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CONTAMINATION OF FOOD WITH MYCOTOXINS AND HUMAN HEALTH

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Mycotoxins are natural contaminants of cereals and other commodities throughout the world. They are produced by various strains of moulds, particularly in tropical countries. Due to significant trade of cereals, humans in temperate countries can also be exposed to mycotoxins. The most common route of exposure to mycotoxins is ingestion, but it may also involve dermal, respiratory, and parenteral routes, the last being associated with drug abuse. Apart from acute and chronic toxic effects on human health called mycotoxicosis, some mycotoxins are proved or suspected human carcinogens. This paper describes various human diseases caused by ergot, aflatoxin, ochratoxin A, 3-nitropropionic acid, trichothecene, zearalenone, and fumonisin. It also gives a quick review of human carcinogenicity evaluations of the International Agency for Research on Cancer and of regulatory limits of mycotoxin concentrations in various commodities.

Key words:
3-nitropropionic acid, aflatoxins, food, fumonisins, mycotoxicosis, ochratoxin A, trichothecenes, zearalenone

Mould and mycotoxin contamination of food is serious although usually neglected. According to Food and Agriculture Organization, 25% of the world crop is contaminated by moulds (1). Fungal invasion of agricultural commodities is common in the fields (*Fusarium spp., Aspergillus spp*. and *Penicillium spp*.) with considerable seasonal variations. Mycotoxins are usually found in mixed form. The production of mycotoxins does not correlate directly with the growth of moulds, and while fungistatic and fungicidal compounds may affect the mould invasion, this does not necessarily entail the drop in the level of mycotoxins.

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There is no doubt about the importance of mycotoxins in the human history. The first recognised acute intoxication was described in France in 945, when a large number of persons were ill of ergotism (2). This potentially fatal disease, caused by metabolites of ergot, has now almost disappeared due to the use of barley resistant to various *Claviceps* strains which produce the ergot alkaloids. The importance of application of hygienic measures in prevention of human exposure to mycotoxins was demonstrated in the eradication of so called »yellow rice disease« (*shosin-kake* in Japanese). This fatal cardiomiopathy similar to the lesions seen in beri-beri, was caused by citreoviridin, the metabolic product of *Penicillium citreonigrum* (3*)*. The disease, common in lower social strata in Japan, disappeared immediately after the introduction of rigorous measures which excluded mouldy (or »yellow«) rice from the market. Another disease, that has not been seen in a severe form for decades and which involved a large number of persons, was the »alimentary toxic aleukia« common in the USSR (4). The population was exposed to trichothecenes from unharvested wheat contaminated by *Fusarium* moulds.

Some moulds and products of moulds are used in food industry in the production of cheese, sausages, beer, wine and in pharmaceutical industry as antibiotics. The classification of mould products as antibiotics or mycotoxins is arbitrary and depends on the toxicity of the compound.

The most common human exposure to mycotoxins is oral, that is, by ingestion of contaminated plant-based food or of residues and metabolites in animal products, such as aflatoxin M_1. Other routes of exposure are respiratory, dermal, and parenteral, though the last is associated with drug abuse. Respiratory exposure occurs during professional contact with large quantities of processed contaminated food (aflatoxins and ochratoxin A)(5–7) or the exposure occurs in highly contaminated households (8)

Table 1. *Postulated human mycotoxicoses*

Mycotoxin	Disease or syndrome
Aflatoxin	Liver lesions, cirrhosis, liver carcinoma, Kwashiorkor, Reye's syndrome
Cyclopiazonic acid	Kodua
Citreoviridin	Cardiomiopathy
Ergot	Ergotism
Fumonisin B_1	Oesophageal carcinoma
Fusarium metabolites	Akakabi-byo
F. equiseti metabolites	Kashin-beck disease
3-nitropropionic acid	Mouldy cane disease
Ochratoxin A	Endemic nephropathy, urothelial tumours
Trichothecenes	Alimentary toxic aleukia
Zearalenone	Premature telarche, cervical cancer

and office buildings with artificial ventilation (9). Dermal exposure is limited to mycotoxins which can pass the dermal barrier (trichothecenes) (10). Heroin abusers in the

European countries are parenterally exposed to aflatoxin B_1 which contaminates heroin imported from tropical countries (11).

