Discovery and Occurrence of the Fumonisins: A Historical Perspective

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This article describes the events leading to the discovery of the fumonisins in South Africa in 1988 and highlights the first 10 years (1988–1998) of fumonisin research. The predominant fungus isolated from moldy corn implicated in a field outbreak of equine leukoencephalomalacia (ELEM) in 1970 was *Fusarium verticillioides* (Sacc.) Nirenberg (synonym: *F. moniliforme* Sheldon; teleomorph Gibberella moniliformis Wineland) is one of the most prevalent seed-borne fungi associated with corn (maize, *Zea mays* L.) intended for human and animal consumption throughout the world (1). The fumonisins, a family of foodborne carcinogenic mycotoxins, were first isolated in 1988 from cultures of *F. verticillioides* strain MRC 826 at the Programme on Mycotoxins and Experimental Carcinogenesis (PROMEC) of the Medical Research Council (MRC) in Tygerberg, South Africa, by Gelderblom et al. (2). Also in 1988, the structures of the fumonisins were also elucidated in a collaborative effort between the PROMEC and the Council for Scientific and Industrial Research (CSIR) in Pretoria (3). Fumonisin B1 (FB1), in a collaborative effort between PROMEC and the Onderstepoort Veterinary Research Institute in South Africa (4), was shown to cause equine leukoencephalomalacia (ELEM).

The isolation and chemical characterization of the fumonisins in South Africa in 1988 was the culmination of 18 years (1970–1988) of intensive dedicated research by a multidisciplinary team with members at each of the above-mentioned three institutions. In this historical perspective, we describe the events during this period that led to the isolation of the fumonisins in 1988, and highlight the first 10 years (1988–1998) of fumonisin research.

**Events Leading to the Characterization of the Fumonisins in South Africa: 1970–1988**

*F. verticillioides* was the predominant fungus isolated from moldy corn associated with a field outbreak of ELEM in South Africa during 1970 characterized by liquefactive necrotic lesions in the white matter of the cerebral hemispheres of horses (1,5). The causative role of *F. verticillioides* in ELEM (6) was subsequently confirmed with several South African isolates of the fungus, and the pathognomonic pathologic changes were described in detail (5,7). The occurrence of bile duct proliferation, increased numbers of mitotic figures, multinucleated hepatocytes, and large, bizarre hyperchromatic nuclei in the livers of these horses (5,7) were the first indications that *F. verticillioides* might be a carcinogenic fungus.

Subsequently, we became involved in a study of the possible role of fungal toxins in the etiology of human esophageal cancer (EC) in the Transkei region of South Africa. The incidence rate of EC in males and females in the southern part of Transkei is among the highest in the world, whereas the rate in the northern part of Transkei is low (8,9). The staple diet in both areas is home-grown corn, and *F. verticillioides* was shown to be the most prevalent fungus in corn consumed by people in areas with a high incidence of EC (10).

In continuing investigations on the toxicology of *F. verticillioides* isolates from corn associated with field outbreaks of ELEM in horses, isolates from corn in areas in Transkei with a high risk of EC were included. One of these Transkei isolates, designated *F. verticillioides* MRC 826, was soon found to cause ELEM experimentally in horses and porcine pulmonary edema (PPE) in pigs (11) and to be highly hepatotoxic and cardiotoxic in rats (11,12). In 1984, culture material of *F. verticillioides* MRC 826 was shown to be hepatocarcinogenic in rats and to cause primary hepatocellular carcinoma and cholangiocarcinoma (13).

Although chemical investigations on the mycotoxin(s) produced by *F. verticillioides* MRC 826 began in South Africa in July 1970, the chemical nature of the metabolite(s) responsible for ELEM still had not been identified in 1984 when the fungus was shown to be carcinogenic. The isolation and chemical characterization of the mycotoxin(s) and carcinogen(s) produced by *F. verticillioides* then became a matter of paramount importance.

The urgency of the matter was accentuated further when researchers in the United States reported that corn implicated in field outbreaks of ELEM and naturally infected by *F. verticillioides* was also hepatocarcinogenic in rats (14). The pathologic changes in these rats were identical to those that had been described in 1984 in rats fed culture material of *F. verticillioides* MRC 826 by Marasas et al. (15). This provided evidence that the unidentified carcinogen(s) produced by *F. verticillioides*
was present not only in culture material of *F. verticilloides* MRC 826 but also occurred naturally in corn in the United States.

