Mycotoxins that Affect the Human Cardiovascular System

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Abstract

Mycotoxins are toxic secondary metabolites produced by fungi in the field or during storage; these fungi are mainly saprophytic molds growing on foodstuffs or animal feeds. These molds produce chemical compounds of low molecular weight that are not detected by antigens and hence are insidious poisons with no obvious symptoms. Since 1960, mycotoxins have been considered responsible for diseases and death in domestic animals and humans. Mycotoxicoses, the diseases caused by mycotoxins, have been responsible for major epidemics in humans and domestic animals since agriculture was developed. Each of these diseases is caused by specific molds that produce one or more potent toxins, usually in one specific type of commodity or feed. Among the main mycotoxicogenic fungi are the genera Aspergillus spp., Penicillium spp. and Fusarium spp.

The symptoms caused by mycotoxins can be acute or chronic, depending on the type of toxin and the dose. The symptoms of acute mycotoxicoses include liver and kidney damage, attacks on the central nervous system, skin disorders, hormonal effects, miscarriage, hemorrhage, vomiting, diarrhea and many others. Mycotoxins are eaten in trace quantities in the daily diet; some, such as aflatoxins, can accumulate, whereas others are quickly eliminated. Examples of chronic mycotoxicoses include Reye syndrome, Kwashiorkor, and cancers that develop in experimental animals or humans long after the mycotoxin is eaten. In the present review, we will describe some mycotoxins that cause circulatory problems, vein breakage, hemorrhage, and heart failure.

Keywords: Mycotoxins; Aflatoxins; Citreoviridin; Moniliformin; T-2 toxin; Cardiovascular system

Aflatoxins

Chemical name: 2,3,6αR,9aS-tetrahydro-4-methoxy-1H,11H-cyclopenta[c]furo[3′,2′:4,5]furo[2,3-h][1]benzopyran-1,11-dione (Figure 1).

The fungal asexual phase and producer of aflatoxins is Aspergillus, a green-yellowish mold of the species A. flavus Link ex Fries, A. parasiticus Speare [1], A. bombycis [2], A. ochraceoroseus [3-5], A. nomius Kurtzman Horn and Hesselt and A. pseudotamarii [6].

The structures, physicochemical properties [7], biosynthesis [8], production conditions and occurrence of aflatoxins are also well known [9,10]. One important property of aflatoxins is that they form links to DNA, RNA and proteins [11,12], and they accumulate over time as adducts of AFB1-formamidopyrimidine (AFB1-FAPY) [13] and AFB1-lysine albumin [14], which are active carcinogens.

Aflatoxins, the most powerful mycotoxins, were discovered in the early 1960s with the outbreak of turkey “X” disease in England and high incidences of liver disease in ducklings in Kenya and hatchery-reared trout in the United States; the causes of all these problems were aflatoxins [15]. Aflatoxins are present in numerous foods, such as cereals, spices [16], oilseeds [17], and dry fruits. After these foods are consumed, the aflatoxins pass into milk, [18,19], all dairy products, eggs [20] and meat [21] derivatives. Aflatoxins are considered unavoidable toxins [22], Biological control measures include lactic acid bacterial fermentation, which is known to render cereal-based foods and beverages safe [23], and the use of aluminosilicates, glucomannans and optimal storage conditions to prevent fungal growth.

Aflatoxin intake is related to kwashiorkor [24] and Reye syndrome [25], and aflatoxins induce liver damage in undernourished individuals [26]. Aflatoxins are classified as Group I carcinogens in humans [27]; they are potent mutagens and teratogens, and they cause abortions, immunosuppression and cardiovascular symptoms. These toxins weaken veins and arterial walls, break platelets and cause internal hemorrhaging [28]. Aflatoxin B1 (AFB1) may interfere with the normal process of protein synthesis and may inhibit several metabolic systems, thus causing damage to various organs, especially the liver, kidney and heart [29,30].