There are several diseases which are supposed to be mycotoxin-related (Table 1). Mycotoxins are suspected to cause a disease in instances when it appears in several persons with no obvious connection to a known etiologic agent such as micro-organisms. However, the causal relationship between exposure to mycotoxins and the disease development should be confirmed by epidemiological studies.

Mycotoxins cause acute and chronic intoxications (mycotoxicoses), allergies, and tumours. In experimental animals and in the experiments *in vitro* they may demonstrate genotoxic, mutagenic, cytotoxic, and teratogenic properties. Some of them, such as sporodesmine, are toxic for animals, but not for humans. Others, such as ochratoxin A or aflatoxins, have the same target organ in all experimental animals. For such mycotoxins it is possible to extrapolate the results from animals to humans. The target organs of other groups of mycotoxins are so different in different animal species that it is extremely hard to infer their effect on humans. For example, protean mycotoxins are fumonisins, which produce pulmonary oedema in pigs, leukoencephalomalacia in horses and are hepatotoxic in rats, mice, rabbits and swine and nephrotoxic in male swine, rats, and rabbits (12). Mycotoxicoses are more frequently noticed in animals, because a large number of animals are fed with specific feed. It was proposed that the following criteria should be met to link a mycotoxin to a specific human disease: occurrence of mycotoxin in food samples, human exposure and incidence, reproducibility of characteristic symptoms in experimental animals, and the similar mode of action in human and animal models (13).

The greatest human health concern related to mycotoxins is the cancer risk based on long-term, low-level exposure to carcinogenic toxins such as the aflatoxins, ochratoxin A, fumonisins, and zearalenone.

ERGOT

Ergot is the common name for sclerotia of fungi of the genus *Claviceps* which produce ergot alkaloids. The sclerotium is a dark coloured, hard fungal mass that replaces the seed or kernel of the plant. Ergot alkaloids are also secondary metabolites of some strains of *Penicillium, Aspergillus* and *Rhizopus* sp. (14). The source of ergot strongly influences the type of alkaloids present, as well as the clinical picture of ergotism (15).

Claviceps purpurea produces ergotamine-ergocristine alkaloids, which cause the gangrenous form of ergotism because of their vasoconstrictive activity. The initial symptoms are the leg oedema with severe pains. Paresthesias are followed by gangrene at the tendons with painless demarcation. In 1977–1978, Ethiopia saw the last recorded outbreak of gangrenous ergotism striking 140 persons of whom 34% died (16). It seems that the cause of this outbreak was the long wet season which favoured the growth of wild oat susceptible to *Claviceps purpurea*.

The other type of ergotism, related to intoxication with clavine alkaloids from *Claviceps fusiformis* is the convulsive form, last seen in India in 1975 and affecting

78 persons (17). It was characterised by gastrointestinal symptoms (nausea, vomiting, and giddiness) followed by neurological symptoms (drowsiness, prolonged sleepiness, twitching, convulsions, blindness, and paralysis). The onset of the symptoms ranged from one to 48 hours after ingestion of contaminated food. No fatalities were recorded.

Ergotism is extremely rare today, primarily because the standard cleaning and milling processes remove most of ergot, leaving very low levels of the alkaloids in flour. In addition, the alkaloids are relatively unstable and are usually destroyed by baking and cooking.

AFLATOXINS

Aflatoxins (B_1, B_2, G_1, and G_2) are highly toxic hepatotoxins produced by various strains of *Aspergillus* in tropical and subtropical regions. The first massive mycotoxicosis which attracted scientific attention occurred in England in 1961, when tons of groundnuts contaminated by *A. flavus* and *A. parasiticus* containing aflatoxin and cyclopiazonic acid were used for the production of formulated feed for turkeys. The most abundant and the most studied is aflatoxin B_1 (AFB_1) which together with other aflatoxins naturally contaminates maize, sorghum, nuts, cotton seed, sunflower seed, coffee, and other energy-rich products. When the feed consumed by cows contains AFB_1, the toxic metabolite aflatoxin M_1 with toxicity similar to AFB_1 is excreted in milk.