In 1984 the following mycotoxins were known to be produced by *F. moniliforme*, according to the literature: deoxynivalenol; diacetylmycotoxin, fusaric acid; fusarins A, B, C, and D; fusariocins; gibberellins; moniliformin; T-2 toxin; and zearalenone (†). We knew, however, that *F. verticilloides* MRC 826 did not produce moniliformin, trichothecenes, or zearalenone (1,12,13). We also knew that a chloroform/isopropanol extract of culture material of *F. verticilloides* MRC 826 was highly mutagenic to *Salmonella typhimurium* in the Ames test (16,17). Consequently, intensive efforts were made to isolate and characterize the mutagen(s) because most mutagens are also carcinogens. A group of structurally related compounds, the fusarins, were isolated. One of these, fusarin C, was very promising, as it was highly mutagenic in the Ames test and occurred naturally in Transkeian corn (13,17) as well as in corn from the United States that had been shown to be hepatocarcinogenic in rats (19). Consequently, short-term carcinogenicity assays with fusarin C and long-term trials in rats with culture material of *F. verticilloides* MRC 826 at high levels of fusarin C were performed (20,21). However, no evidence could be found of the carcinogenicity of fusarin C.

It was concluded that fusarin C was not the carcinogenic metabolite present in culture material of *F. verticilloides* MRC 826. In view of the findings that fusarin C was not carcinogenic and because it is heat and light sensitive, it was concluded that fusarin C is not a threat to human health.

Thus, the search continued for the elusive *F. verticilloides* carcinogen. During our investigations on the carcinogenicity of fusarin C, a short-term initiation/promotion assay in rat liver was developed. This involved partial hepatectomy of rats, followed by administration of an initiator such as diethylnitrosamine (DEN), followed by administration of a promotor such as phenobarbital. After 14 weeks, the gamma-glutamyltranspeptidase (GGT) activity was determined histochemically in the liver (2,20,22). During the application of this short-term carcinogenicity assay, it was found that culture material of *F. verticilloides* MRC 826 initiated the formation of early lesions in the liver and exhibited cancer-promoting activity. The short-term cancer initiation/promotion assay, with DEN as initiator and the ability of fractions of extracts of the culture material to selectively stimulate the development of GGT-altered foci in rat liver, was used as a bioassay in the isolation of the active principle(s) (2). All these efforts finally succeeded in 1988, when the chemical nature of the carcinogen was unraveled. FB1, and fusomin B2 (FB2), novel mycotoxins with cancer-promoting activity in rat liver, were isolated from cultures of *F. verticilloides* MRC 826 at PROMEC 2. The structures of FB1 and FB2 were elucidated in collaboration with the CSIR (3). The elucidation of the chemical structure of the fumonisins, together with the demonstration in 1988 of the biologic activity of FB1, was the end of an era and the beginning of a new one. From 1970–1988, the toxicity of culture material of *F. verticilloides* MRC 826 to horses and pigs and the carcinogenicity to rats were established. From 1988–1991, the stage was set for a new era of research on the biologic activity of these novel chemical carcinogens (4–10).

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The natural occurrence of FB1 in homegrown corn from Transkei was first reported in January 1990 by Sydenham et al. (26). The first quantitative and sensitive high-performance liquid chromatography method for the simultaneous determination of FB1 and FB2 in naturally contaminated corn and mixed feed was published in June 1990 by Shephard et al. (27). Using this analytical method, Sydenham et al. (28) showed that home-grown corn from areas in Transkei with a high incidence of EC contained significantly higher levels of both FB1 and FB2 than corresponding samples from low-incidence areas. In 1981 a correlation was shown between the incidence of the fungus *F. verticilloides* in home-grown corn and the incidence of EC in Transkei (10), whereas in 1990 a correlation was shown between the levels of FB1 and FB2 in home-grown corn and the incidence of EC in Transkei (28).

It is remarkable that the fumonisins were launched into international importance shortly after their discovery in South Africa in 1988 by events that occurred in the United States during 1989 and 1990. These events occurred shortly after publication of the structure of the fumonisins in 1988 (2) but just before the publication of a sensitive chemical analytical method for FB1 and FB2 in June 1990 (27).

