

## FUSARIUM MONILIFORME I NJEGOVI MIKOTOKSINI FUMONIZINI KAO PROMOTORI TUMORSKOG DJELOVANJA

## FUSARIUM MONILIFORME AND ITS MYCOTOXINS FUMONISINS WITH CANCER PROMOTING ACTIVITY

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### SAŽETAK

Fumonizini, nedavno otkriveni metaboliti plijesni *Fusarium moniliforme* Sheldon u inficiranom kukuruzu i drugim žitaricama, razlogom su zabrinutosti u mnogim državama. Trenutačno, čini se da su gospodarski i zdravstveni problemi uzrokovani drugim mikotoksinima daleko manje značajni u usporedbi s FB, do sada najpotentnijim promotorom rasta tumora. Ovi mikotoksini imaju ulogu u pojavi leukoencefalomalacije konja (ELEM), pulmonarnog edema svinja (PPE), različitih zdravstvenih poremetnji u peradi, hepatokarcinoma štakora i moguće karcinoma jednjaka u ljudi. Također, fumonizini značajan su problem zbog proširenosti plijesni *F. moniliforme*, pojavljuju se u visokim količinama i jedinstvenog su načina djelovanja. Fumonizini interferiraju s biosintezom sfingolipida specifičnom inhibicijom enzima sfinganin-N-acil-transferaze što uzrokuje poremećaj u metabolizmu i prenošenju signala u stanici.

### 1. INTRODUCTION

*Fusarium moniliforme* Sheldon is an ubiquitous fungus which is a phytopathogen for many crops including wheat, barley, corn, soybeans, rice, sorghum and oats. This fungus is the primary causative agent of corn stalk, root, and ear rots which has established it as the most widely prevalent and economically important *Fusarium* species on corn (Kommedhal and Windels, 1984). It may cause disease in both farm animals and humans (Marasas et al., 1984; Marasas et al., 1979). According to the literature, it is responsible for equine leukoencephalomalacia (ELEM) (Kellerman et al., 1972) and recently it was found that fumonisin B<sub>1</sub> is a mycotoxin causing this disease in horses (Marasas et al., 1988a). The fungus is toxic for ducklings (Jeschke et al., 1987), chickens (Fritz et al., 1973; Sharby et al., 1973), sheep and swine (Kriek et al., 1981). It causes cirrhosis and nodular hyperplasia of the liver, tumors of various organs, epithelial hyperplasia, papillomas of the esophagus and stomach, and death in rats (Marasas et al., 1984). There is epi-

demiological evidence from Africa and China for an association between human esophageal cancer and consumption of food contaminated with *F. moniliforme* (Marasas et al., 1982; Yang, 1980; Zhen, 1984). Compounds produced by the fungus include gibberellins, moniliformin, fusarins (A, B, C and D), fusariocins, fusaric acid, fumonisin and other mycotoxins of unknown structure (Cole et al., 1973; Wiebe and Bjeldanes, 1981; Ito, 1979; Matuo et al., 1976; Gelderblom et al., 1988).

Fumonisin is a group of structurally related compounds produced by *F. moniliforme* and some other *Fusarium* species. Currently, these mycotoxins are at focus of toxicologists and other scientists as a potent tumor

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promoters (Gelderblom et al., 1988). Also their role in etiology of rat liver cancer, human esophageal cancer, porcine pulmonary edema (PPE), ELEM and some poultry diseases is being evaluated. The health implications of low levels of fumonisins in human foods and safe levels for animals are unknown. At the moment, because of the high level of contamination of U.S. cereals, particularly corn, the Mycotoxin Committee of the American Association of Veterinary Laboratory Diagnosticians recommends that concentrations greater than 5 ppm (equine), 10 ppm (swine) and 50 ppm (beef cattle and poultry) should be acceptable. These recommendations will change as soon as more data becomes available (Riley et al., 1993). Also, the fumonisin fate distribution and subchronic toxicity studies, as a part of the ongoing research in U.S., will answer some of the questions regarding toxicity of these compounds (R. T. Riley, personal communication).

