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«TRAINING ACTIVITIES ON FOOD CONTAMINATION CONTROL AND MONITORING WITH SPECIAL REFERENCE TO MYCOTOXINS»

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MYCOTOXICOSIS CAUSED BY TRICHOTHECENES

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Mycotoxicosis Caused by Trichothecenes

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Introduction

Trichothecenes are a group of chemically related sesquiterpenoids produced by fungi such as Fusarium, Trichothecium, Trichoderma, Myrothecium, Stachybotrys and others.Recently, several trichothecene compounds were isolated from a higher plant. In the present time, more than 60 kinds of the trichothecenes are identified from the metabolites of fungi and plant or from the transformed products of these trichothecenes, as reviewed in literatures (Ueno, 1977a, 1977b, 1980, 1983).

Chemically speaking, these trichothecenes are breafly subdivided into four categories: type A; T-2 toxin, HT-2 toxin,diacetoxyscirpenol and others, which are predominantly produced by by Fusarium sporotrichioides and others: type B; nivalenol and deoxynivalenon (=vomitoxin) from F.graminearum; type C; crotocin from Cephalosporium crotocigenum: type D; satratoxins, verrucarins, roridins and others from Stachybotrys, Myrothecium and others. Baccharinoids belong to this D type.

Toxicologically, all the trichothecenes are highly toxic to animals and human, inducing dermal toxicity, hemorrhage in intestine and muscle, diarrhea, vomiting, cellular destruction

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in thymus, spleen, ovary, testis and epithelial membrane of intestine. The major toxic mechanism of trichothecenes is the inhibition of protein in eukaryotes by binding to ribosomal granules. In animals and human, severe intoxication developed after consumption of trichothecene-polluted feed and food. Alimentary toxic aleukia (ATA), stachybotryotoxicosis, dendrochiotoxicosis, akakabi (red-mold) toxicosis and others are caused by these trichothecenes. Recently, several approaches revealed that some trichothecenes such as deoxynivalenol, nivalenol, T-2 toxin and others are found to be contaminated in cereal grains and feedstuffs, and the contamination with trichothecenes is one of great concern of health authorities.

In the present paper, the detail of trichothecene problems were summarized from the standponts of chemistry, toxicoses, mycology, and natural occurrence of the trichothecenes.

/I/ Chemistry of trichothecenes

Trichothecenes possess the tetracyclic 12, 13-epoxytrichothecene skeleton belonging to sesquiterpenoids. More than sixty naturally occurring derivatives have been isolated from fungal cultures and plants, and can be conviniently divided into four categories according to similarity of functional groups (Ueno, 1977a).

The first is characterized by a functional group other than a ketone at C-8 (type B). Nivalenol and deoxynivalenol belong to this group. The third is characterized by a second epoxide function at C-7, 8 (type C). The last category includes those con-

taining a macrocyclic ring between C-4 and C-15 with two ester-linkages (type D). Satratoxins and verrucarins are representati-
/Fig. 1/ ve of the last group, as summarized in Fig. 1.

The naturally occurring trichothecenes are colorless, mostly crystalline, optically active solids which are generally soluble in chloroform, ethyl acetate, acetone and alcohol. But, their solubility to these solvents are greatly different depending on the chemical features. For example, highly hydroxylated trichothecenes such as T-2 tetraol, deoxynivalenol and nivalenol are sparingly soluble in chloroform, and are much soluble in alcohol and water.

All of the trichothecenes possessing an ester group are hydroxylated to their corresponding parent alcohol upon treatment with base. For example, T-2 toxin changes to T-2 tetraol via HT-2 toxin and T-2 triol. Fusarenon-X (4-acetyl-nivalenol) yields nivalenol.

The 12, 13-epoxy ring is extremely stable to nucleophilic attack. Heating under acid condition causes an intermolecular rearrengement of the trichothecene skeleton to the apotrichothecene ring system.

The absence of conjugated unsaturated structure in most of the trichothecene mycotoxins results in no absorption in the UV region with the exception of end absorption due to the unsaturation at C-9. However, the type D macrocyclic trichothecenes give characteristic UV spectra. The trichothecenes possess no fluorescence property.