### The Great American Outbreaks: 1989–1990

During the fall of 1989 and the winter of 1990, widespread, large-scale outbreaks of ELEM and PPE occurred in the United States. Large numbers of horses and pigs died from consuming commercial mixed feeds containing fumonisin-contaminated corn from the 1989 U.S. corn crop (24,29–33).

### Great Activity and International Agency for Research on Cancer Evaluation: 1990–1993

The disastrous consequences of the contamination of the 1989 U.S. corn crop with high levels of fumonisins triggered a great deal of interest in and research on the fumonisins in the United States and elsewhere (34–40). This resulted in a sharp increase in the number of publications dealing with the fumonisins (41), including several comprehensive

### Table 1. Incidence of Fusarium verticilloides in home-grown corn from Transkei

| Season  | Mean % kernels infected | Low incidence of EC | High incidence of EC | p <  |
|---------|-------------------------|---------------------|----------------------|-----|
| Healthy corn | 1976 | 5.0 | 41.5 | 0.0001 |
|          | 1979 | 5.0 | 23.1 | 0.01 |
|          | 1985 | 8.3 | 42.0 | 0.001 |
|          | 1986 | 5.0 | 43.0 | 0.01 |
|          | 1989 | 8.9 | 42.1 | 0.02 |
| Mouldy corn | 1977 | 17.0 | 25.7 | 0.005 |
|          | 1979 | 9.8 | 33.4 | NS |
|          | 1985 | 34.5 | 67.7 | 0.01 |
|          | 1986 | 21.4 | 61.7 | 0.01 |

*NS, not significant.

*Data from Rheeder et al. (53).*  
*Table 2. Levels of fumonisins in home-grown corn from Transkei.*

| Mean fumonisin levels (µg/g) | Low incidence of EC | High incidence of EC | p <  |
|-----------------------------|---------------------|----------------------|-----|
| Healthy corn | 1985 | 0.3 | 2.1 | 0.001 |
|          | 1989 | 0.6 | 2.0 | NS |
| Mouldy corn | 1985 | 9.0 | 31.5 | 0.01 |
|          | 1989 | 5.1 | 67.4 | 0.005 |

*Data from Rheeder et al. (53).*  
*Table 3. Incidence of *F. graminearum* and levels of DON, NIV, and ZEA in moldy corn from Transkei in 1985.*

| Low incidence of EC | High incidence of EC | p <  |
|---------------------|----------------------|-----|
| *F. graminearum* (%) | 34.9 | 8.0 | 0.01 |
| DON (µg/g) | 2.9 | 0.3 | NS |
| NIV (µg/g) | 4.6 | 1.8 | 0.05 |
| ZEA (µg/g) | 1.2 | 0.4 | 0.01 |

*Data from Sydenham et al. (28) and Rheeder et al. (53).*
reviews (41–48). The First Conference on Fumonisins was held in Ames, Iowa, USA, from 6 to 7 September 1990. This was followed by other international conferences on fumonisins (49,50).

The International Agency for Research on Cancer in Lyon, France, evaluated the toxins produced by F. moniliforme as Group 2B carcinogens (i.e., possibly carcinogenic to humans) in 1993 (51).

**Esophageal Cancer in Transkei Revisited: 1981–1998**

At this juncture we return to Transkei in South Africa, where we first demonstrated a link between F. verticillioides and EC in 1981 (10) and between fumonisins and EC in 1990 (28). These correlations between the incidence of F. verticillioides and fumonisin levels in home-grown corn and EC rate were confirmed in 1988 (52) and 1992 (53). The data obtained in Transkei over six seasons between 1976 and 1989 are summarized in Tables 1 and 2.

It is clear from Table 1 that F. verticillioides is significantly more prevalent in healthy corn as well as moldy corn from areas with a high incidence of EC than from those areas with a low incidence of EC in Transkei. Similarly, fumonisin levels in healthy as well as moldy corn from areas with a high incidence of EC are significantly higher than in areas with low incidence (Table 2). The data clearly identify the area with a high incidence of EC, comprising Bizana and Lusikisiki districts in southern Transkei, as an ecologic zone that favors the infection of corn ears by F. verticillioides and the concomitant production of fumonisins in the infected kernels. Conversely, the areas with low incidence, comprising Bizana and Lusikisiki districts in northern Transkei, are not favorable for the development of F. verticillioides ear rot and fumonisin production in corn. In fact, the area with a low incidence of EC was found to be much more conducive to another Fusarium sp. that causes ear rot of corn, i.e., F. graminearum Schwabe, and the production of three mycotoxins by this fungus, i.e., deoxynivalenol (DON), nivalenol (NIV), and zearalenone (ZEA), in corn than the area with a high incidence of EC (Table 3). The two areas are compared in Table 4 with respect to climatic, geographic, geologic, and soil fertility factors that may be important in determining the mycotoxicologic differences between the areas.

