsorption and biotransformation. Adsorbing agents are usually substances of high molecular weight that can bind mycotoxins, preventing their absorption, and facilitating the fecal excretion of such adsorbent–toxin complexes (Santos et al, 2010). Such mycotoxin-adsorbing agents may include certain silica-based inorganic compounds or carbon-based organic polymers. For example, some feed additives are designed to bind mycotoxins in the gastrointestinal tract, reducing their bioavailability in the respective animals. In this regards, some bentonite clays, such as montmorillonite or Hydrated sodium calcium aluminosilicate clay (HSCAS) and others, as well as zeolitic minerals, are a broad family of silicoaluminosilicates, that have been found to have promising effects on the binding of mycotoxins in the gastrointestinal tract of some animals. They can significantly reduce the bioavailability of some mycotoxins and mitigate their adverse effects. Such clays have been reported to be effective in AFs-contaminated diets and to decrease AFs transmission to the milk of lactating animals (Huwig et al, 2001; Phillips et al., 2006; Kabak et al, 2007). However, it is important to emphasize, that such AFs-sequestering clays must not interfere with the nutritional value of agricultural commodities by binding various nutrients together with the target mycotoxin. The same adsorbents are a suitable approach for application mainly in regards to AFs-contaminated diets, and have only a minor effect on other mycotoxins such as OTA, T-2 toxins, FUMs and DON (Ramos et al., 1996; Kubena et al., 1998; Phillips et al., 2006, Phillips and Zhang, 2019; Schatzmayr et al., 2006a; Stoev, 2013; Di Gregorio et al, 2014). In this regards, T-2 toxin can be adsorbed by bentonite, only if its inclusion rate in the diet is 10 times higher (100 g/kg) than that for AFs (Carson and Smith, 1983). Phyllosilicates such as kaolin and sepiolite, like other clays, are slightly effective against mycotoxins other than AFs (Jouany, 2007).

Biological and natural supplements as a safe approach against mycotoxicoses

Having in mind the circumstance, that clay binders are poorly effective against mycotoxins other than AFs, natural organic binders have been also studied for the same purpose. Organic binders have been found to be more effective against a wide range of mycotoxins in comparison to inorganic binders, making them more suitable for multi-mycotoxin contaminated diets. Natural organic binders are also biodegradable, which prevents environmental pollution after their excretion by animals. On the other hand, clays can accumulate in manure and then spread in the field, causing a harmful effect to the environment (Jouany, 2007; Stoev, 2024a,b).

Another alternative strategy for mycotoxin control is “detoxification by biotransformation”, which is based on microbial degradation of mycotoxins into less toxic metabolites. Such degradation of mycotoxins can also be achieved by some microbial enzymes and target enzyme preparations (Stoev, 2025). Biological detoxification methods have been found to preserve flavor, nutritional quality, organoleptic properties, and have been reported to

be cost-effective and more promising than physical and chemical detoxification methods (Stoev, 2024a,b, 2025). For example, many microorganisms, e.g. actinobacteria, bacteria, filamentous fungi or yeast and/or their enzymes were found to detoxify OTA by biodegradation to its non-toxic form OT α (Chen et al, 2018). Such biological methods have also been reported to have great application prospects in the food/feed industries due to their safety and preservation of nutritional quality (Chen et al, 2018). On the other hand, it has been found that some microorganisms may have dual functions of degrading and/or adsorbing OTA (Péteri et al., 2007; Shi et al., 2013, Stoev, 2024a, 2025).