## 2. *FUSARIUM MONILIFORME*: DISTRIBUTION AND GENERAL CHARACTERISTICS

In toxicological literature, the *F. moniliforme* Sheldon and its perfect form *Gibberella fujikuroi* have been included in the *Liseola* section of genus *Fusarium* (Palti, 1978). This fungus is a major fungal parasite of several economically important cereal grains: corn, rice, wheat, barley, sorghum, soybeans and oats (Ayers, 1972; Booth, 1971). It is distributed worldwide, occurring from the humid and subhumid temperature zones to the subtropical and tropical zones, and contaminates many foodstuffs used for human and animal consumption (Booth, 1971; Cook, 1981). Also, it is the most prevalent, ubiquitous fungus associated with corn (Kommedahl and Windels, 1984). In the identification it is very easy to confuse *F. moniliforme* with other *Fusarium* species (especially *F. graminearum*). There are reports in literature that this fungus can produce trichothecenes (Ghosal et al., 1978). However, these authors failed to demonstrate that *F. moniliforme* present in the corn produced trichothecenes they found. A more likely candidate is *F. graminearum*, which is almost always found in infected corn in the field and produces trichothecenes as well as zearalenone.

In the examination of 105 isolates of *F. moniliforme* (most of these were from collection of Commonwealth Mycological Institute, Kew, England, or received directly from research workes located in various geographical areas during the period of 25 years), it was found that most of the isolates originated from total of thirty five species of plants, one insect species and from five miscellaneous substrates. They originated in twenty five geographical areas (Gordon, 1960).

## 3. FUMONISINS: MODE OF ACTION

Recently, a new group of *Fusarium* mycotoxins called fumonisin (A<sub>1</sub>, A<sub>2</sub>, B<sub>1</sub> and B<sub>2</sub>) has been isolated from corn contaminated with the fungus *F. moniliforme* Sheldon (Bezuidenhout et al., 1988). Since then, structures for fumonisin B<sub>3</sub> and B<sub>4</sub> have been reported (Cawood et al., 1991; Plattner et al., 1992) and they are likely other mycotoxins yet to be discovered. Fumonisin B<sub>1</sub> is a predominant member of the group with tumor promoting activity, although FB<sub>2</sub> and FB<sub>3</sub> appear to be as active as FB<sub>1</sub> in inducing GGT-positive foci in rat liver (Gelderblom et al., 1992a). Fumonisins A<sub>1</sub> and A<sub>2</sub> lack the toxicity and tumor promoting activity of FB<sub>1</sub>. Other than *F. moniliforme* fumonisins can be produced by *F. nygamai*, *F. proliferatum*, *F. anthophilum*, *F. dlamini* and *F. napiforme* (Nelson et al., 1992).

Fumonisins are structurally similar to sphingosine and may exert its biological activity through their ability to block key enzymes (sphinganine and sphingosine-N-acyl transferase) involved in sphingolipid biosynthesis of rat primary hepatocytes (Wang et al., 1991) and LLC-PK<sub>1</sub> cells (Hwan-Soo Yoo, 1992). These enzymes are key components in the pathways for the *de novo* sphingolipid biosynthesis and sphingolipid turnover (Merrill, 1991).

Fumonisin inhibition of *de novo* sphingolipid biosynthesis blocking ceramide synthase results in an increase in the amount of sphinganine and a decrease in sphingosine (Wang et al., 1991). Prolonged inhibition of sphinganine-N-acyl transferase decreases the total sphingolipid content of rat hepatocytes. The toxicity associated with inhibition of the *de novo* sphingolipid biosynthesis is unknown. Preliminary *in vivo* studies with rats indicate that fumonisin B<sub>1</sub> inhibits ceramide synthase *in vivo* when gavaged at 25 mg/kg for two days (Wang et al., 1991).

Currently, because of its toxic effect on sphingolipid biosynthesis and tumor promoting activity FB<sub>1</sub> is extensively studied. Sphingosine is the backbone for the sphingolipids, which have many functions important for membrane integrity and physiological activity of cells. Also, sphingosine may serve as an endogenous regulator of protein kinase C activity (Merrill and Stevens, 1989).

## 4. *FUSARIUM MONILIFORME* AND FUMONISINS: A ROLE IN THE ETIOLOGY OF EQUINE LEUKOENCEPHALOMALACIA

Equine leukoencephalomalacia (ELEM) was first recognized at the beginning of this century (Butler, 1902) and since then it was extensively studied. For some