Incidence rates of EC in high-incidence (Kentani district) and low-incidence (Bizana district) areas in Transkei from 1955 to 1990 are compared in Table 5. It is clear that from 1955 to 1959 the two areas were distinctly different with respect to EC incidence rates in both males and females, i.e., very low (2.6 and 1.8) in Bizana and very high (54.2 and 30.3) in Kentani. The rates in Kentani have consistently stayed very high and in 1985–1990 were very similar (55.6 and 22.1) to those recorded from 1955 to 1959. In Bizana, however, incidence rates in both males and females increased markedly, and from 1985 to 1990 the rates were not much different (37.0 and 11.7) from those in Kentani. Because of the numerous problems and pitfalls associated with cancer registry in remote rural areas of Africa, it is not clear whether the increased EC rates in Bizana are real or are reflections of changes in cancer registry patterns due to demographic, socioeconomic, political, and/or other factors.

In a comparative study of the incidence of esophageal cytologic abnormalities determined by means of brush biopsies in residents of the two areas in 1985, it was found that mild and advanced cytologic changes occurred much more frequently in the high EC area (Kentani, 50.0 and 36.7%, respectively) than in the area with a low incidence of EC (Bizana, 12.5 and 4.2%, respectively) (52). It can be assumed that residents of both areas in Transkei have nutritional deficiencies for several mineral elements and vitamins, as indicated by the blood biochemical parameters of blood biochemical parameters of Table 6.

**Table 6. Some blood biochemical parameters of populations at risk for EC in Transkei.**

| Blood biochemical parameters | Normal values | Transkei |
|-----------------------------|---------------|---------|
| Selenium (ng/mL)            | 112–210       | 58–69   |
| Vitamin A (µg/dL)           | 20–70         | 4–40    |
| Vitamin E (µg/dL)           | > 6.0         | 3.7–5.3 |
| Folic acid (ng/mL)          | 210–980       | 242–307 |

**Table 7. Incidence of esophageal cytologic abnormalities, F. verticillioides, and fumonisins in home-grown corn in areas with low and high incidences of EC in Transkei.**

| F. verticillioides (%) | Healthy | Moldy | Healthy Moldy |
|-----------------------|---------|-------|---------------|
|                       | corn    | corn  | corn          |
| 8.3                   | 34.5    | 42.0  | 67.7          |
| Fumonisins (µg/g)     | 0.3     | 9.0   | 2.1           | 31.5          |

It is clear from Table 7 that fumonisins were much more conducive to another F. verticillioides sp. that causes ear rot of corn and the concomitant production of fumonisins in the infected kernels. Conversely, the areas with low incidence, comprising Bizana and Lusikisiki districts in northern Transkei, are not favorable for the development of F. verticillioides ear rot and fumonisin production in corn. In fact, the area with a low incidence of EC was found to be much more conducive to another Fusarium sp. that causes ear rot of corn, i.e., F. graminearum Schwabe, and the production of three mycotoxins by this fungus, i.e., deoxynivalenol (DON), nivalenol (NIV), and zearalenone (ZEA), in corn than the area with a high incidence of EC (Table 3). The two areas are compared in Table 4 with respect to climatic, geographic, geologic, and soil fertility factors that may be important in determining the mycotoxicologic differences between the areas.

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Although FB1 and FB2 were first reported to occur naturally in corn from Transkei (26), fumonisins have also been reported subsequently to occur in home-grown and/or commercial corn in several other areas throughout the world with a high incidence...
of EC (Table 8). It is clear that fumonisins occur in corn consumed by humans at risk for EC in some areas in Africa, Asia, Europe, and the United States. The question remains whether some individuals (who take in higher levels of fumonisins in corn consumed as the staple diet than others) are at higher risk to develop cytological abnormalities in the esophagus that may terminate in EC. The first step required to answer this question is to assess human fumonisin intake. For this assessment, two approaches are used: calculation of the probable daily intake (PDI) and measurement of biomarkers for fumonisin exposure in humans (67).

