MYCOTOXINS AND THEIR EFFECT ON HUMAN HEALTH

ABSTRACT: Health risks associated with the consumption of products contaminated with mycotoxins are worldwide recognized and depend on the extent to which they are consumed in diversified diet. To some extent, the presence of small amount of mycotoxins in cereals and related food products is unavoidable; this requires risk assessments which are to be carried out by regulatory bodies in several countries to help establish regulatory guidelines for the protection of public health. By assessing the levels at which these substances in food may pose a potential risk to human health, it is possible to devise appropriate risk management strategies. However, several important factors have to be taken into account in making a rational risk management decision, such as adequate toxicological data and information concerning the extent of exposure, availability of technically sound analytical procedures (including sampling), socioeconomic factors, food intake patterns and levels of mycotoxins in food commodities which may vary considerably between countries.

KEY WORDS: health risk, human health, immunosupression, legislation, mycotoxicosis, mycotoxin

INTRODUCTION

From the aspect of human and veterinary medicine, food safety represents a significant problem. Thus, attention is directed to diseases which are closely related to different kinds of mycotoxicoses. Reports from the World Health Organization show that the presence of mycotoxins and toxic metabolites of molds in the food for human consumption is not on the decrease. Due to the obvious increase in the number of diseases caused by mycotoxins, which have been implicated as potential etiological factors, a great effort is made to identify mycotoxins present in the food and thereon to eliminate them. Besides the already known and studied mycotoxin-related diseases, World Health Organization reports also mention other diseases such as Alzheimer, multiple sclerosis and cancers.

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A number of studies have documented that mycotoxins are etiological factors of a number of respiratory and neurological disorders, as well as cancerous changes, nephrotoxicity and hepatotoxicity. Recent studies have shown that mycotoxins have a biological role and direct influence on the initiation and/or recurrence of nervous system disorders. By repeated stimulation of receptors affected by mycotoxins, the relationship between mycotoxicosis and Alzheimer’s disease can be explained. This can be used as the study model for MCS (Multiple Chemical Sensitivity Syndrome) and other syndromes.

The presence of mycotoxins in food is a problem that mankind, especially modern society, is faced with, regardless of the fact that there is a big difference between developed and underdeveloped parts of the world, primarily in the degree of food contamination with mycotoxins. In underdeveloped regions people are constantly exposed to acute or chronic mycotoxicosis. However, having due regard to the ongoing struggle for enough food in these regions, it would be unrealistic to expect a solution to the problem of mycotoxicosis. People in developed or highly developed areas of the world are less exposed to mycotoxins, primarily due to geographic and climatic conditions. In addition, there are considerable food resources, modern processing and storage of food is constantly applied, strict legislation is introduced, and there is a very strict control of mycotoxins presence in food.

Presence of mycotoxins in animal feedstuff

Contamination with mycotoxins and molds is a world problem. According to FAO data, nowadays 25% of world wheat production is contaminated (Devegowda et al., 1998). It is evident that molds and mycotoxins represent a serious problem (SCOOP, 1996), not only in regard to successful harvest and food quality, but also in the productivity and health of animals (Miller and Trenholm, 1994).

High risk foods

Since there are known limits which designate the contaminated food as safe, it is necessary to be able to recognize foods which are the most common sources of intoxication (Sionvec and Resanovic, 2005). Such foods on organoleptic examination usually appear safe, although mycotoxins are described as „cold blooded murderers“. Mycotoxins are most commonly found in cereals, coffee, cocoa, nuts, as well as foods of animal origin in which mycotoxin residues can be found (milk, meat, offal, eggs).

Milk and milk products. The presence of mycotoxins in milk and dairy products is a serious food safety problem, especially for infants and children who are most susceptible to mycotoxins, and who are also most exposed to this source of poisoning. Mammals, which ingest food contaminated with aflatoxin, secrete the toxin in their milk in the form of hepatic 4 – hydroxylated
metabolite known as “milk toxin”, or aflatoxin M1. AFM1 is slightly less toxic than AFB1, therefore, the International Agency for Cancer Research (IARC, 1993) classified AFM1 as potentially carcinogenic to humans. By taking into account the possibility that the OTA and other mycotoxins can be secreted into milk, and that the rumen microflora can greatly transform, it can be concluded that the content of mycotoxins in milk poses lower hazard to human health.

Powdered milk is another source of AFM1 in the human population, and is therefore subject to regulation which is extremely strict concerning this product. In the last decade of the twentieth century, AFM1 contamination in milk was reduced to a minimum in the EU because there was no legal limit on the presence of AFM1 due to the lack of certainty about the effects that very low doses of aflatoxin and its body tissue accumulation can have especially on children (Fremy and Dragacci, 1999).