Interactions between mycotoxins and gut/ruminal microbiota may explain some of the differences in susceptibility across animal species, due to the protective effect of the microbiota against mycotoxin toxicity by degrading the molecules into less toxic metabolites and reducing the digestive absorption of target mycotoxins (Guerre, 2020; Yao and Long, 2020). Recently, the development of some probiotics derived directly from animal digestive flora has been initiated in order to ensure such mycotoxin degradation (Guerre, 2020; Li et al, 2020; Liu et al, 2022). Powdered *Pleurotus ostreatus* was recently tested for detoxification of OTA and ZEA via *in vitro* gastrointestinal digestion in the absence and presence of cornmeal and ground feed. *Pleurotus ostreatus* has been shown to have a high potential for OTA detoxification (Nobre et al, 2022). Another study revealed that the majority of detoxification due to *Lactobacillus* strains seems to be related to the binding of AFB1 and AFM1 (Afshar et al, 2020). *In vitro* detoxification of AFB1 by the probiotic *Saccharomyces cerevisiae* yeast is found to be similar to that observed with *Lactobacillus* (Chlebicz and Śliżewska, 2020). In this regard, the *Eubacterium* strain BBSH 797 has been reported to transform DON to de-epoxy-deoxynivalenol, which is a non-toxic metabolite (Binder et al, 1998). Similarly, the yeast strain *Trichosporon mycotoxinivorans* was found to be capable of detoxifying both ZEA and OTA (Molnar et al, 2004). *T. mycotoxinivorans* was found to cleave OTA into phenylalanine and ochratoxin α (OT α), that has no toxic effect on animals (Schatzmayr et al., 2006b). ZEA is detoxified by the same strain into the nontoxic metabolite ZOM-1, which has no estrogenic activity (Vekiru et al., 2010). In subsequent experimental feeding trials, both strains *Eubacterium* BBSH 797 and *T. mycotoxinivorans* were shown to detoxify the same mycotoxins *in vivo* (Binder et al., 2000; Politis et al., 2005). Another good example of similar degradation is the gene encoding carboxylesterase, which was isolated from a soil bacterium and cloned into *Pichia pastoris*, later renamed to *Komagataella pastoris*. The same enzyme can detoxify FUMs in the gastrointestinal tract of pigs into non-toxic metabolites (Hartinger and Moll, 2011).

On the other hand, mycotoxins can also have various detrimental effects on the intestinal microbiota, including disruption of the barrier effect provided by the gut and the subsequent risk of bacterial translocation or secondary bacterial infections, e.g. carcinogenesis and chronic diseases in human (Guerre, 2020; Mafe and Büsselberg, 2024). For example, DON exposure of broilers at levels of 3–4 ppm increased the percentage of birds, sick by subclinical necrotic enteritis caused by *C. perfringens* (Antonissen et al, 2014).

Another possible way to reduce the toxicity of mycotoxins is to clarify the mechanism of toxicity of each mycotoxin and to use specific supplements to the diet for preventing the specific toxicity of each particular mycotoxin (Stoev, 2008). For example, it has been found that adding 300 ppm ascorbic acid to a diet of laying hens containing 3 ppm OTA reduces its toxic effects, e.g. suppressive effect on the eggs production (Haazele et al., 1993).

Some herbal feed additives or plant extracts have also been shown to protect against various toxic effects of OTA, such as loss of weight gain in stock chicks (Stoev et al., 2000, 2002, 2004) or loss of egg production in laying hens (Stoev, 2010b). For example, water-extract of artichoke (*Cynara scolymus L.*), prepared as a steam infusion, has been shown to protect against OTA toxicity and to improve its elimination from body (Stoev et al., 1999, 2000, 2002, 2004). Feed additives such as Roxazyme-G (polyenzyme complement produced by "*Trichoderma*"), Rosallsat (plant extract of bulbus *Allii Sativi* and seminum *Rosae caninae*) have been found to protect against OTA toxicity in chicks (Stoev et al., 1999, 2002).

Some other herbs given as feed additives, e.g. *Silybum marianum* and *Silymarin*, *Withania somnifera* and *Centella asiatica* have also been found to protect against the hepatotoxic, nephrotoxic and immunosuppressive effects of OTA in chicks (Stoev et al, 2019, 2021b; Zhivkova et al, 2025). Protective effects against various toxic and immunosuppressive effects of OTA in chicks have also been observed with some Indian herbs, such as *Glycyrrhiza glabra* and *Tinospora cordifolia*, given as feed additives (Stoev et al, 2021a).

A protective effect of phenylalanine against toxic and carcinogenic effects of OTA in rats has also been reported, as OTA-induced tumours were much less in rats given phenylalanine as a dietary supplement (Stoev, 2021, 2022a).

A promising and safe strategy to combat ochratoxicosis in farm animals would be the dietary introduction of oleanolic acid, which has a nephroprotective effect and is a ubiquitous constituent in various fruit skins, food materials, and medicinal herbs. Some recent papers reported the alleviating effect of oleanolic acid on the mitochondrial-mediated and endoplasmic reticulum stress (ERS)-triggered apoptosis induced by OTA, with tumor necrosis factor receptor-associated protein 1 (TRAP1) playing an important role in this protective effect of oleanolic acid (Zhang Q et al, 2021).

Another possibility to combat ochratoxicosis would be the use of ursolic acid, which is a water-insoluble pentacyclic triterpene acid, which is also encountered in a wide range of food materials and medicinal plants. Ursolic acid has also nephroprotective effect, which is reported to be due to the alleviation of oxidative stress, reduction of reactive oxygen species (ROS) production and downregulation of ERS-induced apoptosis, all of which were provoked by OTA, with Lon protease 1 (Lonp 1) and Sigma 1-type opioid receptor (Sig-1R) playing important role in this protection (Li et al, 2019; Zhang Q et al, 2023).