Human fumonisin intake can be calculated from analyses of naturally occurring levels of fumonisins in corn and data on corn intake and expressed as the PDI (Table 9). Both the level of fumonisins in the corn and the amount of corn consumed influence the PDI (i.e., the higher the level and the larger the amount consumed, the higher the PDI). Large variations are apparent in the PDI, ranging from 1.2 µg/kg body weight (bw)/day, in urban South Africans consuming commercial corn, to 354.9 µg/kg bw/day, in rural South Africans consuming moldy home-grown corn. The rural population in Transkei who are at the highest risk for EC in South Africa have the highest daily corn intake and also consume home-grown corn containing the highest levels of fumonisins. Thus, the PDI can be a useful estimate of the fumonisins intake of population groups such as the rural population in Transkei, and although it can be applied to individuals by means of food-from-the-plate analyses, this is not easy to do.

Biomarkers are more accurate as measures of individual intakes, but unfortunately, biomarkers for human fumonisin intakes are not yet available. However, fumonisins disrupt sphingolipid biosynthesis (40), and the resulting elevation in the sphinganine/sphingosine (Sa/So) ratio in serum, plasma, or urine has been used as a biomarker in animals, including nonhuman primates (62,63). Moreover, analytical techniques have been developed to determine Sa/So levels in humans, and ratios of 0.09–0.78 have been reported in serum (64) and ratios of 0.04–0.60 in urine (65,66). In a recent article by van der Westeijen et al. (67), Sa/So ratios were reported in the plasma and urine of residents of Kentani district in the area with a high incidence of EC in Transkei (Table 10). Although the mean values were similar to those reported in human serum and urine above, the upper ranges of the ratios in both plasma (2.97) and urine (5.75) were much higher than those previously reported. It remains to be determined whether:

- The Sa/So ratio is sensitive enough as a biomarker of human intake, and fumonisin at the levels of contamination examined to date (Table 10).
- Variation in the ratio between individuals and within an individual over time can be accommodated.
- Genetic polymorphisms of ceramide synthase exist and contribute to individual susceptibility to fumonisins.
- Individuals with high Sa/So ratios in areas in Transkei with a high incidence of EC have high intakes of fumonisins and are at high risk for EC.

Y2K—Much more work remains to be done on the fumonisins in the Third Millennium!