The histopathological features of various abnormalities induced by different doses of ochratoxin A, AFB1, and their combination in rat fetuses have been studied [31]. Histological examination of fetal organs after AFB1 treatment revealed that the liver, brain, kidney, and heart were affected. The incidence of heart lesions, especially valvular defects, was higher in rats treated with the combination diets. There was an
antagonist effect of ochratoxin A with the AFB1, which was responsible for the teratogenic effect [31].

In the case of poultry, serious pathological changes were noted in the heart when crude toxin preparations from Aspergillus flavus mixed with normal foodstuff were given to animals [32]. Some clinical effects of aflatoxins on the cardiovascular system are frequent hemorrhage in different organs in animals such as chickens [33,34], horses [35], dogs [36] and humans [37]. The effects of chronic oral exposure (28 days) to AFB1 and fumonisins B1 (FB1) were studied in weaned piglets. The heart/body weight ratio of the piglets was significantly greater in groups fed with 30 mg of AFB1/kg of feed with or without 50 mg of AFB1/kg added to the feed. The heart effect was more strongly associated with fumonisins than with aflatoxins [38].

Aflatoxin poisoning occurred in Uganda in 1967, in a 15-year-old boy who was diagnosed as suffering from heart failure; he died 2 days after hospital admission. An autopsy revealed pulmonary edema, flabby heart, and interstitial edema of the heart, along with other symptoms, such as liver necrosis [39]. Aflatoxins have been detected in the heart muscle [40].

Cereals (e.g., maize, rice, and sorghum), nuts (e.g., walnut, pecan, pistachio, and cashew) and spices (e.g., black and green peppers and chili) cannot avoid Aspergillus fungal attacks; therefore, all of these foods are heavily contaminated with aflatoxins, and their consumption facilitates the development of human cancer. Physicians recommend maize, cereals and nuts in the diet, which have heavy loads of carcinogens, mutagens, and teratogens and inhibit immunological defenses. AFs are analyzed at the ng/g level, but the amount that a person consumes in cooked foods and desserts exceeds tolerance limits and, depending on frequency, can be considered a risk factor for chronic health effects.

However, maize and nuts have developed substances to inhibit the mutagenicity of the fungus and protect themselves. In this way, cereals and oilseeds have contradictory properties; maize has oleic acid to protect against aflatoxin mutagenicity, and nuts are considered a part of a “healthy” diet that provides oils, proteins, minerals, flavonoids, tannins, phenolic acids, polyphenols, and antioxidants, which protect against fat nodules (atheroma plaques) in the arteries, are anti-inflammatory and anti-mutagenic [41] and contain unsaturated fatty acids and vitamins [42], which protect against diabetes [43].

Additionally, pecans contain compounds that have protective effects on the heart [44] and are a source of monounsaturated fatty acids and heart-protective compounds, including vegetable sterols, vitamins A, B and E, folic acid, calcium, magnesium, phosphorus, zinc and fiber [44]. Pecans are a cholesterol-free food with a high protein content, and its oleic acid is similar to that of olives [45].

Cashews contain cardiol, which has antimicrobial activities [46]. They contain more ascorbic acid than oranges, vitamins B1 and B2, pantothenic acid, and minerals, such as magnesium [47], and they are rich in unsaturated fatty acids, such as oleic and linoleic acids. The cashew has raw protein and lysine levels comparable to those of peanuts [48] and soybean, and it has higher amounts of sulfur amino acids and oils and gums with cardol, which is a caustic and poisonous substance that evaporates when the nuts are heated [49]. The cashew contains a group of phenolic compounds known as “cashew nut shell liquid” (CNSL) [50-52], which includes anacardic acid, cardanol and cardol, the last of which has been reported to have antimicrobial activities [46], possibly conferring resistance to Aspergillus invasion. Thus, a dialectic situation is established: the food that cures you has toxins that can also kill you, and life and death are united in a single nut or maize cob.

Aflatoxins have an effect on the cardiovascular system, with hemorrhage being the most frequent symptom, although their main symptoms are as liver carcinogens.