The toxic effects of some mycotoxins could be avoided, when mycotoxin-contaminated feeds are given to animal species that are less sensitive to a particular mycotoxin. For example, ruminants are less sensitive to OTA and can hydrolyze it in their rumen to nontoxic metabolite OT α and can therefore safely utilize OTA-contaminated feeds (Sreemannarayana et al., 1988).

Another similar protection was seen with the combination of sodium bicarbonate and citric acid, given as additives to apple juice, which was reported to decrease PAT levels (Kim et al., 2018; Diao et al., 2018).

Some other studies have found that diets with low quantity of carbohydrates or increased content of proteins or diet with calorie restriction, could be used to alleviate the toxic effects of AFs (Meizhen and Ping, 2023; Nurul Adilah and Mohd Redzwan, 2017).

Therefore, any piece of knowledge about the metabolism of toxicity and the way of detoxification or elimination of each mycotoxin in each animal species is very important for finding a possible way to reduce the toxicity of each particular mycotoxin.

Risk assessment and possible hazard of multiple mycotoxin exposure of animals or humans

It is well known that cereals are invaded by fungi both in the field and after harvest, and the same fungi often produce more than one mycotoxin and, therefore, multi-mycotoxin contamination is usually observed in field conditions or during feeds/foods storage. The production of each mycotoxin usually depends on variety of circumstances, but mainly on the climate (Mafe and Büsselberg, 2024), the appropriate drying after the harvest, the type of cereal, and the storage conditions (Stoev, 2013).

It is important to note, that some weaknesses in the evaluation of the risk assessment should be taken into account. The use of HBM (human biomonitoring) data for various mycotoxins implies extensive knowledge of the metabolism of the same mycotoxins, but unfortunately there are still some gaps regarding toxicokinetic data of some mycotoxins that could make difficult an appropriate risk assessment to be made (Lorenz et al, 2019).

Such exposure to multiple mycotoxins often causes various adverse effects, that should be taken into account when assessing the combined risk of different mycotoxin combinations. The approaches used by some authors, e.g. assessment groups with a common target organ (such as liver and/or kidneys) or a common adverse effect, to evaluate the combined exposure to mycotoxins can be realized by Monte Carlo Risk Assessment (MCRA) (van den Brand et al, 2022). In the same study, the risk related to such combined exposure was estimated by toxicological reference values, e.g., health based guidance values. The authors revealed that estimation of the combined risk by adding the single compounds' risk distributions slightly overestimates the combined risk, as compared to combining the exposures at an individual level. However, the authors concluded that relative potency factors can be used to refine the mixture risk assessment (van den Brand et al, 2022).

Another similar study provides such realistic assessments of the risks related to cumulative mycotoxin exposure (Huang et al, 2021). A biomonitoring investigation of exposure to 23 mycotoxins/metabolites in 227 adults (between 20–88 years) in Yangtze River Delta region of China showed a presence of 8 mycotoxins in 110 urine samples, and mycotoxins co-contamination of two or more mycotoxins was reported in 51 of urine samples (22.47%), with DON, FB1 and ZEA being the most frequent contaminants. Combined Margin of Exposure (MOE_T) and Hazard Index (HI) models were used to evaluate cumulative risks of exposure to single or multiple mycotoxins (EFSA, 2013). The co-occurring mycotoxins in the same study were grouped together based on their similar toxicological effects on the target system or organ. For example, FB1 and AFB1 display similar toxicological qualitative profiles, with liver toxicity being the common toxic effect. Similarly, DON and ZEA have common estrogenic activity. Therefore, cumulative risk assessments were performed in regard to hepatotoxic effect (FB1 and AFB1) and endocrine effect (ZEA and DON). The single mycotoxin risk assessment in this study showed, that FB1, ZEA, AFB1, and OTA have potential adverse effects. However, in 12 samples co-contaminated with DON and ZEA, where none of the samples posed a hazard

risk (being within the TDI limits), the combination of DON and ZEA in two of the samples was found to have potential disrupting risks on the endocrine system of humans evaluated by HI method. It was also concluded, that the MOE_T for FB1 and AFB1 may pose a potential liver-related health problem. The cumulative health risks of exposure to multiple mycotoxins in this study were elucidated by using urinary biomarkers. The approach used provides an efficient methodology and strategy for assessing the cumulative risks associated with different mycotoxins and revealed new possibilities for correct interpretation of health hazards associated with such exposure to multiple mycotoxins (Huang et al, 2021). Such a strategy can avoid underestimating the health risks of exposure to multiple mycotoxins. However, it doesn't take into account the strong synergistic effect between some mycotoxins "*in vivo*", such as that between OTA and PA (Stoev et al, 2001, 2004).