In several episodes of acute aflatoxicosis in Asia and Africa aflatoxins caused severe lesions of liver in malnourished adults, often with the fatal outcome (18–20). Due to seasonal appearance of childhood diseases such as kwashiorkor, Reye's syndrome, and neonatal jaundice in tropical countries which coincided with periodical high concentrations of aflatoxins in food, it was believed that aflatoxins were involved in the etiology of these diseases. In several studies AFB_1 and aflatoxicol (metabolic product of AFB_1) were found more frequently in the serum, liver, urine, and stool of children suffering from kwashiorkor than in controls (21–24). However, it is still not clear whether the finding of aflatoxins is the cause or the conequence of kwashiorkor. The role of aflatoxins in the development of Reye's syndrome (encephalopathy with severe lesions of kidney and liver following influenza or varicella) was never proved, regardless of frequent findings of aflatoxins in the liver of children who died of this syndrome (25–31). The syndrome was also connected with the use of salicylates and phenotiazines (31, 32). The last two decades saw a drop in the incidence of Reye's syndrome, which associated with the diminished use of salicylates in the treatment of fever in children (33). However, a large investigation performed in Nigeria on 327 babies with jaundice and 80 matching controls proved that serum glucose-6-phosphate dehydrogenase deficiency and aflatoxins were significant risk factors for the development of neonatal jaundice (34).

In the organs of experimental animals with a high incidence of tumours caused by aflatoxin B_1 (liver after oral and lungs after respiratory exposure), the DNA lesions were caused by the formation of aflatoxin B_1-DNA adducts (REDUNDANTNA REČENICA: THE DNA LESIONS IN ORGANS (IN LIVER AFTER ORAL AND IN LUNGS AFTER RESPIRATORY EXPOSURE) OF EXPERIMENTAL ANIMALS WITH A HIGH INCIDENCE

OF TUMORS WERE CAUSED BY THE FORMATION OF AFLATOXIN B1-DNA ADDUCTS. A good correlation of aflatoxin B_1-DNA adducts production in target organs and aflatoxin B_1-DNA adducts on albumin and their excretion in urine was found. The production of aflatoxin B_1-DNA adducts depends on exposure, nourishment, the intake of antioxidants, viral infection, and genetic polymorphism (35). It was also found that AFB_1 triggers mutation of the p53 tumour suppressor gene.

The incidence of primary liver carcinoma is unusually high in some African and Asian regions. Exposure to aflatoxins and of the incidence of primary liver carcinoma were investigated in Thailand (36), Kenya (37), Mozambique (38), Swaziland (39), and Mozambique/Transkei (40). Although the populations of those countries were not serologically tested for HbsAg, the results pointed to the role of aflatoxins in the development of this disease. The role of aflatoxins in the development of the primary liver carcinoma, irrespective of the hepatitis B virus, was confirmed in investigations performed in China and Swaziland (41–43). Based on these data, the Working Group of the International Agency for Research on Cancer (44) declared in 1987 that there was enough evidence of the carcinogenicity of aflatoxin in humans. In 1992, another group of scientists relied on the epidemiological data to declare that there was enough evidence that the mixture of aflatoxins was hepatocarcinogen in humans and that the metabolite aflatoxin M_1 was a potential hepatocarcinogen in humans (45). A study in Taiwan showed that the risk of development of the primary liver carcinoma is considerably higher if the exposure to aflatoxin is combined with the presence of hepatitis B virus. The authors believe that the hepatitis B vaccination could be an effective prevention of tumours in countries with high aflatoxin contamination (35).

Aflatoxins are considered unavoidable contaminants of food, since they cannot be prevented or eliminated by the current agricultural practice. However, blanching and electronic eye colour sorting may reduce the concentration of total aflatoxins to 5 μg/kg of peanuts (46). Specific limits have already been set in a number of countries and they range from 0 to 30 μg/kg for aflatoxin B_1 in foodstuffs and from 0 to 50 μg/kg for total aflatoxins.