period of time it was described as »moldy corn poisoning« of horses (Schwarte et al., 1973). *F. moniliforme* contamination of corn causes a specific syndrome characteristic for equine and which can not be induced in non-equine species (Kriek et al., 1981). There is a report on the alteration of brain neurotransmitter levels in rats fed *F. moniliforme* culture material (Porter et al., 1990). However, clinical signs and typical lesions that occur in ELEM did not develop. Clinical signs of ELEM at the beginning of the disease include lethargia, disorientation and feed refusal. Typical signs for the progressive stage include ataxia, convulsions, sweating and eventually death (Schwarte et al., 1937). The outstanding feature of ELEM is focal necrosis of the white matter of one or both cerebral hemispheres. Lesions in visceral organs are occasionally noted and may include hepatic congestion, hemorrhagic enteritis, and cystitis. Their relationship to the brain lesions is obscure. Distinctive gross and microscopic neuroanatomic lesions permit differentiation of this disease from viral encephalitis; attempts at bacterial and viral isolations from brains of affected animals have been generally unsuccessful (Badiali et al., 1968) and no other organisms have been isolated. ELEM has been produced experimentally by feeding horses both corn naturally contaminated with *F. moniliforme* (Wilson and Maronpot, 1971; Buck et al., 1979) and corn inoculated and cultured with isolates of the fungus (Haliburton et al., 1979; Kriek et al., 1981). For a long time it was not certain which mycotoxin(s) is responsible for development of ELEM. Discovery of a fumonisins, isolated from *F. moniliforme* culture material (Gelderblom et al., 1988) opened a new era in research on the etiology of this disease.

After repeated intravenous administration of fumonisin B<sub>1</sub>, a horse developed ELEM (Marasas et al., 1988b). Ten days later, after the horse received 7 doses of 0.125 mg of FB<sub>1</sub>/kg of body weight, it suffered a convulsion. At necropsy, a brain lesion similar to those seen in ELEM cases was noticed. In this study clinical signs were nervousness, ataxia, paresis of the lower lip and some others less characteristic of ELEM. When pure FB<sub>1</sub> was administered orally, horse developed signs typical for ELEM (Kellerman et al., 1990). Animals were dosed 20 or 21 times during 33 or 21 days. Doses received were 1-4 mg of FB<sub>1</sub> body weight. At necropsy clinical diagnosis of ELEM was confirmed by the presence of brain lesions. Therefore, serum samples from horses dosed with fumonisin containing feed were analyzed for changes in sphingosine and sphinganine levels (Wang et al., 1992). The levels for both markers increased in proportion to FB<sub>1</sub> intake by horses. These changes occurred much sooner than elevation of serum enzymes which are indicative of liver damage. The most sensitive indicator of the *in vivo* effects of fumonisins

is elevation of the ratio of sphinganine level to sphingosine, and use of the ratio has been proposed as a diagnostic tool (Wang et al., 1992; Riley et al., 1992).

## 5. HEPATOTOXICITY AND LIVER CANCER

Liver toxicity caused by feeding corn contaminated with the *F. moniliforme* appears in all the animal species studied. One of the extensively tested strains of *F. moniliforme*, MRC 826 (Medical Research Council Collection, Tygerberg, South Africa) isolated from corn grown in the high risk area of esophageal cancer in the Republic of Transkei, Southern Africa has been demonstrated to be highly toxic to a wide range of experimental animals, including primates, sheep, swine, horses (ELEM), rats and ducklings (Kriek et al., 1981). In short term feeding trials this strain produced hepatic cirrhosis and nodular hyperplasia in rats (Kriek et al., 1981). In life-long feeding trials in rats, strain MRC 826 produced primary liver cancer and esophageal basal cell hyperplasia (Marasas et al., 1984). Monkeys fed diets containing corn inoculated with strain MRC 826 developed hepatitis (Jaskiewicz et al., 1987). In contrast, strain MRC 1069 (which did not produce hepatotoxicity in rats following subchronic exposure) was not hepatocarcinogenic under the same experimental conditions. Hepatosis is the predominant symptom seen in rats, as well as in equines, if the dose given is sufficiently high. In a separate trial, feeding rats for a long period of time with corn naturally contaminated with *F. moniliforme* induced liver cancer (Wilson et al., 1985). A feeding study in rats has shown that FB<sub>1</sub> is an hepatocarcinogen (Gelderblom et al., 1991). However, these results need to be confirmed with a purer preparation of fumonisin and with more animals and multiple doses.