In another study (under European project MYCHIF), mycotoxins of major toxicological relevance to humans and target animal species were studied in a range of crops of interest. In this regard, extensive literature searches were undertaken to collect data on analytical methods for native, modified and co-occurring mycotoxins, as well as their toxicity, toxicokinetics, toxicodynamics and biomarkers relevant to humans and animals. *In vitro* toxicokinetic and *in vivo* toxicity databases were used, both for single compounds and mixtures. The main objective of the study was to develop an integrated innovative method, supported by modelling, for the risk assessment of mycotoxin mixtures in foods and feeds. The authors conclude that the available literature on the toxicity of multiple mycotoxins mixtures, including their toxicokinetic and toxicodynamic properties, is rather scarce. The available data only cover a very limited combination of mycotoxins. However, major data gaps have been found in terms of the lack of common statistical and study designs within the literature. Furthermore, the authors state that harmonization is still lacking in the experimental settings and design of biomonitoring studies, in the data collection, and in the definition of performance criteria. The same issues make extremely difficult to use the available data for exposure assessment purposes. The authors advise that international research guidelines should be prepared to support the production of data, that can better contribute to future toxicological studies (Battilani et al, 2020).

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has also identified the potential risk from combined exposure to mycotoxins as a possible concern during its review of mycotoxins in the diet of infants and young children. Based on the available information, the COT was unable to complete a risk assessment on the potential risk from combined exposure to mycotoxins due to a lack of harmonisation of approaches/methodologies and data analysis/modelling for toxicological investigations. It was found that co-occurrence data in food are scarce, and the available methods for detection of multi-mycotoxins in food samples are still not harmonised for use in a regulatory setting (COT Evaluations, 2021).

Safety and quality control measures throughout the entire food supply chain are crucial for preventing some target foodborne diseases. However, such measures need to be integrated into a well-coordinated system. The ensuring of well qualified experts possessing necessary knowledge in some target scientific fields, e.g. agriculture, food science, veterinary medicine, environmental health science and food technology, in addition to the provision of target professional courses to upgrade current knowledge is of crucial importance for introducing such

safety and quality control measures in the real practice. It is clearly recognized, that only an integrated approach and systematic identification and assessment of various hazards in the food chain and/or food supply, as well as the effective control measures, e.g. the introduction of HACCP system in most of the countries, could resolve the current food safety problems in each separate country (Stoev, 2013, 2023). It is already of great importance to adopt more effective measures aimed at preventing unsafe food from entering the market and at resolving the current food security problems in the internal market to protect human or animal health.

Another major problem is that regular monitoring of food quality is mainly carried out in developed countries due to the well-designed infrastructure, while developing countries often do not enforce safety regulations. Furthermore, when food safety standards are introduced in such countries, the same could stimulate the export of the highest quality crops to meet the standards introduced in the respective importing countries and to keep the export market. However, by leaving the low-quality crops (heavily contaminated with mycotoxins) in the domestic market a higher risk of mycotoxins exposure of the people in developing countries could be realized (Stoev, 2013). Unfortunately, such strict import regulations can lead to additional health problems and risk burden among the population of the exporting country. Moreover, the meeting EU or US safety standards regarding mycotoxin contamination often results in subsequent loss of the export markets or, alternatively, the exportation of the best quality crops with the lowest mycotoxin contamination in order to preserve the export market. Therefore, the balance between economic issues and consumer risk should be also taken into account in such cases (Stoev, 2023, 2024b; Goda et al, 2025).