**Human milk.** Mycotoxins, primarily aflatoxins, represent a serious prenatal problem as it is known that some toxins easily pass through the placental barrier and can be found in a fetus when a mother consumes contaminated food. As mycotoxins (Miraiglia et al., 1995) are, as a rule, excreted by milk, the highest risk of intoxication in newborns is primarily mother’s milk.

**Meat and meat products.** Foodstuff, which originates from animals fed with contaminated feed, represents a potential hazard to health. Ruminant meat represents a slight danger in comparison to pork and poultry due to physiological characteristics of the rumen and specific degradation of the majority of present mycotoxins.

Aflatoxin is deposited in the tissues and organs of animals which consume contaminated feed. Deposition occurs in liver, muscles, stomach, kidneys, adipose tissue and meat, the highest deposition of aflatoxin is in the liver (Resanović, 2000).

Ochratoxin is deposited primarily in kidney and liver, as well as in muscle and adipose tissue (Jonker and Petterson, 1999). Contamination of pork meat with OTA is a major problem, and that is why some European countries have introduced special monitoring in slaughterhouses where the presence of OTA is determined based on post mortem examinations (Moussing et al., 1997).

Zearalenone and its derivatives can be determined in edible portions such as liver and muscles of animals fed with contaminated feed (Ciégler and Vesonder, 1983), as well as in the meat of clinically healthy animals (Milićević et al., 2005).

Relatively rapid metabolic degradation of T-2 toxin is probably the main reason for very difficult identification of its presence in meat (Pace, 1986).

**Eggs.** The presence of mycotoxins in eggs represents a health hazard for human population. Aflatoxin B1 residues pose the highest hazard since their transformation into AFB1 in the liver of hens causes the formation of a set of hydroxylated derivatives which can pass into the egg. Besides the excretion of aflatoxin (Radoskić, 1997), there is also a possibility of OTA, ZON and T-2
toxin elimination in eggs, mostly in the yolk and to a smaller extent in the egg white (Fuchs and Hult, 1992).

Grains. Given that cereals are the main source of carbohydrates in the diet of people around the world, they represent the main source of mycotoxins in food. Cereals can easily be infested with fungi in various stages of production and storage. A large number of mycotoxins can be found in cereals, and many countries have enacted legislation on maximum allowed levels (Smith, 1997) of mycotoxins in cereals. Corn grain is considered to be the grain most highly contaminated with mycotoxins, followed by rice, barley and wheat, oilseeds and seeds of peanuts, soybeans and sunflower. The combination of more toxins is a pressing problem for the detection of mycotoxins, as well as for the monitoring of the effects that they exert in the body of humans and animals.

Aflatoxin B1 and human health hazard

Humans are most commonly exposed to the effects of aflatoxin in three ways:

- ingestion of food of vegetable origin (mainly corn and peanuts) contaminated with aflatoxin (AFB1),
- Ingestion of contaminated milk and dairy products, including cheese and powdered milk (AFM1) and,
- Ingestion of aflatoxin residues present in meat and meat products, as well as in eggs (to a lower degree than in the previous two ways).

A number of health disorders are developed as a result of aflatoxin ingestion; they differ based on the degree, character and intensity relative to the quantity of ingested aflatoxin, length of exposure, general health status and age of the patient.

Hepatocellular carcinoma is one of the most common malignant diseases, and it is the fourth most common cause of death. Early epidemiological studies indicated to the close relationship between hepatocellular carcinoma and exposure to aflatoxin B1, i.e. exposure to contaminated food. The incidence of primary hepatocellular carcinoma increases logarithmically with an increase in aflatoxin ingestion which was proven by further studies. In geographic regions where hepatocellular carcinoma is rare, AFB1 contamination in food is very low.

Aflatoxins, particularly AFB1, show an emphasized carcinogenic effect (Eaton and Groopman, 1994). The International Agency for Research on Cancer (IARC, 1993) classified the AFB1 in the group 1 carcinogens, since the risk of human primary liver cancer is very high (Henry et al., 2001).

Acute toxic hepatitis is a disease which has been described in many geographic regions, but the highest prevalence was recorded in India. The examination performed on 674 patients in 150 cities of India showed that all patients consumed moldy corn, and that aflatoxin B1 was present in most samples in quantities of 0.25-15.6 mg / kg. Considering the fact that adults eat at least 400 g of corn daily on the territory where the survey was conducted, it can be con-
cluded that exposure to aflatoxin was above 6 mg / day. Histopathological examination of the liver of patients who died of acute toxic hepatitis revealed bile duct proliferation accompanied by periductal fibrosis and cholestasis. Aflatoxin was also detected in the tested urine of affected patients.