**Citreoviridin**

Chemical name: 2,5-anhydro-1,6-dideoxy-2-C-[[8-(4-methoxy-5-methyl-2-oxo-2H-pyran-6-yl)-2-methyl-1E,3E,5E,7E-octatetraen-1-yl]-4-C-methyl-D-iditol (Figure 2).

The history of mycotoxic research in Japan began in 1891, when Sakaki demonstrated that moldy, unpollished rice was fatal to experimental animals, with symptoms indicating paralysis of the central nervous system (Shoshin-kakke) [53,54]. In 1920, Miyake and Takada first reported that Penicillium commune, known as a causal agent of “Mossy diseased rice”, was toxic when fed to rabbits and rats [53]. Miyake and collaborators discovered the first sample of yellow rice grains from Taiwanese and domestic rice containing Penicillium citreorignum (=P. toxicarium), which produced citreoviridin [53,55]. Among isolates from imported rice, Tsunoda et al. found Penicillium islandicum, which that produced brownish, discolor rice containing two hepatotoxic metabolites: luteoskyrin and cyclochlorotine [53,56]. Toxic disturbances associated with the consumption of rice contaminated with Penicillium species occurred and became known as “Yellow rice syndrome” [56,57]. Although no human cases of poisoning have been recorded, mycotoxicologists recommended that the Japanese government take action to protect citizens against “yellow rice poisoning” caused by a metabolite of Penicillium citreorivride called citreoviridin. This disease, which is manifested in humans and experimental animals by respiratory and circulatory failure, paralysis, convulsions and death, is identical to beriberi, originally considered to be a thiamin nutritional deficiency [53,58].

Citreoviridin plays a major role in causing myocardial injury (degeneration and necrosis) in adult Wistar rats exposed to it, and citreoviridin combined with deficiencies in selenium and protein can aggravate the damage at the biochemical level [59]. Cardiac toxicity of citreoviridin in selenium-protein with citreoviridin group caused the intercalary discs of cardiac myocytes to become fragmented; the conjunctions between myocytes were broken; in some regions, cardiac myocytes became edematous and even dissolved; the structure of sarcomeres was not obvious; mitochondrial cristae were loosened; cavities in myocytes were occasionally observed; and there was substantial disseminated sarcoplasmic reticulum extension. In selenium-protein with no citreoviridin group, the change in cardiac myocytes’ membrane structures was not obvious; the filament structure disappeared around the nucleus, and the deposition of mass floccule was observed. The authors concluded that citreoviridin is the main risk factor for inducing myocardial damage [60].

![Figure 2: Structure of citreoviridin, a mycotoxin produced by Penicillium citreo-viride [52].](image-url)
Acute cardiac beriberi

Acute cardiac beriberi is caused by citreoviridin, a mycotoxin produced by Penicillium citreonigrum. Acute cardiac beriberi was a common disease in Japan, especially in the second half of the last century. This disease is characterized by difficulty breathing, nausea and vomiting, and, after 2 to 3 days, severe pain and distress. Progressive paralysis may lead to respiratory failure and death. There was also an outbreak of beriberi deaths reported in 2006 in the Maranhao State of Brazil, which was caused by citreoviridin from Penicillium citreonigrum strains and was associated with rice consumption [61].

Beriberi is the general name for vitamin deficiencies resulting from the consumption of polished rice. Acute cardiac beriberi may be a toxicosis rather than a vitamin deficiency [62]. In 1910, the incidence of acute cardiac beriberi suddenly decreased in Japan when government inspection led to a reduction in the sale of moldy rice. The incidence of true beriberi, resulting from the consumption of polished rice, was unaffected. The victims of acute cardiac beriberi were often young, healthy adults. This mycotoxicosis is characterized by precordial distress with palpitation and tachycardia, as the dyspnea worsens, nausea and vomiting are experienced. After a few days, the victim suffers severe angina, pain, and restlessness and can become violently maniacal at times. The right heart is dilated, and the heart sounds are abnormal. In the final stages, as the dyspnea increases, the extremities become cold and cyanotic, the pupils dilate, and the person loses consciousness. The neurotoxic mycotoxins of Penicillium citreoviride Biourge may also cause acute cardiac beriberi [62].