Many countries around the world have elaborated their own limits to control some target mycotoxins in foods or feeds (Stoev, 2015, 2023; Long et al, 2025). For example, the EU has developed maximum permitted levels or guidance values for the most dangerous mycotoxins in certain animal feeds (EC Directive 2002/32/EC, EC Directive 2003/100/EC, EC Recommendations 2006/576/EC and 2013/165/EU) and human foods (EC Regulation No 2023/915 and EC Recommendation 2013/165/EU). The USDA (United States Department of Agriculture) has also developed such limits for USA (USDA, 2017). Unfortunately, simultaneous exposure to several mycotoxins via the foods/feeds has not been taken into account in all these limits and guidance values (Stoev, 2023). In such cases, simultaneous exposure to several mycotoxins, even at very low levels for a long period of time (e.g. simultaneous exposure to OTA and PA), represents a significant hazard for animal/human health (Stoev et al, 2001, 2004; Stoev, 2017; Bulgaru et al, 2025). This circumstance imposes to clarify and assess the real toxic effects of some target combinations of mycotoxins, as occurs in real practice, and to adopt new limit values in such cases (Stoev, 2023). Therefore, the current Maximum Permitted Levels (MPL) of individual mycotoxins in foods or feeds (**Table 3, Table 4**) or TDI values of mycotoxins set by EU- or US regulations are not very helpful, because these regulations are mainly based on the assessment of toxic effect of each individual mycotoxin on different animals or humans and don't take into consideration the interactions between some mycotoxins as occurs in practice. It has been found, that some target combinations of mycotoxins, naturally occurring in spontaneously contaminated food commodities, often have significantly stronger synergistic toxic or carcinogenic effects at much lower contamination levels than permitted ones (MPL or TDI) for each individual mycotoxin (Stoev, 2023). This imposes elaboration of new carefully designed international biomonitoring and control, in

addition to the current one, which should take into consideration the stronger toxic effects of some mycotoxins when they are ingested in certain combinations similarly to those between OTA and PA (Micco et al, 1991; Stoev et al, 2001, 2004) (**Figure 4, Figure 5**) or between OTA and FB1 (Stoev et al, 2012) (**Figure 6**), in order to achieve appropriate food safety and control measures (Stoev, 2023).

Table 3. Maximum permitted content of some target mycotoxins in various feeds designed for animals according to EU legislation and regulation (EC Directive 2002/32/EC, EC Directive 2003/100/EC, EC Recommendations 2013/165/EU and 2006/576/EC)

Mycotoxins	Cereals or Cereal Products	Maximum permitted levels µg/kg (ppb)
AFB1	-Complete feedstuffs for pigs and poultry (except young animals) -Complete feedstuffs for cattle, sheep and goats with exception of: ✓ Complete feedstuffs for dairy animals ✓ Complete feedstuffs for calves and lambs -Complimentary feedstuffs for cattle, sheep and goats (except dairy animals , calves and lambs)	20 20 5 10 20
OTA	-Cereals and cereal products -Complimentary and complete feedstuffs with exception of: -Complimentary and complete feedstuffs for pigs -Complimentary and complete feedstuffs for poultry	250 5000 50 100
DON	-Cereals and cereal products without maize by-products -Maize by-products -Complimentary and complete feedstuffs with exception of: ✓ Complimentary and complete feedstuffs for pigs ✓ Complimentary and complete feedstuffs for calves, lambs and kids	8000 12000 5000 900 2000
ZEA	-Cereals and cereal products without maize by-products -Maize by-products -Complimentary and complete feedstuffs for dairy cattle, calves, goats (e.g. kids) and sheep (e.g. lambs) -Complimentary and complete feedstuffs for piglets, gilts (young sows) -Complete and complimentary feedstuffs for fattening pigs and sows	2000 3000 500 100 250
Fumonisin FB1 + FB2	Maize and maize by-products -Complimentary and complete feedstuffs for pigs, horses, rabbits, pets	60000 5000 20000

	-Complimentary and complete feedstuffs for poultry, calves, lambs, kids -Complimentary and complete feedstuffs for adult ruminants and mink -Complimentary and complete feedstuffs for fish	50000 10000
T-2 + HT-2	-Unprocessed barley (e.g. malting barley) and maize -Unprocessed rye, wheat and other cereals -Unprocessed oats (with husk) -Oat milling products (husks) for feed and compound feed -Other cereal products for feed and compound feed -Compound feed, excluding the feed for cats	200 100 1000 2000 500 250
Rye ergot	-All feedingstuffs containing unground cereals	1000000

Table 4. Maximum permitted content of some target mycotoxins in various food products intended for human food according to EU legislation and regulation (EC Recommendation 2013/165/EU and EC Regulation 2023/915)

Mycotoxins	Food Products	Maximum permitted level (EU) µg/kg (ppb)
AFs sum of B1, B2, G1 and G2	-All cereals and processed cereal products excluding: ✓ Maize/rice subjected to physical treatment before placing on the market for the final consumer or being used as a food ingredient, and chillies, chilli powder, cayenne, white or black peppers, paprika, ginger, turmeric and nutmeg	4 10
	-Dried fruit subjected to physical treatment, before placing on the market for the final consumer or use as ingredient in feedstuffs	10
	-Dried fruits used as only ingredient or processed products from dried fruits, placed on the market for the final consumer or use as a food ingredient	4
	-Groundnuts and oilseeds subjected to physical treatment, before placing on the market for the final consumer or use as a food ingredient with exception of that for refined vegetable oil production	15 4
	-Groundnuts and oilseeds used as only ingredient or processed products from groundnuts and oilseeds, placed on the market for the final consumer or use as a food ingredient with the exception of: crude vegetable oils and refined vegetable oils	10
	-Tree nuts to be subjected to physical treatment before placing on the market for the final consumer or use as a food ingredient	4