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/II/ Trichothecene-producing fungi

T-2 toxin is one of important toxic trichothecenes belonging to the type (A). This mycotoxin first isolated from the culture of F. tricinctum (Bamburg et al., 1968). Subsequently, its chemical derivatives such HT-2 toxin, acetyl T-2 toxin and neosolaniolwere isolated from the culture of F. tricinctum and others. Taxonomy of Fusarium spp. were proposed by several researchers, and recently F.tricinctum is classified into F.sporotrichioides.

Deoxynivalenol and nivalenol are important mycotoxins belonging to the type (B). Nivalenol and its 4-acetyl derivatives were isolated from the cultures of F.nivale Fn 2B (Tatsuno et al, 1968; Ueno et al., 1971). Deoxynivalenol was isolated from Fusarium-infected barley (Morooka et al., 1972) and the cultures of F.roseum (Yoshizawa et al., 1973). Vesonder et al. (1973) also isolated this mycotoxin from molded corn with F.graminearum and reported it under the name of vomitoxin. F.culmorum is also reported to produce vomitoxin.

F.graminearum (imperfect stage of Gibberella zeae) is widely distributed in cereal grains and fields. By adopting single spore isolation technique, Ichinoe et al. (1983) examined the producibility of deoxynivalenol and nivalenol in G.zeae. The data revealed that all strains of G.zeae were chemotaxonomically subdivided into two types; one produces only deoxynivalenol and its 3-acetyl derivative (DON-type), and the other produces nivalenol and its 4-acetyl derivative (fusarenon-X)(NIV-type), and no cross production of these two type trichothecenes. This

chemotaxonomical approach to G.zeae or F.graminearum gives a key for natural contamination of cereal grains by nivalenol and deoxynivalenol.

As for F.nivale Fn 2B, several taxonomists recognized it as F.sporotrichioides, and other groups considered it as F.graminearum. Taxonomical position of F.nivale Fn 2B is remained to be solved.

Other non-macrocyclic trichothecenes have been isolated from the cultures of Trichothecium roseum (trichothecin, trichothecolone), and Cephalosporium croticingenum (crotocin, crotocol, type C). Trichoderma viride, T.hamatum, T.harzianum, Hypocrea pachybasioides, H. peltata, H. albofulva and H.shweinitzii are reported to produce trichodermin and trichodermol. Hypocrea is the perfect stage of some species of the genus Trichoderma.

Macrocyclic trichothecenes (type D) are produced by several genera of fungi such as Myrothecium, Cylindocarpon, Verticimonosporium, and Stachybotrys. On these fungi, the most important species implicating mycotoxicosis is Stachybotrys atra.The Stachybotrys is a kind of saprophytic fungi and frequently found in cellulose-rich materials such as hay, straw, cereal grains and others, and Eppley and Baily (1973) isolated toxic macrocyclic trichothecenes such as satratoxin C, D, F, G and H. Among these trichothecenes, satratoxin C and D had been previously identified as verrucarin J and roridin E, respectively, which were produced by Myrothecium verrucaria.

Beside these trichothecenes, Myrothecium verrucaria and M.roridum produce verrucarin A, B J, roridin A, D, E, and H. Verticimonosporium diffractum produces vertisporin, and Clindrocarpon sp. produces roridin H, isororidin E, epoxyisororidin E and H, and diepoxyroridin H (Minato et al., 1975; Matsumoto et al., 1977).

The unique occurrence of trichothecenes in a higher plant appears species specific since none of the other species of Baccaris plants has exhibited biological activity expected of macrocyclic trichothecenes. Brazilian shrub Baccharis megapotamica was found to contain ca, 0.02 % (dry weight) of a series of macrocyclic trichothecenes (called baccharinoides) closely related in structure to the roridins and verrucarins (Kupchan et al., 1977).

Bacchrinoides can be divided into two subclasses based on the substitution pattern of the A ring; the baccharins, which possess a 9, 10-epoxide ring and the baccharinols, which possess an 8 -hydroxy group. One possibility of unique occurrence of the macrocyclic trichothecenes in this plant is that the plant possesses a unique interaction with a soil fungus (e.g. a Myrothecium) that produces roridins, and these fungal trichothecenes are then taken up by the plant and altered to baccharinoides.

/III/ Trichothecene toxicoses

The direct evidences which prove the involvement of trichothecene mycotoxins in human and animal toxicoses are not clearly reported in the present time, and only some evidences

of implication by toxigenic fungi capable of producing the trichothecenes, or of isolation of the trichothecenes from the food and feedstuffs explain some of the symptoms of the toxicoses. In this respect, no analytical epidemiology was carried out for explanation of trichothecene toxicoses.