Keshan disease

Keshan disease is also caused by citreoviridin toxin [63]. An individual with Keshan disease will have an abnormally large heart. Keshan disease can also lead to higher rates of cancer, cardiovascular disease, hypertension, and stroke. In addition, an individual can experience eczema, psoriasis, arthritis, cataracts, alcoholism, and infections. There has been controversy because some authors initially thought that Keshan disease was caused by coxsackievirus B3 viral infection [64,65]. Currently, many other authors attribute Keshan disease to the mycotoxin citreoviridin [60,63,66,67]. Tsunoda et al. found that P. citrinum was responsible for yellowish rice, which was associated with the high nephrotoxic toxicity produced by citrinin [53,56].

Moldy millet or maize, but not wheat, eaten for 4-12 months produced an outbreak of Keshan disease. Rats fed with 4 mg/kg (body weight) of citreoviridin-contaminated grain every day for 4-6 weeks exhibited necrosis of myocardium and cell mitochondrial swelling, proliferation and damage, identical to what was observed in cases of death from Keshan disease.

A number of genes in peripheral blood mononuclear lymphocytes of patients with Keshan disease are significantly differently expressed from those of healthy people [67]. These genes are mainly involved in cell proliferation, apoptosis and cell function restoration, and they may play an important role in the development of Keshan disease. Keshan disease must not be confused with Kashin-Beck disease, which is a permanent and disabling osteoarticular disease involving growth and joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter (humic acids and fulvic acids) in drinking water, and fungi on self-deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter joint cartilage with multifactorial etiology associated with selenium deficiency. "The gene expression profiles of Kashin-Beck and Keshan diseases occurring within the same endemic areas of China were compared [66]. Total RNA was isolated from peripheral blood mononuclear cells from 36 patients and 28 controls, and gene expression profiles were analyzed using oligonucleotide microarrays. Sixteen genes that were differentially expressed in both Kashin-Beck and Keshan disease (versus controls) were identified, including nine genes with synchronous expression and seven with asynchronous expression. The comparative toxicogenomics database shows that the expression and biological function of these genes can be affected by multiple environmental factors, including mycotoxin and selenium content, which are potential environmental risk factors for the two diseases. Thus, these shared differentially expressed genes may contribute to the distinct organ lesions caused by the common environmental risk factors for Kashin-Beck and Keshan diseases [66].

Onyalai

Onyalai is an acute disease of the circulatory system characterized by hemorrhaging lesions in the mouth. Onyalai has been endemic in Africa, especially in Southern Sahara regions, for at least 80 years [68]. This disease is much more common in rural than in urban populations. Many of the people affected by onyalai subsist on millet; therefore, Rabie et al. (1975) [68] suggested a possible role of a mycotoxin in this cereal. Toxicogenic isolates of Phoma sorghina were found to be common in millet consumed by affected populations, and Rabie et al. (1975) [68] reproduced many of the symptoms of onyalai in rats fed maize and wheat on which P. sorghina had been grown.

Moniliformin

Chemical name: Sodium 3,4-dioxo-1-cyclobutenolate. The condensed formula of moniliformin is K or Na C4H03 (Figure 3).

Moniliformin or semiquaric acid is a mycotoxin formed by 3-hydroxy-3-cyclobuten-1,2-dione acid. This toxin was discovered in 1973 in maize in the USA [69], and the fungus was incorrectly identified as Fusarium moniliforme Sheldon emend. Snyder and Hans., leading to its being named moniliformin. The following Fusarium spp. produce moniliformin [70,71):

I. Section Liseola: F. anthophilum (A. Braun) Wollenw., F. dlaminii, F. napiforme, F. nymatil, F. proliferatum (Matsushima) Nirenberg [72], F. subglutinans (Wollenw. and Reinking) Nelson, Toussoun and Marasas. [73-75].