	-Tree nuts used as only ingredient or processed products from tree nuts, placed on the market for the final consumer or use as a food ingredient -Almonds, pistachios and apricot kernels subjected to physical treatment, before placing on the market for the final consumer or use as a food ingredient -Almonds, pistachios and apricot kernels, placed on the market for the final consumer or use as a food ingredient -Hazelnuts and Brazil nuts subjected to physical treatment, before placing on the market for the final consumer or use as a food ingredient -Hazelnuts and Brazil nuts, placed on the market for the final consumer or use as a food ingredient	15 10 15 10
AFB1	-Groundnuts and oilseeds subjected to physical treatment, before placing on the market for the final consumer or use as a food ingredient with exception of that for refined vegetable oil production -Groundnuts and oilseeds used as only ingredient or processed products from groundnuts and oilseeds, placed on the market for the final consumer or use as a food ingredient with the exception of: crude vegetable oils and refined vegetable oils -Tree nuts to be subjected to physical treatment before placing on the market for the final consumer or use as a food ingredient -Tree nuts used as only ingredient or processed products from tree nuts, placed on the market for the final consumer or use as a food ingredient -Almonds, pistachios and apricot kernels subjected to physical treatment, before placing on the market for the final consumer or use as a food ingredient -Almonds, pistachios and apricot kernels, placed on the market for the final consumer or use as a food ingredient -Hazelnuts and Brazil nuts subjected to physical treatment, before placing on the market for the final consumer or use as a food ingredient -Hazelnuts and Brazil nuts, placed on the market for the final consumer or use as a food ingredient -Dried fruit subjected to physical treatment, before placing on the market for the final consumer or use as ingredient in foodstuffs -Dried fruits used as only ingredient or processed products from dried fruits, placed on the market for the final consumer or use as a food ingredient -All cereals and processed cereal products excluding:	8 2 5 2 12 8 8 5 5 2 2 5

	✓ Maize/rice subjected to physical treatment before placing on the market for the final consumer or use as a food ingredient, and chillies, chilli powder, cayenne, white or black peppers, paprika, ginger, turmeric and nutmeg ✓ Processed cereal-based foods and baby foods for infants or children and food for special medical purposes	0.1
AFM1	-Raw milk, heat-treated milk and milk-based products -Dietary foods for special medical purposes and infant milk	0.05 0.025
OTA	-Unprocessed cereals -Processed cereal products and products derived from unprocessed cereals placed on the market for the final consumer -Bakery wares, cereal snacks and breakfast cereals not containing oilseeds, nuts or dried fruits -Dried vine fruit (currants, raisins and sultanas) and dried figs -Other dried fruits -Roasted coffee beans, cocoa powder, and ground roasted coffee, excl. soluble instant coffee -Soluble coffee (instant coffee) -Wine (incl. wine-based drinks,), wine-products or cocktails and grape juice or nectar placed on the market for the final consumer -Processed cereal-based foods, baby foods for infants/children and food for special medical purposes intended for infants -Dried spices and ginger -Dried herbs -Chillies, chilli powder, cayenne, paprika, -Licorice root, ingredient for herbal infusion -Licorice extract, for use in food in beverages and confectionary -Pistachios subjected to physical treatment before placing on the market for final consumer or use as a food ingredient -Pistachios placed on the market for final consumer or use as a food ingredient -Sunflower seeds, pumpkin seeds, (water) melon seeds, hempseeds, soybeans -Non-alcoholic malt beverages	5 3 2 8 2 3 5 2 0.5 15 10 20 20 80 10 5 5 3
PAT	-Fruit juices, fruit nectars, spirit drinks, cider and other fermented drinks derived from apples or containing apple juice -Solid apple products placed on the market for the final consumer, incl. compote or apple puree -Baby foods and apple juice or solid apple products for infants and children incl. compote or apple puree	50 25 10
DON	-Unprocessed cereals other than durum wheat, oats and maize	1250 1750