However, many approaches from mycology, chemistry, pathology, and so-called "epidemiology" are demonstrating that some of trichothecenes play an important role for development of human and animal toxicoses by consumption of food and feedstuffs molded with Fusarium and other trichothecene-producing fungi.

(1) Alimentary toxic leukia (ATA)

The disease, a serious problem in the 1940's in the rural region of the Soviet Union, seems to have now become a thing of the past, having almost disappered since the 1950's.

From 1942 to 1947, mostly in 1944, over 10% of the whole population of Orenburg near Siberia was totally affected by wintered millet, wheat, and barly. The poisoning was characterized by leukopenia, agranucocytosis, necrotic angina, hemorrhagic diathesis, sepsis, and exhaustion of the bone marrow, sometimes causing death (Mayer, 1953; Forgacs and Carll, 1962).

By adopting skin-bioassay technique, F. sporotrichioides, F. poae and other fungi were identified as the causative fungi of this intoxication (Sarkisov and Kvashnina, 1948), and sporofusarin, poaefusarin, epicladosporic acid and fagicladosporic acid were reported as the causative agents (Olifson, 1957a, 1957b).

However, from the similarity between the symptoms of ATA and toxicological features of the trichothecene mycotoxins, the author and our collaborators analyzed the toxic principles of F. sporotrichioides NRRL 3510 and F. poae NRRL 3287, which were originally isolated by Joffe and used for detection of the trichothecenes, with the results that these fungi were able to produce T-2 toxin and related trichothecene mycotoxins (Ueno et al., 1972). Toxicological approaches also demonstrated that these toxins induced dermal necrosis, hemorrhagic changes, vomiting, and exhaustion of bone marrow, in similar to the reported cases of ATA in man and farm animals. Another experiment made by Mirocha and Pathre (1973) also demonstrated the presence of T-2 toxin in the sample of poaefusarin obtained from V.I.Bilai.

But unfortunately no field experiment has been known to prove whether the fungus can produce T-2 toxin in the natural conditions as in Siberia, at concentration reasonably high enough to induce ATA in man, and whether the toxicity of T-2 toxin was enhanced by other toxic metabolites of Fusarium and other species of fungi.

A feeding experiment using adult Rhesus monkey revealed that male animals receiving T-2 toxin in dose of 1 mg/kg body weight/day died in 15 days with respiratory failure, petechial hemorrhages on the skin, leuko- and thrombo-cytopenia. With a smaller dose (0.1 mg/kg/day), leukocytopenia developed more slowly (Rukmini et al., 1980). The author's data also revealed

that cats intubated with T-2 toxin in dose of 0.05 mg/kg for 12 days caused a severe leukopenia (Sato et al., 1975). Extrapolating from these data, symptoms of ATA can develop in a few weeks in men ingesting several milligrams of T-2 toxin/day.

(2) Akakabi (red-mold) toxicoses

The damage caused by Fusarium spp.in wheat, barley, oarts, rye, rice, and others is called by akakabi-byo (red-mold disease, or scab disease) in Japan. Excessive rainfall during earing, flowering, maturing and harvest seasons was favorable for endemic development of this disease.

At an agricultural institute in Hokkaido, the northern island of Japan, 75 persons suffered from nausea, vomiting and diarrhea after 5-30 min of eating noodles. The wheat kernels from which the noodles were made contained about 10-20% of scabby grains. Similar food-borne intoxication developed frequently in Tokyo, Kanagawa, and sometimes in Korea, as summarized by Yoshizawa (1983).

Mycological surveys on these toxic grains revealed the presence of Gibberella zeae (F. graminearum), F. moniliforme, F. herbarium, F. avenaceum and others. From F. nivale Fn 2B isolated from damaged wheat samples, nivalenol, fusarenon-X, and diacetylnivalenol were isolated as the toxic principles of this strain, and from the metabolites of F.roseum (= F. graminearum) were isolated deoxynivalenol and its acetate.

Experimental toxicology revealed that these trichothecenes

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induced vomiting, dermal toxicity, diarrhea, hemorrhage and damages in hematopoitic tissues. Furthermore, chemical analysis indicated that nivalenol and deoxynivalenol are the major toxic trichothecenes in these cereal grains and products (Ueno, 1983).