OCHRATOXIN A

Ochratoxins are a group of mycotoxins produced during grain storage by several *Penicillium* and *Aspergillus* strains all over the world (47). The most toxic and the most frequent is ochratoxin A (OTA), found in various commodities of plant and animal origin such as cereals, coffee, bread, wine, beer, pork meat, sausages, eggs, and milk.

OTA has been shown to be nephrotoxic, immunosupressive, carcinogenic, and teratogenic in all experimental animals tested so far. Owing to the similarity of morphological and functional kidney lesions in OTA-induced porcine nephropathy, this mycotoxin has been proposed as the causative agent of endemic nephropathy (48). Endemic nephropathy occurs in rural population of some regions of Croatia, Bosnia and Herzegovina, Yugoslavia, Bulgaria, and Romania. It has been estimated that about 20,000 people are either suffering from or are suspect of the disease (49). The main

features of this fatal renal disease are bilateral, primarily chronic lesions of the renal cortex (tubular degeneration, interstitial fibrosis, and hyalinisation of the glomeruli) (50). Many samples of food and feed produced in the endemic area of Croatia contained ochratoxin A (51–53). It was recently shown that concentrations of OTA in maize samples collected in the endemic regions in years with favourable climate for the production of ochratoxin A were higher than in other regions of Croatia (54). Blood ochratoxin A is found more frequently and in higher concentrations in inhabitants from endemic regions than in controls (53, 55).

In Tunisia, ochratoxin A has been detected in high concentration in the blood and food of patients with kidney impairment of unknown etiology (56, 57). In Italy, significantly higher OTA concentration was found in patients treated with dialysis than in transplanted subjects, patients with chronic glomerulonephritis, renal calculus, cysts, chronic renal failure and healthy subjects (58). It is not clear weather the high concentration of OTA in blood of patients with serious impairment of kidney function is caused by this mycotoxin or it is only the consequence of reduced glomerular filtration rate.

Furthermore, OTA was found in food and feed in a number of countries where endemic nephropathy has not been recorded so far (47). Although it was frequently found in low concentration in human blood (59), the significance of such finding is not clear.

In endemic regions of Croatia, Bulgaria, and Yugoslavia, the respective incidence of otherwise rare urothelial tumours of the pelvis and urethra is 50, 90, and 100 times greater than in non-endemic regions (60–62). As the incidence, clinical course, and prognosis of those tumours differs from urothelial tumours found in non-endemic regions, it was suggested that OTA may be the causal agent for both endemic nephropathy and urothelial tumours (63).

International Agency for Research on Cancer classified ochratoxin A as a compound possibly carcinogenic to humans (Group 2B) (44). Regulatory limits for OTA in various food have been set in six, mostly Scandinavian countries and range between 1 and 300 μg/kg.

3-NITROPROPIONIC ACID

3-nitropropionic acid (3-NPA) is the secondary metabolite of *Arthrinium* sp. considered to cause acute food-poisoning called »Mouldy sugarcane poisoning« (MSP) (64). MSP occurs in winter (February and March) in 13 provinces of Northern China as a consequence of the ingestion of sugarcane stored for two months or longer and infested with *Arthrinium* sp. In the period 1972–88, 884 persons were affected by the outbreaks of MSP and 88 (10%) died (65). The main epidemiological feature is the small number of persons in one outbreak (one to five persons), victims being mostly children and young persons (65). Generally, the incubation period is 2–3 hours after ingestion of mouldy sugar cane, and the main clinical symptoms are vomiting, dystonia, stare to one side, convulsions, carpopedal spasm, and coma. Delayed dystonia develops in 10–50% of patients as the consequence of bilateral symmetric necrosis of

the basal ganglia. The development of delayed symptoms may be predicted by abnormal basal ganglia visible on cranial computerised tomography scans (66). In adults 3-NPA causes gastrointestinal symptoms, whereas signs of severe encephalopathy are not common (67).