	-Unprocessed durum wheat, oats and unprocessed maize, with the exception of unprocessed maize intended for wet milling -Cereals placed on the market for the final consumer such as flour, semolina, bran, pasta and germ except rice products -Bread and bakery wares, pastries, biscuits, cereal snacks or breakfast -Processed cereal-based foods and baby foods for infants and children except rice products -Maize flour not placed on the market for the final consumer	750 500 200 1250
ZEA	-Unprocessed cereals other than maize -Unprocessed maize except the maize intended for wet milling -Cereals placed on the market for the final consumer such as cereal flour, semolina, bran, germ, except rice and rice products -Refined maize oil -Bread and bakery wares, pastries, biscuits, cereal snacks or breakfast, excluding maize-snacks and maize-based breakfast cereals except rice and rice products -Maize placed on the market for the final consumer such as snacks and breakfast cereals -Processed cereal-based foods and baby foods for infants and children -Maize flour not placed on the market for the final consumer	100 350 75 400 50 100 20 300
Fumonisin FB1+FB2	-Unprocessed maize, except the maize intended for wet milling -Maize and maize-based food placed on the market for the final consumer, excluding: ✓ Maize-based breakfast cereals and maize-based snacks ✓ Processed maize-based foods or baby foods for infants and children -Maize flour not placed on the market for the final consumer	4000 1000 800 200 2000
Ergot sclerotia	-Unprocessed cereal grains except unprocessed rye grains, maize and rice -Unprocessed rye grains	200000 500000
Ergot alkaloids (sum of ergocornine, ergocristine, ergocryptine , ergometrine,	-Milling products of barley, wheat, spelt and oats (with an ash content lower than 900mg/100g dry matter) -Milling products of barley, wheat, spelt and oats, incl. barley, wheat, spelt and oats grains placed on the market for the final consumer (with an ash content equal or higher than 900mg/100g dry matter) -Rye milling products and rye placed on the market for the final consumer -Processed cereal-based food for infants and young children	100 150 500 20

ergosine and ergotamine)		
T-2 + HT-2	-Cereal grains for direct human consumption: ✓ Maize ✓ Oats ✓ Other cereals -Cereal products for human consumption: ✓ Oat bran and flaked oats ✓ Cereal bran except oat bran, oat milling products other than oat bran and flaked oats, and maize milling products ✓ Other cereal milling products ✓ Bread, bakery wares, pastries, biscuits, cereal snacks, pasta ✓ Breakfast cereals including formed cereal flakes ✓ Cereal-based foods for infants and young children	100 200 50 200 100 50 25 75 15
Citrinin (CIT)	-Food supplements based on rice fermented with red yeast <i>Monascus purpureus</i>	100

In this regard, knowledge about the metabolism and the mode of detoxification and elimination of each mycotoxin in each animal species is of particular importance. The mechanism of interaction between target mycotoxins should be evaluated not only “in vitro”, but also “in vivo”, because it could be completely different in the both cases. For example, the increase in OTA-toxicity in spontaneous cases of mycotoxic nephropathy is often due to impaired detoxification of OTA by PA, when the both mycotoxins are present in spontaneously contaminated feeds (Stoev et al, 2001, 2004). The pancreatic enzyme carboxypeptidase A is known to play an important role in the detoxification of OTA in small-intestine, but PA can inhibit carboxypeptidase activity (Parker et al, 1982), which significantly alters the primary detoxification of OTA in the gut and it may be partly responsible for the increase of OTA toxicity (in combination with PA) (**Figure 5**). Therefore, any piece of knowledge in the metabolism and interaction between any couple of mycotoxins will be very important for elaboration new mycotoxin regulations that take into account such interactions between mycotoxins.

It is also necessary to achieve adequate international harmonization of mycotoxin regulations and to implement global control of the content of different mycotoxins and mycotoxin combinations in order to facilitate the international food trade and to prevent possible hazards from exposure to multiple mycotoxins. Such global food safety should be based on the multiple mycotoxin exposure as happen in real practice. Therefore, a carefully designed risk assessment of the hazard of any combination of certain mycotoxins for all different animals or humans must be developed in order to ensure adequate protection of animal/human health (Stoev, 2024b).

In this regards, a well developed networking system should be also elaborated for ensuring adequate dissemination of new knowledges. It is also important to provide reasonable education of the staff and to ensure adequate training at regional and international level. The elaborated new mycotoxin regulations, should be scientifically sound and based on the close cooperation between interested parties, e.g. consumers, industry and policy makers, traders, in

order to achieve adequate protection of human/animal health and to avoid unjustified rejections of raw food commodities. Implementing such a networking system and international control measures on a global scale would be a difficult task, as many factors should be taken into consideration when developing such regulatory measures. In addition to the scientific factors, e.g. risk assessment of target mycotoxin combinations in each animal species and analytical accuracy, some important economic and political factors, including the necessity of sufficient food supply and the commercial interests of each individual country, could also influence the decision making process (Stoev, 2023). It should also be taken into consideration that very restrictive international regulations could create some additional trade barriers and subsequent economic troubles for producers.