(3) Moldy corn toxicosis in USA

Development of toxicosis in farm animals after ingestion of moldy corn is an irregularly occurring, long-standing problem of great importance in the United States and others. The problems occurred in Wisconsin and other Midwestern states in 1962, 1964, and 1965. These moldy corn samples induced diarrhea, reduced mild production, unthreiftness, lack of weight gain, and general feed refusal. In some cases, death with massive hemorrhage in stomack, heart, intestine, lungs, bladder, and kidneys was observed in farm animals. By employing skin bioassay method, toxic fungus F. tricincum B24 was isolated from moldy sweet corn and a highly toxic sesquiterpenoid was isolated (Gilgan et al., 1966). This compound, diacetoxyscirpenol, was identical with the metabolite of F. scirpi and F. equiseti. Since the toxigenicity of the strain B24 was lost, a more potent toxin-producer (T-2) of the same fungus was examined and a new metabolite, named T-2 toxin, was isolated as a crystalline material (Bamburg et al., 1968). HT-2 toxin (4-deacetoxy T-2 toxin) was also isolated from the T-2 strain when the same strain was cultured at lower temperature.

Toxicology with T-2 toxin and related trichothecenes indicated that LD_{50} (mg/kg, oral) to a-day-old broiler chicks,

was 3.22 (8-acetylneosolaniol), 3,8 (diacetoxyscirpenol), 4.97 (T-2 toxin), 7.22 (HT-2 toxin), 24 (neosolaniol), and 33 (T-2 tetraol). In guinea-pigs, the LD_{50} (mg/kg, oral) was 0.5 (8-acetylneosolaniol and HT-2 toxin), 1-2 (T-2 toxin and diacetoxyscirpenol), 4 (T-2 triol, T-2 tetraol, and neosolaniol). The substitution at the C-4 and C-8 positions gives a great effect on toxicity of the trichothecenes of type A.

In animals administered with 8-acetylneosolaniol, HT-2 toxin or T-2 tetraacetate, hemorrhage in uterus and gastric mucosa, but no such symptoms were observed with T-2 toxin and diacetoxyscirpenol (Mirocha, 1983).

In cattle, no hemorrhagic sings were observed in the animals treated with T-2 toxin and it is doutfull that T-2 toxin is responsible for the hemorrhagic syndrome noted in "moldy corn toxicosis". Weaver et al. (1980) indicated that: the cow refused a ration containing 50 ppm of T-2 toxin, T-2 toxin produced clinical signs in the cow and its calf characterized by extreme congestion, no hemorrhagic lesions, and no changes in blood chemistry and bone marrow. These data indicated that T-2 toxin is not involved in "moldy corn toxicosis". As described in later, the only hemorrhagic sign in calves was observed with stachybotryotoxicosis which was induced by the macrocyclic trichothecenes of Stachybotrys atra.

(4) Stachybotryotoxicosis

The first report of this disease came from the Ukranian

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scientist, K.I.Vertinskii (1940) in 1931. This toxicosis was extremely important in the Soviet Union and was designated by the term "massive illness (massovie zaboliavanie, MZ)", since it caused the death of thousands of horses.

The major clinical signs were divided into three stages; Stage I is characterized by irritation of the mouth, throat, nose and lips, swelling and soreness of the glands, and lasts from 8-12 days; Stage II is leukopenia and prolonged prothrombin time, and lasts 15-20 days; and Stage III is elevation of body temperature, necrotic ulcers on mucous surface of the mouth and throat, and it terminated with death (Forgacs and Carll, 1962).

According to the recent epizootological observation of Salikov and Dzhilavyan (1977), the outbreak of stachybotryotoxicosis took place in Russia during 1950-1960, and the feed contaminated with S. atra induced massive illnesses in cattle.

In Hungary, several investigators reported stachybotryotoxicosis in farm animals and human. In 1973-1975, outbreaks occurred in calves by feeding of straw and hay contaminated with S. atra (= S. alternans). Massive hemorrhages in muscles, subcutaneous connective tissues, serous and mucous membranes were observed. In some cases, necrotic lesions with degenerative changes of the adjointing tissue were reported. Field observations suggested that swine also show susceptibility to stachybotryotoxins when contaminated straw is used for bedding. Handling of contaminated litter and fodder may also be responsible for human disease. Inhalation or direct contact of the

skin or mucous membranes gives rise to rhinits and conjestion (Szathmary, 1983).