II. Section Arthrosporiella: F. concolor, F. semitectum Berk. and Rav (Syn F. roseum).

Figure 3: Moniliformin in the form of sodium (a) or potassium salt (b), which is how it is found in nature because the free acid is very unstable [69].
III. Section Discolor: F. culmorum (W.G. Smith) Sacc. [76], F. sambucinum Fuckel (Syn F. roseum) and F. graminearum Schwabe;

IV. Section Elegans: F. beamiforme, F. oxysporum Schlecht emend. Synd. and Hans. (Syn F. redolens);

V. Section Gibbosum: F. acuminatum Ell. and Ev. (Syn F. equiseti);

VI. Section Martiella and Venticricosum: F. solani (Mart.) Appell and Wollenw. emend. Synd. and Hans.

VII Section Roseum: F. arthrosporioides Sherb. (sometimes identified as a clone of F. avenaceum), F. avenaceum (Fr.) Sacc. [77].

VIII. Section Sporotrichiella: F. chlamydosporum Wollenw. and Reinking (Syn. F. fusarioides (Frag. and Cif.) Booth. Syn F. sporotrichioides [76], F. tricinctum).

Springer et al. (1974) [78] first characterized the structure of moniliformin as a small cyclic molecule with a molecular weight of 136.11 g/mol, which is found in nature as a water-soluble sodium or potassium salt (Figure 3) because the free acid has a very low pKa (<1.7). The physicochemical properties of moniliformin have been described [79-81]. Moniliformin is a free acid decomposes when it is heated to 150-153 °C without melting, and the maximum absorbance with UV light is 229 nm to 260 nm in methanol.

The fungi that produce moniliformin also produce other mycotoxins, such as fumonisins, beauvericin, fusaproliferin, fusarins, trichothecene, and zearalenone [82-89] [82], which are generally found in mixtures with moniliformin [83-88].

Moniliformin is produced by at least 30 Fusarium species isolated from different substrates and geographical areas [70,71,77]. F. proliferatum and F. subglutinans parasitize maize, and F. avenaceum parasitizes wheat [89]. There is great variability in the moniliformin content of Fusarium spp. in both the percentage of producer lines and the amount produced. Moniliformin was isolated and chemically synthesized by Fusarium spp. in both the percentage of producer lines and the amount produced. Moniliformin was isolated and chemically characterized from F. nygamai Burgess and Trimbori NRRl-6022 (ATCC-12763), a millet isolate from Nigeria strain 4364, which produces large amounts of this toxin [80]. Other producer strains were isolated from cotton from North Carolina, USA. F. proliferatum in rice incubated at 25°C for 21 days is produced at up to 16,000 ppm; these amounts in maize cause rejection syndrome in cattle [90]. Moniliformin occurs naturally in different cereals (maize, rice, wheat, oat and barley). Its incidence varies from 1/1 to 57/57 and 47/104, its concentration ranges from 0.02 to 530 ng/g, and it has been reported in countries such as South Africa, Tanzania, Canada, USA, China, Austria, The Netherlands, United Kingdom, Italy and Poland [71,86,89,91].

Moniliformin in large amounts acts at the level of sugar metabolism; it inhibits the oxidative decarboxylation of pyruvate, increasing its level in serum, causing a decrease in oxalate and an increase in the Krebs cycle, and is cytotoxic at high concentrations in mammalian cells. This toxin causes intoxication, and the lesions include intestinal hemorrhage, muscle weakness, breathing difficulty, cyanosis, coma and death [73]. However, in studies in barnyard fowls and rodents using subacute and chronic dosages, its effect was on the heart.