## 6. TOXICITY IN POULTRY

*F. moniliforme* has been shown to be highly toxic to ducklings (Jeschke et al., 1987), chickens (Fritz et al., 1973; Sharby et al., 1973) and turkey poults (Engelhardt et al., 1989). A total of 25 cultures of *F. moniliforme* were tested and 24 proved to be toxic to ducklings, and none of these produced moniliformin in culture (Jeschke et al., 1987). Ducklings are the most sensitive species to corn based diets contaminated with various concentrations of a moniliformin producing isolates of *F. moniliforme* compared with chicks and turkey poults (Engelhardt et al., 1989). Gross lesions noticed were ascites, hydropericardium, and myocardial pallor. Microscopic lesions were limited to the heart and liver, and they consisted of degeneration and necrosis of the



myocardium and degeneration of hepatocytes. Cardio-toxicosis was the apparent cause of death. In the same study, the sensitivity to the moldy feed was about equal in turkey poults and chicks, although there were some signs of greater sensitivity in turkey poults. Feed consumption was not greatly reduced in birds fed contaminated diet, however, terminal body weights were markedly less in treated birds than in control birds. Average body weight in treated chicks and turkey poults was approximately 50% lower than that of the controls, while treated ducklings averaged 75% less than the controls. Clinical signs observed before death included dyspnea, cyanosis, and reluctance to move in the cage (Engelhardt et al., 1989). Kriek et al. (1981) reported that 15 isolates of *F. moniliforme* including MRC 826 and MRC 602 from home-grown corn in Transkei were acutely toxic to ducklings and that none of these isolates produced moniliformin in culture.

One isolate of *F. moniliforme* from moldy corn in Wisconsin, U.S., was cultured on autoclaved corn at either 10° or 25°C for 21 days and fed to day-old White Leghorn cockerels by Marasas and Smalley (1972). The cultures caused the death of 1 of 10 and 9 of 10 chicks respectively, within 14 days.

Fritz et al. (1973) reported that cultures of *F. moniliforme* isolated from moldy feed implicated in a outbreak of a hemorrhagic disease in swine in the midwestern U.S., caused paralysis with the head retraction typical of polyneuritis in White Plymouth Rock chicks. Four other isolates of *F. moniliforme* did not have this effect. Affected chicks made a dramatic recovery after injection of thiamine hydrochloride, and addition of thiamine to the diet containing *F. moniliforme* culture material also prevented the development of polyneuritis. Sharby et al. (1973) reported that cultures of two isolates of *F. moniliforme* (ATCC 24088 and 24089) from poultry feed in Arkansas, U.S., induced a severe leg abnormality in broiler chicks described as a »cowboy leg« disease. Also, *F. moniliforme* culture material was shown to be immunosuppressive in chickens which may result in increased susceptibility of chicken to bacterial infections (Marijanović et al., 1991). Recently it was reported that FB<sub>1</sub> exposure induced morphological and functional alterations in chickens macrophages (Qureshi and Hagler, 1992). This mycotoxin together with known immunosuppressive fusarin C, might be responsible for suppression of humoral immune response to a specific antigens in chickens (Marijanović et al., 1991).

## 7. PORCINE PULMONARY EDEMA (PPE)

Recently, reports have been received on an acute porcine pulmonary edema syndrome (PPE) associated

with feeding corn or corn-based feeds. This outbreak (1989) was reported in the U.S., particularly in Georgia (Harrison et al., 1990) and the Midwest (Osweiler et al., 1992). Feeds involved have been shown to be contaminated with *F. moniliforme* and to contain a high level of fumonisins (Ross et al., 1990). *F. moniliforme* was the only fungus isolated from feed from 6 of 11 cases in Iowa, and with *F. proliferatum* was a co-contaminant of the other 5 feed samples from Iowa. The corn screenings collected from the affected farms contained 20-330 ppm of FB<sub>1</sub>. The amount of fumonisins produced by both *F. moniliforme* and *F. proliferatum* isolated from the corn samples ranged from 960-2350 mg/kg corn of FB<sub>1</sub> and 120-320 mg/kg corn of FB<sub>2</sub> (Ross et al., 1990). After i.v. administration of FB<sub>1</sub> (Osweiler et al., 1992) and both intravenous and oral administration in the separate study (Haschek et al., 1992) PPE was induced.

The disease is characterized by acute pulmonary edema. In the field case all ages of swine were affected with death losses of 10 to 40%. Clinical signs observed are mainly breathing difficulty and lethargy with death occurring within a short time. About half of the sow herds affected also had late gestation abortions (Harrison et al., 1990). A possible mechanism of induction of PPE by FB<sub>1</sub> has hypothesized by Haschek et al. (1992). They proposed that due to effects on sphingolipid biosynthesis by FB<sub>1</sub>, plasma membrane of the hepatocytes is damaged and later released into the blood stream. These membrane fragments are phagocytized by pulmonary interstitial macrophages (PIM's) which initially release enzymes responsible for increased capillary permeability in the lung tissue. The lungs of pigs are especially rich in PIM's while in other species these cells are present in very low levels, or do not exist as in rats (Winkler, 1988).