**REFERENCES AND NOTES**

1. Marasas WFO, Nelson PF, Toussoun TA. Toxigenic Fusarium Species. Identity and Mycotoxicology. University Park, PA:Pennsylvania State University Press, 1984.
2. Gelderblom WCA, Jaskiewicz K, Marasas WFO, Thiel PG, Horak MJ, Vleggaar R, Kriek NPJ. Fumonisin B1, a toxic metabolite of Fusarium moniliforme. Appl Environ Microbiol 54:1806–1811 (1988).
3. Beuzidemoutoux DC, Gelderblom WCA, Gort-Alffman CP, Horak RM, Marasas WFO, Spitters G, Vleggaar R. Structure elucidation of the fumonisins, mycotoxins from Fusarium moniliforme. J Chem Soc Chem Comm 1988-743-745 (1988).
4. Marasas WFO, Gelderblom WCA, Coetzer JAW, Thiel PG, van der Lugt JJ. Leukoencephalomalacia in a horse induced by fumonisin B1 isolated from Fusarium moniliforme. Onderstepoort J Vet Sci 55:197–203 (1988).
5. Kellerman TS, Marasas WFO, Pienaar JG, Naude TW. A mycotoxicosis of Equidae caused by Fusarium moniliforme. Onderstepoort J Vet Sci 59:205–218 (1972).
6. Wilson BJ. Recently discovered metabolites with unusual toxic manifestations. In: Mycotoxins in Human Health (Purchase JFH, ed). London:MacMillan, 1971:223–229.
7. Marasas WFO, Gelderblom WCA, Thiel PG. Leukoencephalomalacia in a mycotoxicosis caused by Fusarium moniliforme. Onderstepoort J Vet Res 43:113–122 (1976).
8. Jaskiewicz K, Marasas WFO, van der Walt FE. Oesophageal and other main cancer patterns in four districts of Transkei, 1981-1984. S Afr Med J 72:273–280 (1987).
9. Makaua NA, Marasas WFO, Venter FS, Badenhorst CJ, Brashou D, Swanevelder S. Oesophageal and other cancer patterns in four selected districts of Transkei, southern Africa: 1985-1990. Afr J Health Sci 11:15–19 (1989).
10. Marasas WFO, Venter FE, van Rensburg SJ, van Schalkwyk DJ. Mycotoxins of corn produced in human esophageal cancer areas in Transkei, southern Africa. Phytopathology 71:792–796 (1981).
11. Kriek NPJ, Kellerman TS, Marasas WFO. A comparative study of the toxicity of Fusarium verticillioides (F. moniliforme) to horses, primates, pigs, sheep and rams. Onderstepoort J Vet Res 45:129–131 (1981).
12. Kriek NPJ, Marasas WFO, Thiel PG. Hepato- and cardiotoxicity of Fusarium verticillioides (F. moniliforme) isolates from southern African maize. Food Cosmet Toxicol 19:447–455 (1981).
13. Marasas WFO, Kriek NPJ, Fincham JE, van Rensburg SJ. Primary liver cancer and oesophageal basal cell hyperplasia in rats caused by Fusarium moniliforme. J Cancer 34:383–397 (1984).
14. Wilson TM, Nelson PE, Kneip DP. Hepatic neoplastic nodules, adenomas, and cholangiocarcinomas in male Fischer rats fed corn naturally contaminated with Fusarium moniliforme. Carcinogenesis 6:1155–1160 (1985).
15. Marasas WFO. Fusarium moniliforme: a mycotoxicological mimic. In: Mycotoxins and Phytoalexins (Stein PS, Vleggar R, eds). Amsterdam:Elsevier, 1986:19–28.
16. Gelderblom WCA, Thiel PG, van der Merwe KJ. A mutagen produced by Fusarium moniliforme. Toxicon 21:487–493 (1983).
17. Gelderblom WCA, Marasas WFO, Stem PE, Thiel PG, van der Merwe KJ, van Rooyen PH, Vleggar R, Weissel E. Structure elucidation of fusarin C, a mutagen produced by Fusarium moniliforme. J Chem Soc Chem Comm 1984:122–124 (1984).
18. Gelderblom WCA, Thiel PG, Marasas WFO, van der Merwe KJ. Natural occurrence of fusarin C, a mutagen produced by Fusarium moniliforme, in corn. J Agric Food Chem 32:1064–1067 (1984).
19. Thiel PG, Gelderblom WCA, Marasas WFO, Nelson PE, Wilson TM. Natural occurrence of fusarin C and fusarin B in corn screenings known to be hepatitis carcinogenic in rats. J Agric Food Chem 34:773–775 (1986).
20. Gelderblom WCA, Thiel PG, Jaskiewicz K, Marasas WFO. Investigations on the carcinogenicity of fusarin C—a mutagenic metabolite of Fusarium moniliforme. Carcinogenesis 7:1899–1901 (1986).
21. Jaskiewicz K, van Rensburg SJ, Marasas WFO, Gelderblom WCA. Carcinogenicity of Fusarium moniliiforme culture material in rats. J Natl Cancer Inst 78:321–325 (1984).
22. Gelderblom WCA, Marasas WFO, Jaskiewicz K, Conbrick S, van Schalkwyk DJ. Cancer promoting potential of different strains of Fusarium moniliforme in a short-term cancer initiation/promotion assay. Carcinogenesis 9:1405–1408 (1988).