The high metabolic rate of heart tissue makes it a target organ for the toxic effects of the energetic inhibition of metabolism. Moniliformin inhibits the basal mechanism of enzymes (thiamine, pyruvate dehydrogenase, ketoglutarate dehydrogenase, pyruvate decarboxylase and acetylcoenzyme acid synthetase). Because these enzymes share a cofactor, it is possible that the action of moniliformin is based on its attack on thiamine. Reductions in glutathione peroxidase and reductase are due to the reduced activity of these antioxidants, which might be the cause of the myocardial damage observed in animals treated with this mycotoxin. Another suggested mechanism is the alteration of the electrolyte composition of cardiac myocytes, causing bradycardia and heart failure [91].

The use of a moniliformin-producing isolate of Fusarium moniliforme in corn as the base diet of chicks, ducklings and turkey pouls was found to be lethal, with the ducklings being the most sensitive to the toxic feed. The gross lesions were ascites, hydropericardium, myocardial pallor, kidney failure [92,93], high levels of pyruvate in the serum, immunodeficiency [94], cardiomyopathy, heart lesions, ventricular arrhythmia, heart fibrosis, hemorrhage in the brains of treated birds, stunting, alterations in the electrical conductivity of the heart muscle and death. The microscopic lesions showed degeneration and necrosis of the myocardium and degeneration of hepatocytes. Cardiotoxicity was the apparent cause of death [75,92]. Thiamine supplementation can overcome the cardiotoxic effects of F. proliferation [95,96]. In human food, 12 of 14 maize tortillas had moniliformin concentrations ranging from 0.022 to 0.1 ng/g [75], although human exposure has not been studied.

**Fumonisins**

Formal name: 1,2,3-propanetricarboxylic acid, 1,1'-[1-(12-amino-4,9,11-trihydroxy-2-methyltridecyl)-2-(1-methylpentyl)-1,2-ethanediy] ester (Figure 4).

Fumonisins are a group of mycotoxins found in corn contaminated with Fusarium fungi, mainly F. verticillioides (= F. moniliforme), the source of the name of these toxins. Fumonisins are chains of approximately 20 carbons with acidic ester, acetylamine and sometimes other radicals. The most important fumonisins are B1 and B2. At least 15 different fumonisins have been reported, and other minor metabolites have been identified, although most of them have not been shown to occur naturally [96].

Fumonisins inhibit the ceramide synthetase-catalyzed conversion of sphingolipids to ceramides, and they cause leukoencephalomalacia in equines and porcine pulmonary edema and liver cancer in rats. The hepato- and cardiotoxicity of Fusarium verticillioides (F. moniliforme) isolates from Southern African maize that produced only fumonisins and their toxicity to ducklings and rats were determined. Cirrhosis and nodular hyperplasia of the liver, as well as the occurrence of acute and proliferative endocardial lesions and concurrent intraventricular thrombosis were frequently encountered and were considered to be the most important lesions; thrombosis of the larger vessels of the heart occurred less often [97]. The individual and combined effects of the Fusarium mycotoxins Fumonisin B1 (FB1) and moniliformin were studied in broiler chicks. The interactive effects of moniliformin and fumonisins were not synergistic; moniliformin was much more toxic to broilers than FB1 [98].

**Figure 4: Structure of Fumonisin B1 [96].**
The teratogenic, embryopathic and embryocidal effects of purified fumonisin B1 and moniliformin on chicken embryos were studied. Early embryonic changes in the exposed embryos included hydrocephalus, enlarged beaks and elongated necks. Pathologic changes were noted in the liver, kidneys, heart, lungs, musculoskeletal system, intestines, testes and brains of the toxin-exposed embryos [99].