*Kwashiorkor* is a protein deficiency which manifests as hypoalbuminemia, generalized edema, dermatosis, enlarged fatty liver, and it is common in geographic regions where seasonal occurrence of aflatoxin is present. Aflatoxin was recorded in liver samples of 36 children who deceased due to Kwashiorkor (Hendrickse, 1985). This implies that aflatoxin is one of the possible etiological factors along with the possibility that malnutrition alters aflatoxin metabolism (De Vries, 1989).

*Reye’s syndrome* is a form of hepatic encephalopathy in children accompanied by fatty degeneration of parenchymal organs. Although Reye’s syndrome occurs in many countries around the world and geographical link with the areas with a high risk of aflatoxin ingestion has not been observed, aflatoxin is considered as one of the etiological factors. The first hypothesis of a causal connection dates back in 1963 when the presence of aflatoxin B1 and G2 in the serum of patients suffering and dying from Reye’s syndrome was recorded. Also, AFB1 was detected in the liver of 27 patients suffering from Reye’s syndrome, while AFM1 was detected in only 4 patients (Bryden, 2007). Taking into account the research carried out in conjunction with Reye’s syndrome, it was concluded that the disease etiology was multifactorial, and aflatoxin played an important role in the pathogenesis.

*T4 lymphocyte deficiency* may be caused by the presence of aflatoxins in human food because it is known that aflatoxins are mitogenic factors for T4 lymphocytes and cause symptoms related to deficiency of T4 lymphocytes (Griffiths et al., 1996).

There are exact data on the dietary intake of aflatoxins, but they are based only on available data and different models for certain given values. Average daily intake of aflatoxin B1 ranged from 2-77 ng / man or 0.4-0.6 ng AFM1/man (SCOOP, 1996).

**Ochratoxin A and human health hazard**

It has been believed for a long time that ochratoxin is responsible for nephropathies and urinary tract tumors in man. High exposures to OTA, high concentration in blood serum and long half-life (35 days), as well as the deposition in the kidneys foster the development of nephrotoxicity.

OTS is significant for its relationship with Balkan Endemic Nephropathy (BEN) which is a chronic kidney disorder (Krogh et al., 1977) with lethal outcome (Radovanovic, 1991). BEN has an endemic character and it was recorded in rural regions of the Balkans (parts of Bosnia and Herzegovinia, Croatia, Serbia, Romania, and Bulgaria) and it is more common in woman than in man. Kidneys are smaller, tubules are degenerated, and interstitial fi-
brosis and glomerule hyalinisation are present in the cortex. Tubular function is decreased and this is one of the first clinical signs.

High levels of OTA and β-2 microglobulins in the serum characterize chronic interstitial nephropathy. Previously performed studies (Radic et al., 1986) confirmed that 56.6% of tested sera from patients with nephropathy from the Western Posavina region were positive for ochratoxin A. Data from Vraca (Bulgaria), where entire families were affected with BEN, showed high concentrations of OTA in the sera samples from patients. In some North African countries, especially Tunisia, epidemiological studies show a high relationship between OTA and chronic interstitial nephropathy.

On the other hand, there are contradictory data which state that there is no connection between BEN and high OTA concentrations in serum (Grosso et al., 2003; Abid et al., 2003). Therefore, the question on the relationship between OTA and BEN still remains unanswered. Difficulties arise due to the seasonal presence of OTA in food, allowed limits for OTA in serum and food, qualitative and quantitative laboratory procedures for OTA determination, and still incomplete knowledge about synergistic effects of different mycotoxins. In fact, citrinin stimulates the effects of OTA and citrinin concentrations in the food samples from Vrac were 200 times higher than OTA concentrations.

With high content of OTA in food (Ciegl er and Veson der, 1983), there was a high incidence of renal adenomas and carcinomas (Radovanovic et al., 1991), and there is a correlation between the occurrence of BEN and urinary tract tumors. The importance of OTA induced renal carcinomas is increased due to frequent metastases in the lymph nodes and liver in humans, and multiplication of the mammary gland – fibroadenoma in women. This is why the International Agency for Research on Cancer (IARC, 1993) classified OTA as carcinogenic potential for human population (group B).

The exact data on the dietary intake of ochratoxin do not exist, and most of the information is obtained from Europe where, unlike other regions of the world, OTA is a common food contaminant. Average daily intake of OTA was estimated to be 45 mg / kg bw / week, out of which 25 ng was from grains, 10 ng from wine and meat and only 1.5 ng from pork (WHO, 1985). According to the other data and model calculations, it was believed that the daily intake of OTA was up to 92 mg / kg bw / week in countries where the consumption of grains was significant. Data from countries that had a very low incidence of nephropathy showed that daily intake of OTA ranged 1-5 mg / kg bw / day (SCOOP, 1997).