23. Kellerman TS, Marasas WFO, Thiel PG, Gelderblom WCA, Carwood M, Coetzer JAW. Leukoencephalomalacia in two horses induced by oral dosing of fumonisin B1. Onderstepoort J Vet Res 57:269–275 (1990).
24. Harrison LR, Calvin BM, Green JT, Newman LE, Cole JR. Pulmonary edema and hydrothorax in swine exposed by fumonisin B1, a toxic metabolite of Fusarium moniliforme. J Vet Diagn Invest 2:217–221 (1990).
25. Gelderblom WCA, Kriek NPJ, Marasas WFO, Thiel PG. Toxicity and carcinogenicity of the Fusarium moniliforme metabolite, fumonisin B1, in rats. Carcinogenesis 12:1247–1252 (1990).
26. Sydenham EW, Gelderblom WCA, Thiel PG, Marasas WFO. Evidence for the natural occurrence of fumonisin B1, a mycotoxin produced by Fusarium moniliforme, in corn. J Agric Food Chem 38:295–300 (1990).
27. Shepherd GS, Sydenham EW, Thiel PG, Gelderblom WCA.
Quantitative determination of fumonisin B1 and B2 by high performance liquid chromatography with fluorescence detection. J Liq Chromatogr 19:2077–2087 (1996).
28. Sydenham EW, Thiel PG, Marasas WFO, Shephard GS, van Schalkwyk DJ, Koch KR. Natural occurrence of some Fusarium myotoxins in corn from low and high esophageal cancer prevalence areas of the Transkei, southern Africa. J Agric Food Chem 38:1800–1903 (1990).
29. Ross PF, Nelson PE, Richard JL, Osweiler GD, Rice LG, Plattner RD, Wilson TM. Production of fumonisins by Fusarium moniliforme and Fusarium proliferatins isolated associated with equine leukoencephalomalacia and pulmonary edema syndrome in swine. Appl Environ Microbiol 56:3225–3228 (1990).
30. Ross PF, Rice LG, Osweiler GD, Wilson TM, Owens DJ, Nelson HA, Richard JL. Concentrations of fumonisin B1 in feed associated with animal health problems. Mycopathologia 114:129–135 (1991).
31. Ross PF, Rice LG, Reagor C, Osweiler GD, Wilson TM, Owens DJ, Plattner RD, Hartin KA, Richard JL, et al. Fumonisin B1 concentrations in feeds from 45 confirmed cases of equine leukoencephalomalacia. J Vet Diagn Invest 3:238–241 (1991).
32. Wilson TM, Ross PF, Rice LG, Osweiler GD, Nelson HA, Owens PI, Plattner RD, Riegards C, Noon TH, Pickrell SW. Fumonisin B1 levels associated with an epizootic of equine leukoencephalomalacia. J Vet Diagn Invest 3:213–216 (1991).
33. Wilson TM, Nelson PE, Marasas WFO, Thiel PG, Sydenham EW, Nelson HA, Ross PF. A mycological evaluation and in vivo toxicity evaluation of feed from 41 farms with equine leukoencephalomalacia. J Anim Sci 72:352–354 (1994).
34. Jackson MA, Bennett GA. Production of fumonisin B1 by Fusarium moniliforme NRRL 13616 in submerged culture. Appl Environ Microbiol 56:2296–2298 (1990).
35. Norred WP, Bacon CW, Porter JK, Voss KA. Inhibition of protein synthesis in rat primary hepatocytes by extracts of Fusarium moniliforme strain MRC 826 culture material. Mycopathologia 112:81–82 (1990).
36. Wang E, Norred WP, Bacon CW, Riley RT, Merrill AH. Inhibition of sphingolipid biosynthesis by fumonisins. J Biol Chem 266:14486–14490 (1991).
37. Marasas WFO. Fumonisins: history, worldwide occurrence and impact. In: Fumonisins in Food (Jackson LS, De Vries JW, Bulterman LB, eds). New York:Plenum Press, 1991;1–17.
38. Merrill AH, Wang E, Gilchrist DG, Riley RT. Fumonisins and other inhibitors of de novo sphingolipid biosynthesis. Adv Lipid Res 26:193–234 (1990).
39. Wilson TM, Reijnders AE, Plattner RD, Fumonisin. Production of Fusarium sp. isolates and fumonisins produced by Fusarium moniliforme. J Toxicol Environ Health 38:309–320 (1990).
40. Riley RT, Norred WP, Bacon CW. Fungal toxins in foods: recent concerns. Annu Rev Nutr 13:167–189 (1993).
41. Neale RJ, van der Westhuizen L. Concentrations of fumonisin B1 in maize and fumonisins produced by Fusarium moniliforme. J Appl Mycol 117:11–16 (1992).
42. Gelderblom WCA, Vleggar R, Thiel PG, Coward ME. Fumonisins: isolation, chemical characterization and biological effects. Mycopathologia 117:11–16 (1992).