As for the toxic components of S. atra, several macrocyclic trichothecenes, named as satratoxin F, G, H, and verrucarin J, and roridin E, were isolated from the cultures (Jarvis et al., 1983). All these toxins are highly cytotoxic and induce dermal necrosis. But no detailed toxicological data were reported.

(5) Dendrochiotoxicosis

Originally, dendrochiotoxicosis was described in 1937 in the southern district of Russia as a disease of horses. It was characterized by quick death, mostly within 12-24 hr, cyanosis around the mucous membranes of mouth and nose, hemorrhage, accerelation of pulse, tachycardia, retardation of semimentation of the erythrocytes, and rise in hemoglobin, erythrocytes, and leukocytes. These findings indicated the impairment of cardiovascular systems of horses (Bilai and Pidoplisko,1970). Dendrodochium toxicum Pidopt et Bil was suspected to be the ceusal fungus of this disease, and four toxins, DI to DIV, were fractionated from the mycelia but their chemical structures were not clarified. Since D. toxicum is presumed to be synonymous with Myrothecium roridum which produces roridins and verrucarins, and this evidence indicated that this toxicosis was induced by uptake of these macrocyclic trichothecenes.

(7) Vomi'ing and feed refusal problems

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Fusaria representative of the Gibbosum and Fusarium sections

are common colonists in cereal grains in the U.S. corn belt. Grains infected with members of these sections, especially F. graminearum, often caused vomiting and refusal of feed in swine and other farm animals. A very severe G.zeae (perfect stage of F. graminearum) outbreak occured in 1972 in the U.S. corn belt extending from Pennsylvania to Kansas. Sporadic outbreaks have occurred in Indianna in 1958 and 1965 and in northwest Ohio in 1970, 1975, and 1977. Excessive rainfall and mean temperature below 70°F during silking were important for this type of infection.

Field corn from northwest Ohio in 1972, infected premodinantly with F. graminearum which caused vomiting and refusal to eat in swine,.was shown to contain 40 g of vomitoxin per gram (Vesonder et al., 1976). Toxicological as well as chemical approaches strongly revealed that the vomiting and refusal of food were caused by vomitoxin (=deoxynivalenol) contaminated in corn and other cereal grains.

(6) Other toxicoses

Other several toxicoses of farm animals and human are suspected to be caused by the trichothecenes, but these observations were made mostly from the evidences that some toxigenic Fusarium spp. were isolated from the causal feed and food samples, and these Fusarium strains produced the trichothecenes in laboratory cultures.

Bean-hull poisoning of horses was developed sporadically in Hokkaido, the northern island of Japan. Konishi and Ichijo

(1970) reported 270 cases of horse poisoning during 1955-1959. The high incidence was observed during winter or early spring when the stored bean-hulls were used as a feed, and the mortality reached to 10-15 % with the major findings of disturbance of central nervus and cardiovascular systems. Histologically, venous hyperemia, hemorrahge in the leptomeninges and brain, scattered degeneration of the nervus cells in the cerebral cortex, and malfunction of livers.

Several toxigenic strains of Fusarium spp. were isolated from bean-hulls, and from the strain M-1-1 of F. solani (revised to F. sporotrichioides) was isolated T-2 toxin, neosolaniol and other trichothecenes (Ueno et al., 1972). In a horse administered with fusarenon-X or T-2 toxin, massive hemorrhage in the intestine and muscle tissues were observed but no disturbance in the central nervus system was observed (Ohkubo and Ueno, published). It is not certain whether the bean-hull poisoning of horses was induced by the trichothecenes.

Equine leukoencephalomalacia reported in South Africa (Marasas et al., 1979) is very similar to the above bean-hull poisoning of horses in respects of nervus disorder and hepatopathy. F. moniliforme had been a putative fungus but one of its metabolite, moniliformin, has not been proved as the causative agent (Kriek et al., 1977).