T-2 Formal name: \((3\alpha,4\beta,8\alpha)-12,13\text{-epoxy}-4,15\text{-diacetate} 8-(3\text{-methylbutanoate})\) trichothec-9-ene-3,4,8,15-tetrol (Figure 5) T-2 (synonyms are Fusarioxin T-2, Insaritoxin and Mycotoxin T-2) is a trichothecene mycotoxin. T-2 is a naturally occurring mold that is a byproduct of Fusarium spp. fungi and is toxic to humans and animals. The clinical condition caused by T-2 is alimentary toxic aleukia (ATA) [100], with symptoms in diverse organs such as the skin and airway, and stomach ingestion, which may come from the consumption of moldy whole grains. T-2 can also be absorbed through human skin [101]. Skin contact with T-2 causes acute disturbances in the circulatory system (hypotension and arrhythmia), which may result from general pathophysiological responses to the T-2 toxin, including a central effect on blood pressure and catecholamine elevation, which have been reported in pigs and rats [102,103]. General arteriosclerosis and hypertension have been reported as delayed sequelae of repeated exposure to T-2 toxin [104]. In a series of studies of rats exposed to a limited course of T-2 toxin, doses caused the thickening of coronary arteries, including myocardial changes. Four injections of 3 mg of T-2 toxin/kg bw on alternate days led to vacuolization and swelling of endothelial cells, basement membrane changes and enlarged medial smooth muscles. After the topical application of T-2 toxin (1-20 \(\mu g\)) to rat skin, dilated microvessels packed with erythrocytes and an increased number of degranulated mast cells were observed [105-107]. In experimental animals, cardiovascular responses to T-2 toxin administration included tachyarrhythmia, hypotension, and shock [104,108].

T-2 mycotoxin has been used as biological weapon: flour contaminated with Fusarium was produced and distributed in bread, causing significant morbidity and mortality [101]. T-2 was also used in Vietnam and was known as "yellow rain" [109].

Conclusions
Among the most important mycotoxins that cause cardiovascular problems, aflatoxins have the risk of forming adducts and being stored for years in the DNA of all cells, causing hemorrhage and heart malformations. Among the typical cardioactive mycotoxins, the two potent toxins that cause the worst damage are citreoviridin and moniliformin. Considering the worldwide occurrence of moniliformin together with its high acute toxicity, research into the subchronic toxicity is of vital importance to identify the possible risk in human or animal health. Fumonisins are very frequent and related to malformations as has been reported here. It is impossible to produce food completely free of mycotoxins, improvements in storage and handling of grains, can minimize mold growth, and so reduce the risk of mycotoxin contamination in food supplies.

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References


68. Rabie CJ, Van Rensburg SJ, Van Der Watt JJ, Lübben A (1975) Oenalya—
1326.
important moniliformin-producing strains of Fusarium, NRRLE5022 and
Revista Mexicana de Micología 19: 103-112.
Mycotoxin production by Fusarium proliferatum isolates from rice with Fusarium
sheath rot disease. Mycopathologia 147: 97-104.
73. Kriek NP, Marasas WF, Steyn PS, van Rensburg SJ, Steyn M (1977) Toxicity
of a moniliformin-producing strain of Fusarium moniliforme var. subglutinans
moniliformin moniliformin in maize (Zea mays L.) ears infected by Fusarium
subglutinans (Wollenw. and Reinking) Nelson et al. Food Addit Contam 13:
321-324.
75. Sewram V, Nieuwoudt TW, Marasas WFO, Shephard GS, Ritieni A, Aastveit AH,
subglutinans (Wollenw. and Reinking) Nelson et al. Food Addit Contam 13:
321-324.
of moniliformin by Fusarium sporotrichioides and Fusarium culmorum. Appl
Environ Microbiol 53: 196-197.
moniliformin in cultures of Fusarium subglutinans and in naturally contaminated
maize by high performance liquid chromatography-atmospheric pressure chemical
moniliformin by Fusarium sporotrichioides and Fusarium culmorum. Appl
Environ Microbiol 53: 196-197.
pp: 139-188.
Human skin penetration of selected model mycotoxins. Toxicology 301: 21-32.
83. WHO (1990) Selected mycotoxins: Ochratoxins, Trichothecenes, Ergot
cardiovascular lesions found in rats given T-2 toxin, a trichothecene secondary
85. Yaron R, Yagen B (1986) T-2 toxin effect on the ultrastructure of myocardial
effect on rat aorta: cellular changes in vivo and growth of smooth muscle cells in
Cardiorespiratory, sympathetic and biochemical responses to T-2 toxin in the
Review/Spring 25-42.