43. Gelderblom WCA, Snyman SD, Abel S, Lebbe-Mazu S, Smuts CM, van der Westhuizen L, Marasas WFO, Victor TC, Knausmüller S, Huber W. Hepatotoxicity and carcinogenicity of the fumonisins in rats. A review regarding mechanistic implications for establishing risk in humans. In: Fumonisins in Food (Jackson LS, De Vries JW, Bulterman LB, eds). New York:Plenum Press, 1996:279–296.
44. Norred WP, Bacon CW, Porter JK, Voss KA. Inhibition of protein synthesis in rat primary hepatocytes by extracts of Fusarium moniliforme strain MRC 826 culture material. Mycopathologia 112:81–82 (1990).
45. Chu FS, Li GY. Simultaneous occurrence of fumonisin B1 and B2 by high performance liquid chromatography. In: Atti 2 Congresso Nazionale di Chimica degli Alimenti. Messina, Italy: La Grafica Editore, 1995;1047–1071.
46. Sydenham EW, Shephard GS, Gelderblom WCA, Thiel PG, Marasas WFO. Fumonisins: their implications for human and animal health. In: Occurrence and Significance of Mycotoxins (Scudamore KA, ed). Slough, UK:Central Sci Lab 1993;42–48.
47. Pascale M, Ozzo MB, Visconi A. Determination of fumonisins in poultry by high performance liquid chromatography. In: Atti 2 Congresso Nazionale di Chimica degli Alimenti. Messina, Italy: La Grafica Editore, 1995;1047–1071.
48. Gelderblom WCA, Vleggar R, Thiel PG, Coward ME. Fumonisins: isolation, chemical characterization and biological effects. Mycopathologia 117:11–16 (1992).
49. Gelderblom WCA, Snyman SD, Abel S, Lebbe-Mazu S, Smuts CM, van der Westhuizen L, Marasas WFO, Victor TC, Knausmüller S, Huber W. Hepatotoxicity and carcinogenicity of the fumonisins in rats. A review regarding mechanistic implications for establishing risk in humans. In: Fumonisins in Food (Jackson LS, De Vries JW, Bulterman LB, eds). New York:Plenum Press, 1996:279–296.
50. Norred WP, Bacon CW, Porter JK, Voss KA. Inhibition of protein synthesis in rat primary hepatocytes by extracts of Fusarium moniliforme strain MRC 826 culture material. Mycopathologia 112:81–82 (1990).
51. Marasas WFO. Risk assessment of fumonisins produced by Fusarium moniliforme in corn. Cereal Res Commun 25:399–408 (1997).
52. Shephard GS, van der Westhuizen L. Liquid chromatographic determination of the sphinganine/sphingosine ratio in serum. J Chromatogr B 710:219–222 (1998).
53. Casteignaro M, Garren L, Galdeti D, Gelderblom WCA, Chelule P, Dutton MF, Wild CP. Analytical method for the determination of sphinganine and sphingosine in serum as a potential biomarker for fumonisin exposure. J Chromatogr B 720:15–24 (1998).
54. Casteignaro M, Garren L, Galdeti D, Gelderblom WCA, Chelule P, Dutton MF, Wild CP. Determination of the sphinganine/sphingosine ratio in serum. J Chromatogr B 720:15–24 (1998).
55. Voss KA, Norred WP, Plattner RD, Bacon CW, Norred WP. Comparative studies of hepatotoxicity and fumonisins B1 and B2 content of water and chloroform/methanol extracts of Fusarium moniliforme strain MRC 826 culture material. Mycopathologia 112:81–82 (1990).
56. Jaskiewicz K, Marasas WFO, Rassouw JF, van Nierkerk FE, Heine ERF. Selenium and other mineral elements in populations at risk for esophageal cancer. Cancer 62:2835–2839 (1988).
57. Chu FS, Li GY. Simultaneous occurrence of fumonisin B1 and other mycotoxins in moldy corn collected from People’s Republic of China in regions with high incidences of esophageal cancer. Appl Environ Microbiol 60:847–852 (1994).
58. Sydenham EW, Shephard GS, Gelderblom WCA, Thiel PG, Marasas WFO. Fumonisins: their implications for human and animal health. In: Occurrence and Significance of Mycotoxins (Scudamore KA, ed). Slough, UK:Central Sci Lab 1993;42–48.
59. Pascale M, Ozzo MB, Visconi A. Determination of fumonisins in poultry by high performance liquid chromatography. In: Atti 2 Congresso Nazionale di Chimica degli Alimenti. Messina, Italy: La Grafica Editore, 1995;1047–1071.
60. Gelderblom WCA, Shephard GS, Gelderblom WCA, Thiel PG, Marasas WFO. Fumonisins: their implications for human and animal health. In: Occurrence and Significance of Mycotoxins (Scudamore KA, ed). Slough, UK:Central Sci Lab 1993;42–48.