Concluding remarks

Nowadays, the official national or international regulations for control, prevention and monitoring of mycotoxin exposure of animals/humans are determined on the base of toxicological data coming from experimental studies addressing only one mycotoxin exposure at a time, without taking into account the joint mycotoxin exposure. Unfortunately, the mycotoxins co-occurrence in the field is the most common case of mycotoxins contamination (Annunziata et al, 2025; Bulgaru et al, 2025), and it is explained by multiple mycotoxins production by a single fungus or by simultaneous contamination of foods and feedstuffs by several fungi. In addition, animal diets are usually prepared using multiple grain sources, which further contribute to multiple mycotoxin contamination of the final ground complete feeds. Considering the current regulation in EU or USA, based on the MPL and TDI of each individual mycotoxin, it is really difficult to predict the toxicity of various mycotoxins combinations based on the individual toxicities of each single mycotoxin, because the multiple mycotoxins exposure often shows additive, synergistic or antagonistic toxic effects between target mycotoxins (Speijers G and Speijers M, 2004; Mafe and Büsselberg, 2024).

The frequent occurrence of mycotoxin co-contamination and the reported data on additive or synergistic interaction of many co-occurring mycotoxins, suggest that rules and guidelines for MPL and TDI should be elaborated not only for each individual mycotoxin, but also for some target combinations of mycotoxins commonly found in feeds or foods and having synergistic or additive interaction. However, before such guidelines can be developed, more data and further experimental studies are necessary to determine the effects of different combinations of mycotoxins on various animal species, poultry or humans. The same studies should be directed towards improving the available knowledge on the toxicological effects of co-occurring mycotoxins, in order to make possible the revision of current guidelines and permissible limits for mycotoxins in feeds or foods and to ensure better protection of animal/human health. Therefore, the supposed synergistic or additive interactions between all often encountered mycotoxins should be thoroughly investigated, but the possible interaction between all emerging mycotoxins such as enniatins, beauvericin, moniliformin, fusaproliferin, fusaric acid, culmorin, butenolide, sterigmatocystin, emodin, mycophenolic acid, alternariol, alternariol monomethyl ether, and tenuazonic acid should be also taken into account. Obviously, not all of the same mycotoxins (compounds) are toxicologically relevant at their naturally occurring levels and therefore do not pose a particular risk to the health of consumers.

However, some gaps in knowledge have been identified for some of the same compounds and these gaps should be closed by the scientific community in the coming years to allow a proper risk assessment (Gruber-Dorninger et al, 2017).

Such control measures, taking into account any possible interaction between mycotoxins, should be introduced worldwide for ensuring reliable control and synchronization of existing national regulations. The same control measures should be based on recent scientific achievements and the risk analysis of human/animal health hazard (Kaur and Anand, 2025; Long et al, 2025). In the cases of some difficulties in the creation of such internationally recognized regulations for mycotoxins, more easy and profitable measure could be the introduction of some temporary guideline limits, when a significant hazard for animal or public health is seen.

Currently, the scarce toxicokinetic and toxicodynamic studies make it difficult to evaluate adequately the risk assessment and possible hazard of masked mycotoxins, because the contamination levels of such mycotoxins in feeds or foods are often not really being taken into account. Therefore, the data on their levels of exposure to different animals or humans are often obscured, having in mind the scarce information about the occurrence of masked mycotoxins in feeds or foods. Nowadays, more data should be collected on actual toxic properties of such mycotoxins in different animals, taking into account toxicokinetic or toxicodynamic profile of such mycotoxins in each kind of animal or humans. Also, it is important to clarify the fate of masked mycotoxins during food processing or digestion in each animal or human in order to estimate adequately the real toxic effect of these mycotoxins. The lack of commercially available analytical standards and certified reference materials, in addition to the absence of validated analytical methods for the simultaneous quantification of target mycotoxins such as ZEA or DON and their modified forms, make it incredible difficult to estimate the real human/animal health hazard of simultaneous exposure to the same modified mycotoxins together with their parent forms.

Acknowledgements

This research was partially supported by European Community under Marie Curie Outgoing International Fellowship under the 6th framework and Marie Curie International Research Staff Exchange Scheme under 7th framework (PIRSES-GA-2012-316067) and Department of Science and Technology in South Africa.

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Received: 29 V 2025

Accepted: 30 X 2025