**Zearalenone and human health hazards**

Due to its estrogenic structure, it is considered that zearalenone and/or its derivatives, especially zearalanol, cause precocious puberty in children at the age of 7-8 (Painter, 1977). Epidemiological study performed in Puerto Rico (Sandez Rodriguez et al., 1985) showed that areas where
children suffer from *praecox* puberty are characterized with high concentration of estradiol and its equivalent in meat, and zearalenone and its metabolites were recorded in the blood plasma of affected children. It is believed that exposure to zearalenone occurred during pregnancy of their mothers who consumed contaminated food at the time of pregnancy. A similar phenomenon was investigated in the southeastern region of Hungary, and zearalenone concentration in the blood of patients with precocious puberty ranged from 18.9-103.5 mg / ml.

F-2 toxin can cause oestrogenisation and pseudopregnancy in women and, inhibition of the normal development of testicles in men. It is also associated with the development of prostate cancer in men, and there is a hypothesis that zearalenone can be an etiological factor not only for premature puberty but for cervical cancer as well (Hsiieh, 1989). However, the International Agency for Research on Cancer (IARC, 1993) believes that there has not been data reliable enough to classify F-2 toxin as potential carcinogen in the population of people (group 3). On the other hand, the use of derivatives of zearalenone was used to relieve the symptoms of menopausal disorders.

The exact data on the dietary intake of zearalenone do not exist, except for Canada and Northern Europe. Average daily intake of F-2 toxin was estimated to be from 0.03 to 00:06 mg / kg bw / day (WHO, 1985), and 1.2-1.5 ng / day, or 0:01 to 00:02 mg / kg bw / day (Erikseen and Alexander, 1998). The determined values were below PTDI of 0.2 mg / kg bw / day. However, the assumption is that the mean intake of zearalenone in Europe ranges from 1-420 ng / kg body weight (EC, 2003).

**T-2 toxin and human health hazard**

Trichotheccene toxicity mechanisms reside on strong inhibition of protein synthesis, and this results in a set of negative effects to human health.

Alimentary toxic aleukia (ATA) is a disorder characterized by necrotic angina, hemorrhagic diathesis and sepsis accompanied by granulocitosis as a result of bone marrow atrophy. The disease had fatal consequences in 80% of cases (Joffe, 1978). The disease is caused by the ingestion of cereals contaminated with molds of the *Fusarium* genus (*F. poae* and *F. sporotrichoides*).

Nowadays, ATA is considered to be largely eradicated disease since there is a high exposure of large number of people to trichotheccene mycotoxins. In addition, the International Agency for Research on Cancer (IARC, 1993) classified T-2 toxin as carcinogenic potential for the population of people (group 3).

In addition to ATA, diseases related to ingestion of food contaminated with *Fusarium* molds and / or T-2 toxin (Canady et al., 2001) appeared sporadically in the second half of the twentieth century, mainly in Asia (Japan, Korea, China and India, Kashmir). The disease occurs shortly (5-30 min, max 1 hour) after the ingestion of contaminated food (0.2-0.8 mg T-2/kg) mainly wheat, and it is followed by nausea and abdominal pain (100%), irritation of
the mouth and larynx (63%), diarrhea (39%), melena (5%), vomiting (7%). Unlike ATA, none of the diseases had fatal consequences.

Based on the results of analysis performed on food for humans, the average daily intake of T-2 toxin was estimated to be 7.6 ng / kg bw (WHO, 1985). In any respect, more detailed studies need to be performed in different regions of the world, especially in European countries in order to obtain more accurate information about the overall intake of this toxin in humans.

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МИКОТОКСИНИ И ЊИХОВ ЕФЕКТ НА ЉУДСКО ЗДРАВЉЕ

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Резиме

Здравствени ризици повезани са конзумацијом производа контаминираних микотоксинима су препознати у целом свету. У извесној мери присуство малих количина микотоксина у житарцима и другим производима је очекивано и неми-новно. То изискује процену ризика од стране регулаторних тела која морају имати улогу у успостављању регулаторних смерница за заштиту јавног здравља. Након процене нивоа микотоксина у храни потребно је осмислити одговарајуће страте-гије за управљање ризиком. Неколико важних фактора треба узети у обзир при доношењу одлука о рационалном управљању ризиком, укључујући токсиколошке податке, ниво изложености, доступност аналитичких процедура, социоеконом-ске факторе и националну легислативу.

КЉУЧНЕ РЕЧИ: болест, имуносупресија, микотоксикозе, микотоксини, за-конска регулатива, здравље људи