TRICHOTHECENES

Trichothecenes are large group of 148 mycotoxins, produced mostly by *Fusarium* genus, although other genera (e.g. *Trichoderma*, *Trichotecium*, *Myrothecium*, and *Stachybotrys*) are also known to produce these compounds (68). Mycotoxins producing strains of *Fusarium* contaminate grain with mycotoxins in fields throughout the world (69) The most frequent contaminants are deoxynivalenol (DON), also known as vomitoxin, nivalenol (NIV), and diacetoxyscirpenol (DAS), while T-2 toxin is rarer (68).

The most severe manifestations of trichothecene toxicity with the fatal outcome in 60% of involved persons were seen in the USSR from 1932 to 1947 (4). This trichothecenes mycotoxicosis called »alimentary toxic aleukia« was the consequence of grain contamination with *Fusarium sporotrichoides*. The contamination of grain samples taken from the affected regions was 5–40%, whereas the regions not affected by the disease showed only a 2–8% contamination of samples with the fungus. The initial symptoms were gastritis, gastro-enteritis, abdominal and oesophageal pain, and diarrhoea. Longer consumption of contaminated grain (3–4 weeks) entailed generalised indisposition with vertigo, unpleasant taste in the mouth with progressive leukopenia, granulocytopenia, and lymphocytosis. In the terminal phase of the disease the patients had haemorrhagic diathesis and angina with petechial rash, catarrhal diphteric gangrenous laryngitis, aphonia, and asphyxia.

More recent outbreaks of trichothecenes mycotoxicoses were less severe and without the fatal outcome. Trichothecenes mycotoxicosis, called also »scabby grain toxicosis«, occurred in Japan (70), China (71, 72), and India (73, 74). The main symptoms were abdominal pain, nausea, vomiting, diarrhoea, dizziness, and headache. The symptoms usually appeared within hours after the ingestion of wheat, corn, or rice contaminated by DON, NIV, T-2 toxin, deoxynivalenol, and zearalenon.

The regulatory limit in wheat for deoxynivalenol is from 1000 to 4000 μg/kg in five countries, and for diacetoxyscirpenol 100 μg/kg in Israel. The limit for T-2 toxin is 100 μg/kg in two countries.

ZEARALENONE

Zearalenone (previously known as F-2 toxin) is a mycotoxin generated in the field or during storage of humid grain contaminated by various *Fusarium* spp. in the preharvest period. It is often found together with other *Fusarium* mycotoxins on maize,

wheat, and other cereals. Contrary to the other *Fusarium* mycotoxins, zearalenone is more frequently found in ecologically than in conventionally produced wheat (75). Zearalenone and its metabolic products may be found in food of animal origin (meat, milk, and cheese) (76).

Zeranol, a growth-promoting derivative of zearalenone, has been approved by the USA Food and Drug Administration for use in animal husbandry instead of diethylstilbestrol. Zeranol is formed in cattle *in vivo* from feed contaminated by zearalenone (77).

In experimental and domestic animals zearalenone and zeranol have uterotrophic effect, and, being weak oestrogens, they cause inhibition of the hypothalamus and anterior pituitary and the atrophy of the ovaries, testes, prostate, and seminal vesicles (78–80). There are several reports on breast enlargement and precocious sexual development of children possibly connected with food-related exposure to oestrogens. In Puerto Rico, zearalenone was found in the blood of children with precocious sexual development (81). As maize is not produced in Puerto Rico, the authors believe that the affected children consumed chicken meet fed on the fodder imported from the USA. Since 1989, the south-east part of Hungary has been recording an ever increasing number of telarche and mastopathy in patients most of whom consumed »healthy« food (82). Zearalenone was found in 5 out of 36 serum samples.

The carcinogenicity of zearalenone for humans could not be evaluated because of the absence of epidemiological data (44).

FUMONISINS

Fumonisins are the most recent isolated group of mycotoxins. They are produced by *Fusarium verticillioides* (Sacc.), Nirenberg (=*Fusarium moniliforme* Sheldon), and related species on maize that has been affected by the moulds before the harvest. Maize and maize products may contain significant amounts of fumonisins, and fumonisin contamination of maize was found in many countries (83) including Croatia (54). Fumonisins are heat-stable (84), light-stable, and water soluble (45). Natural contamination of maize by fumonisin B_1 is more frequent than contamination with the other 14 fumonisins (12).

