ENVIRONMENTAL BIOTECHNOLOGY 3 (1) 2007, 25-29

Multi-mycotoxicosis*

Maciej Gajęcki, Łukasz Zielonka, Kazmierz Obremski, Ewa Jakimiuk, Magdalena Gajęcka

Division of Veterinary Prevention and Feed Hygiene, Department of Veterinary Health Protection, Faculty of Veterinary Medicine, University of Warmia and Mazury in Olsztyn, 10-950 Olsztyn, Oczapowskiego 13, Poland
Phone and fax: (+48) 89 523 36 18; e-mail: gajecki@uwm.edu.pl
Keywords: antagonism, feed materials, mycotoxicosis, synergism

ABSTRACT

Contamination of food and feeds with mycotoxins is a major problem of human and animal's health concern, and it is also extremely detrimental to economy. Mycotoxin-producing moulds may produce the most known mycotoxins, such as aflatoxins, ochratoxin, trichothecenes, zearalenone and fumonisin. Although toxicological, environmental and epidemiological studies have addressed the problem of these toxins one by one, more than one mycotoxin is found usually in the same contaminated commodities. That raises the incommensurable problem of multi-mycotoxicosis in which the respective metabolites are also involved. These mycotoxins bear potential toxicity leading to acute and chronic effects in humans and animals, depending on species. The mechanisms that lead to toxic effects, such as immune toxicity and carcinogenicity, are complex. The risk assessment for humans potentially exposed to multi-mycotoxins suffers very much from the lack of adequate food consumption data. Furthermore, for a given mycotoxin additive, synergism and antagonism with other mycotoxins found in the same food commodities are usually not taken into account.

INTRODUCTION

Both humans and animals are exposed to an influence of undesirable substances disturbing their homeostasis. These effects derive from: (i) active substances produced by plants in a natural way (Lephart et al. 2005; Schreihofer 2005), e.g. mycotoxins (Gajęcki 2002; Gareis et al. 2003); (ii) industrial pollution emitted to the environment (Inadera 2006; Vidaeff and Sever 2005); (iii) pest control products (Zala and Penn 2004); and (iv) residues of medicinal products (Stolker and Brinkman 2005). These substances are usually ingested and hence penetrate into animals (Cavret and Lecoeur 2006) as well as humans (Gajęcki et al. 2004, Gajęcki 2007).

Mycotoxins constitute a group of secondary metabolites of moulds, especially of *Penicillium*, *Aspergillus* and *Fusarium* genera (Moss 1991), which may demonstrate acute toxic properties, mutagenic (aflatoxins, fumonisin, ochratoxin A, luteoskyrin, T-2 toxin), teratogenic (ochratoxin A, patulin, aflatoxin B, T-2 toxin) (Szkudelska et al. 2005; Wangikar et al. 2004a, b) and estrogenic (zearalenone) properties (Cavaliere et al. 2005; Jarvis and Miller 2005). The contamination of food and feedstuffs with toxic secondary metabolites of saprophytic and pathogenic plants has been regarded as a global problem (WHO Technical Report Series 906, 2002 – Evaluation of Certain Mycotoxins in Food. 1-74 p. Fifty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives) and is being constantly investigated in many countries (Gareis et al. 2003; Pohland 2003; Sapsford et al. 2006; Schollenberger et al. 2006).

Mycotoxins in terms of the chemical structure rank among low molecular weight aromatic hydrocarbons (sometimes among aliphatic hydrocarbons), what determines their resistance to environmental factors and the absence, or traces, of immunogenic properties (Cavaliere et al. 2005; Speijers and Speijers 2004).

Mycotoxins may be produced under diverse environmental conditions and in a vast range of food commodities. On account of diverse toxic actions and great resistance to high temperature, the presence of mycotoxins in food and feedstuffs (Hazel and Patel 2004; Schollenberger et al. 2006) pose hazards to human and animal health (Gajęcki 2002).

* Presented at The First International Environmental Best Practices Conference, 07-10 August 2006, Olsztyn, Poland

Mycotoxins have a significant impact on the industry since they bring losses in livestock and cause difficulties in rearing and breeding of animals. According to the legally binding regulations related to the mycotoxins (The Commission Regulations [EC] how No 123/2005, No 856/2005 and No 1126/2007; the annexes projects as regards to The Directive 2002/23/EC of The European Parliament and of The Council in SANCO/00226/2005) (Berg 2003), food commodities containing these substances must be the subject of neither the internal nor global turnover (Wiśniewska-Dmytrow et al. 2004).

IMPACT OF MYCOTOXIN ON HUMANS AND ANIMALS

Acute toxic effects are observed sporadically. However, long-term exposure to low concentrations of certain mycotoxins may contribute to the development of some chronic conditions, e.g. hepatic or renal neoplasias (Xu et al. 2006) or allergies (Bush et al. 2006; Gajęcki et al. 2006; Jarvis and Miller 2005).