## II. Association of the *Fusarium moniliforme* and fumonisins with human esophageal cancer (EC):

Human esophageal cancer is a common disease in some parts of China (Yang, 1980), the Transkei region of South Africa (van Rensburg, 1985), Iran (Kmet and Mahboubi, 1972), Charleston, SC, U.S. (Fraumeni and Blot, 1977) and Northern Italy (Franceschi et al., 1990).

The etiology of EC is not clear, although there is strong epidemiological evidence between the incidence of EC and the contamination of corn and corn-based diets with *F. moniliforme* (Marasas et al., 1979; Marasas et al., 1988a; Cheng et al., 1985). Feeding studies with different isolates of *F. moniliforme* from this region produced liver tumors and basal cell hyperplasia of esophagus in rats (Marasas et al., 1984a). Also, it is known that people in this region are producing home-brewed beer from moldy corn (W.F.O. Marasas, personal communication, 1992).



In areas where EC is prevalent, foodstuffs are frequently contaminated with fungi. Several fungi are prevalent, but by far the most prevalent is *F. moniliforme*. Cornmeal infested by *F. moniliforme* or *F. semitectum* was found to induce tumors on several different tissues. Carcinoma of the esophagus was not observed, but epithelial hyperplasia was induced by *F. moniliforme* infested samples (Liu et al., 1978). To date, fumonisin assays of corn from Linxian county, China, have not been done.

In Italy the relationship between maize consumption and risk of cancer of the upper digestive tract was investigated in 107 patients with oral cancer, 107 with pharyngeal cancer, 68 with esophageal cancer, and 505 hospital controls who permanently resided in Pordenone Province in the northeastern part of the country. The analysis was restricted to males. The population of this province has a high incidence of these neoplasms and has particularly elevated levels of alcohol and tobacco use, in addition to high maize consumption. Highly significant associations with frequent intake of maize emerged for oral cancer, pharyngeal cancer, and esophageal cancer (Franceschi et al., 1990). Finally, Rossi et al. (1982) reported a 4.5-fold increased risk of developing esophageal cancer among individuals who ate two or more slices of polenta per day in an investigation conducted in the Veneto region in Italy. This region borders Pordenone Province and is economically and historically similar to it. There is insufficient data on the presence of *F. moniliforme* and

fumonisin in corn from northern Italy and further research needs to be done.

Fumonisin have been implicated as a possible cause or contributing factor in esophageal cancer. A sample of corn from the Transkei (an area with high incidence of esophageal cancer) was analyzed for FB<sub>1</sub> and found to contain 44 ppm of the toxin (Sydenham et al., 1990b). Other evidence that fumonisins might be associated with esophageal cancer (Sydenham et al., 1990a) emerged from a study in which healthy and moldy corn samples were taken from high and low EC rate areas of the Transkei. In moldy corn, the *Fusarium* species that predominated in the low EC region were *F. graminearum* and *F. moniliforme*, which occurred in similar incidences. In the high EC region, however, the predominant fungus was *F. moniliforme* (68%) incidence. In the samples from low EC incidence several mycotoxins were found: moniliformin, zearalenone, nivalenol and deoxynivalenol. However, the amount of FB<sub>1</sub> in samples from the high rate area was about 4 times higher than those from the low EC area. Whether FB<sub>1</sub> is a complete carcinogen has not been established, but it does at least appear to be a potent tumor promoter (Gelderblom et al., 1988; Gelderblom et al., 1991). *F. moniliforme* produces a compound, fusarin C, that is a potent mutagen (Gelderblom et al., 1991). *F. moniliforme* produces a compound, fusarin C, that is a potent mutagen (Gelderblom et al., 1983). A possible interaction of fusarin C and FB<sub>1</sub> in the etiology of EC has not been investigated yet.

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## ABSTRACT

Fumonisin, recently discovered metabolites of *Fusarium moniliforme* Sheldon, occurring naturally in infected corn and other cereals are an area of growing concern in many countries. Presently, it seems that the economic and health risk of other mycotoxins is far below the significance of potent tumor promoter fumonisin B<sub>1</sub>. These compounds are involved in incidence of equine leukoencephalomalacia (ELEM), porcine pulmonary edema (PPE), disease problems in poultry, hepatocarcinoma in rats and possibly esophageal carcinoma (EC) in humans. Fumonisin is a significant problem because *F. moniliforme* in corn is widespread, naturally they occur in ppm range, and their mode of action is unique. They interfere with sphingolipid biosynthesis by specifically inhibiting an enzyme sphinganine-N-acyl transferase. Because of this, the activity of secondary messenger system in the cells is affected.