Thanks to poor absorption and rapid excretion in animals, fumonisins are not significantly transferred into pork, chicken meat, eggs, and milk (85, 86). Fumonisins disturb the sphingolipid metabolism, and the resulting increase in the sphinganine/sphingosine ratio is used as a biomarker of animal exposure. It was shown that the target organs of fumonisin toxicity are liver (mice, rats, equids, rabbits, pigs, and non-human primates), kidney (pigs, rats, sheep, mice, and rats), brain (horses), and lungs (pigs) (12). The carcinogenicity of fumonisin B_1 in rodents varies between species, strains, and the sexes.

A single outbreak of acute human mycotoxicosis was reported in 27 villages of India, when the poorest social strata were exposed to fumonisin B_1 in mouldy maize and sorghum (87). Fumonisin B_1 was found in much higher concentrations in food consumed by the affected than by the control households. The main features of the

disease were transient abdominal pain, borborygmus, and diarrhoea which started half an hour to one hour after the consumption of unleavened bread.

In some regions of Africa (Transkei), Asia (China), and Europe (Italy) the exposure to fumonisins from maize is connected with higher incidence of oesophageal cancer (45).

Fumonisins have a weak cancer-initiating and a strong cancer-promoting potential, which was proved on rats which developed hepatocellular carcinoma and cholangiocarcinoma. The promoting potential of fumonisins is suspected to be the causative agent of the primary liver carcinoma which is very frequent in the Chinese region of Haimen (88). Concentrations of aflatoxin B_1, deoxynivalenol and fumonisins B_1, B_2, and B_3 were measured in samples of maize from Haimen and Penlai, a region with low incidence of the primary carcinoma. The aflatoxin concentration was low and the incidence of aflatoxin positive findings was similar in both regions, but the concentrations of fumonisins and deoxynivalenol were much higher in Haimen.

An IARC working group classified the toxins from *F. moniliforme* as possibly carcinogen to humans (Group 2B) (44). Limits for human daily exposure, as well as the limits of fumonisins in maize are yet to be determined.

CONCLUSIONS

Mycotoxins are frequent food contaminants. Validated analytical methods for mycotoxins in various commodities should be accepted all over the world to enhance the control of food quality. International organizations (World Health Organization and Food and Agriculture Organization) have recommended regulatory levels and the tolerable daily intake for most mycotoxins, yet those do not oblige national legislations to introduce them. Regulatory levels of mycotoxins should follow the ALARA (as low as reasonably achievable) principles in order to reduce grain trade barriers. The main scope of all these efforts is to decrease the risk of mycotoxin exposure.

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Sažetak

MIKOTOKSINI U HRANI I NJIHOV UČINAK NA LJUDSKO ZDRAVLJE

Mikotoksini su metaboliti plijesni čija važnost za rast i razvoj plijesni nije razjašnjena. Ti spojevi vrlo različitih kemijskih struktura onečišćuju žitarice i druge namirnice osobito u tropskim krajevima, jer viša temperatura i vlažnost pogoduju rastu plijesni. Čovjek je najčešće izložen mikotoksinima putem hrane, no u nekim slučajevima može doći do njihova udisanja, prolaska kroz kožu ili parenteralne izloženosti. Akutno i kronično oštećenje zdravlja zbog djelovanja mikotoksina naziva se mikotoksikoza, a za neke se mikotoksine pretpostavlja ili je dokazano da su karcinogeni za ljude. U ovom radu opisani su različite bolesti ili sindromi u ljudi koje uzrokuju alkaloidi ergota, aflatoksini, okratoksin A, 3-nitropropionska kiselina, trihoteceni, zearalenon i fumonizini. Iznesene su i procjene Međunarodne agencije za istraživanje karcinoma o karcinogenosti pojedinih mikotoksina, kao i zakonski propisi o dopuštenim koncentracijama pojedinih mikotoksina u različitim namirnicama.

Ključne riječi:
3-nitropropionska kiselina, aflatoksini, fumonizini, hrana, ljudi, mikotoksikoze, mikotoksini, okratoksin A, trihoteceni, zearalenon

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