Nowadays, our knowledge on the presence of mycotoxins in moulds tissues (being transported on protein carriers in animals) and allergy-inducing proteins that trigger certain pathologic conditions is scarce (Gajęcki et al. 2006; Jarvis and Miller 2005). On the other hand, endogenic as well as environmental (e.g. zearalenone) estrogens possess the ability to modulate the endocrine system (endocrine disrupters – EDs) (Sweeney 2002; Teilmann et al. 2002). They probably take part in inducing pathological lesions in the course of autoimmune and allergic conditions. The environmental estrogens, including zearalenone, are likely to provoke certain alterations within the immune system either directly (in combination with other mycotoxins) or indirectly in some non-lymphatic tissues by non-estrogenic receptors that normally act as mediators. Additionally, the environmental estrogens (zearalenone) influencing the immune system directly or, what is more probable, indirectly by other tissues alter the immune system so as to modify a composition of cytokines (Ansar Ahmed et al. 1999; Gajęcki 2007; Krakowski et al. 2004).

Detection of mycotoxins may be difficult due to low concentrations of these substances in the natural environment (Sapsford et al. 2006). The analysis of feedstuffs does not always provide a detailed assessment of mould metabolites, that is, among other things, due to imperfect analytic techniques or a presence of some new, yet unknown, derivatives (Berthiller et al. 2005; Sapsford et al. 2006). The lack of a precise procedure of identification of mycotoxins in feedstuffs prevents adequate analyses.

MYCOTOXICOSIS

In animals, clinical symptoms of mycotoxicosis are diverse depending on the species, ingested dose, physiological condition, age and sex. Some mycotoxins influence the immune system, e.g. enhance animals' susceptibility to pathogens and hence contribute towards the occurrence of subclinical stages of infectious diseases (Cast 1989; Pfohl-Leszkowicz et al. 2002). Individual mycotoxicoses occur seasonally on certain areas that hinder an implementation of an effective prophylactic measure (Pfohl-Leszkowicz et al. 2002). These authors have also pointed some problems in establishing a diagnosis that is partly due to the fact that veterinary surgeons and human practitioners have limited knowledge of acute forms of mycotoxicosis. Moreover, interactions between given mycotoxins are still unclear (Speijers and Speijers 2004). The presence of a mixture of these toxins may present a problem in terms of determining clinical symptoms of an individual mycotoxicosis (Gajęcki 2002). The atypical clinical picture of a disease is a result of mixed intoxication and interactions between mycotoxins (Creppy et al. 2004; Speijers and Speijers 2004; Tritscher and Page 2004).

Our knowledge on the intoxications with mixed mould toxins is incomplete owing to a minor number of case reports. In the literature the intoxications with ochratoxin A in combination with some other mycotoxins are usually presented (Mantle 2002; Molinié et al. 2005). While reporting the cases of multi-mycotoxicosis the authors did not consider either antagonistic, synergistic and adding-up interactions, or the course of a given mixed mycotoxicosis and potential relationships. In general, they claimed that mycotoxin-induced conditions were extremely difficult to interpret. The conclusions, which are based on the results and statistical analyses, presented in many papers (such as Tajima et al. 2002) may allow for making an observation that a direct explanation of the mechanisms of interactions between individual mycotoxins or a group of mycotoxins will be only found in research on a cellular level (Ansari et al. 1991; Benford et al. 2001; Eaton and Gallager 1994; Minervini et al. 2004; Skorska-Wyszyńska et al. 2004; Tiemann et al. 2003; Versantvoort et al. 2005). An understanding of an impact of mycotoxins on some alterations in cell activities is necessary to determine a mechanism and an influence of xenobiotics on some other structures and molecules. There are many examples that explain the interaction between mycotoxins and mammal cellular functions as well as biologically active molecules that protect the biosynthesis of mycotoxins (Canady et al. 2001; Ueno 1991).

In some publications the authors explain or point a stage, on which a mycotoxin or a group of mycotoxins was incorporated into a life cycle of a cell (Wangikar et al. 2004b). The authors try to determine pathological lesions in tissues (organs) or cells. Some mycotoxins appear to be a triggering factor for a pathological condition (Cavaliere et al. 2005). However, one should pay attention to the fact that certain mycotoxins act just inversely and induce a negative interaction, e.g. patulin prevents lipid oxidation (Riley 1998; Riley and Norred, 1996).

There are some reports covering the results of the experiments on interactions between deoxynivalenol, fumonisin or ochratoxin A and infectious agents (Jarvis

and Miller 2005; Kuhn and Ghannoum 2003). The interaction between aflatoxin B_1 and hepatitis type B virus is generally well-known (Etzel 2006). Fumonisin or cyclopiazonic acid may probably interact with this agent in a similar way though it is still unclear. More reports suggest that an interaction between ochratoxin A and some viruses exists, e.g. Hantaan virus endemically present in the Balkans, but it is not entirely understood (Pfohl-Leszkowicz et al. 2002). Both mentioned bacteria, viruses and mycotoxins, i.e. ochratoxins, are responsible for triggering a condition called chronic kidney damage (Maciorowski et al. 2007; Pfohl-Leszkowicz et al. 2002).

The suppressive impact of trichothecenes on the immune system in animals is also reported in many publications (Pestka et al. 2005; Riley 1998; Zielonka et al. 2003, 2004). From the above mentioned examples it may be concluded that mixed intoxications will be accompanied with a diverse clinical picture. The kidneys (Braunberg et al. 1994) or liver (Kuhn and Ghannoum 2003; Obremski et al. 2005) were the organs that were most severely affected. Systemic reactions, such as oedema and allergic conditions, may also occur (Bush et al. 2006; Fischer and Dott 2003; Jarvis and Miller 2005).

INTERACTION BETWEEN MYCOTOXINS

While speculating on an interaction between mycotoxins on a cellular level, a lot of questions arise which are left unanswered. Nowadays it is understood that in humans and animals toxico-kinetic interaction, metabolic processes (Versantvoort et al. 2005) and toxico-dynamic interaction result from a simultaneous influence of both the amount and the type of mycotoxins (Tritscher and Page 2004).

Owing to the above mentioned, some questions arise: what is the result of mycotoxic interaction in tissues and cells?; what is the final effect of multi-mycotoxicosis for a human or an animal?; or a question related to toxico-kinetic interactions – on what kind of an experimental model should an assessment be based on?

ASSORTED INTOXICATION

Nowadays there are few reports that cover a subject of multi-mycotoxicosis. Morris et al. (1999), for example, administered deoxynivalenol (20 mg) and moniliformin (100 mg) to turkey poults in combination and alone. During 21 days of the study any effects of toxicological synergism have not been noted. In other studies, weaned piglets were administered a mixture of fumonisin B, deoxynivalenol, T-2 and ochratoxin A at the amounts most frequently noted in Central Europe. The clinical symptoms were the same as those observed after the administration of ochratoxin A alone (Müller et al. 1999). The suppressive mechanism of a mixture of ochratoxin A with deoxynivalenol or fumonisin B_1 on antibodies formation was reported, that was the reverse of the action noticed after administering ochratoxin A alone.

Lusky et al. (2001) investigated the results of the administration of ochratoxin A, zearalenone and deoxynivalenol throughout the period of 50-60 days. They administered these xenobiotics alone or as mixtures in feed, and then examined physical condition of pigs and determined the levels of the metabolites of these mycotoxins. Owing to a very quick metabolism of zearalenone and deoxynivalenol in the course of a given mycotoxicosis (Obremski et al. 2004), it is very difficult to confirm the presence of these xenobiotics in animals' tissues. Hence the above mentioned mycotoxicosis is thought to occur only in the experimentally-induced multi-mycotoxicosis models. The authors conclude that neither an adding-up nor synergistic effect was observed.

Some reports presenting the results of *in vitro* studies also exist in the literature (Groten et al. 1998; Tajima et al. 2002; Versantvoort et al. 2005). The authors quite frequently claim that the experimentally-induced multi-mycotoxicosis result from adding-up of the effects (Tiemann et al. 2003), whereas only a few studies confirm a synergistic interaction between them. The researchers suggest that these interactions are similar to those observed in nature (Creppy et al. 2004; Minervini et al. 2004).

In some studies, several mycotoxins (nivalenol, diacetoxyscirpenol and deoxynivalenol) were added to human lymphocyte culture, and then the extent of proliferation was determined and hence the level of immunoglobulin production calculated. The results of the experiments suggest that the combined action of those trichothecenes resulted in adding-up or antagonistic effects. Any synergistic interactions between these micotoxins have not been observed (Thuvander et al. 1999). Similar adding-up or antagonistic actions of ochratoxin A and zearalenone on cattle lymphocyte or swine granulomatous cell cultures were reported during the experiments aimed at investigating genotoxic and apoptotic effects (Lioi et al. 2004; Wąsowicz et al. 2005).

CONCLUSION

In the future the studies on the interactions between mycotoxins (chemical mixtures of e.g. trichothecenes) should be conducted on animal models and promptly implemented (Creppy et al. 2004; Speijers and Speijers 2004; Trischer and Page 2004). However, it is equally important to choose animal species that would be used in experiments, and to determine a specific purpose that will be subsequently achieved (Krska and Molinelli 2007).

ACKNOWLEDGEMENTS

The study was supported by the Ministry of Science, Warsaw, Poland, grant No. PB KBN P06K 007 26.

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