An disease of an obscure etiology, having syndrome similar to chronic ergotism and fescue toxicity, occurs in certain rice growing areas of India and Pakistan. It affects buffaloes (Bubalus bubalis) and occasionally zeru cattle. Poisonous plants and

fodder, bacteria, protozoa, ergotism and others were suspected as the cause but no specific cause was clarified. This disease is associated with winter season when rice straw was fed to the animals, especially buffalo and cattle, and characterized with lesions on the tail, ears, tongue and others. Upon feeding rice straws from the affected field, gangrene of the tail developed and died within 25 days, and no significant lesions were observed in buffalo fed control straw. Fusarium equiseti was suspected to one of causative fungi and some mycotoxins were presumed to be causative of this disease (Kalra et al., 1977). Chemical analysis of the ether extract of rice straw samples revealed the presence of trichothecenes (Bhatia et al., unpublished).

In Africa, there is a clear association between corn cultivation and esophageal cancer occurrence. The highest known esophageal cancer rate in Africa occurs in the southwestern districts of the Republic of Transkei, while the rate in the northern region of the country is relatively low. Corn is the main dietary staple in both areas, and the level of natural contamination of corn kernels with deoxynivalenol and zearalenone was considerably higher in the high-incidence area of esophageal cancer than in the low-incidence area (Marasas et al., 1979). All the trichothecenes are highly irritant to the mucous membranes, and basal cell hyperplasia of the rat esophageal squamous epithelium was resulted after T-2 toxin exposure (Schoental et al., 1979). From these observation, incidence of esophageal cancer was suspected to be caused by uptake of the trichothecene mycotoxins. Recentyl, a mutagenic product was isolated from the

metabolites of F. moniliforme, one of wide-spreading fungi in cereal grains (Gelderblom et al., 1983).

Further experiments are needed for the evaluation of toxic metabolites of Fusarium spp. in association of cancerous changes of human tissues.

Peragra is a condition found in peaple subsisting on poor diets, mainly among corn and millet eaters, as a result of tryptophan deficiency. Originally pellagra was suspected to be due to deficiency of niacin, but subsequently it was recognized the deficiency of other vitamins B, especially riboflavine. It is well known that contamination with Fusarium mycotoxins in corn can sometimes be very serious. The possibility that the trichothecenes may be involved in pellagra is supported by its seasonal increased occurrence during spring and early summer, when food supplies became exhausted in the developing contries. Furthermore, experimental toxicology revealed that the trichothecenes are a skin irritant, can cause depigmentation of dark hair and a transitory increase in the urinary excretion of coproporphyrins in rats. The symptoms of pellagra involve striking skin changes, hyperkeratosis, patchy distribution of black hyperpigmented black area interspersed with hypopigmented pale ones, gastrointestinal disorders and neurological disturbances. These similarities between pellagra and trichothecene toxicoses present a hypothesis that the trichothecenes may cause pellagra in those who consume Fusarium-molded cereals (Schoental, 1979, 1980).

/IV/ Natural occurrence of trichothecenes

During the past ten years, several methods for detection

and quantitation of the trichothecene mycotoxins have developed and applied for monitoring the contamination level in feed and foodstuffs. After the finding that Canadian grains are heavely contaminated with vomitoxin, extensive researches are now conducting in several countries.

Accumulated data indicated that Canadian and the U.S. corn, barley and wheat samples are contaminated with vomitoxin (=deoxynivalenol) in range of 10-7000 g/kg. In England, 90% of U.K. grown barley samples was contaminated with vomitoxin in level of less than 20 g/kg, and the barleys containing deoxynivalenol (0.02-0.36 mg/kg) were mostly feeding samples.

In South Africa, deoxynivalenol was detected from corn samples in significant level of 250-4000 g/kg. In Japan, both deoxynivalenol and nivalenol are detecting from freshly harvested barley and wheat in ppm level. Furthermore, 27-65 ppb of deoxynivalenol and 37-190 ppb of nivalenol were detected from commercial parched-barley flours, which are commonly used as a food in local region.

These findings pointed out the following two evidences: (i) deoxynivalenol is the major pollutant of grains in the U.S., Canada, England and South Africa, while both deoxynivalenol and nivalenol are presented in Japanese grains; and (ii) the trichothecenes are still remained in flours after milling processing.

Toxicological data for vomitoxin suggested that the contaminant is "not very toxic", since that single dose tests on adult mice showed an LD_{50} of 46 mg/kg for males fed orally, and 70 mg/kg for males via intraperitoneal injection. LD_{50} for female

mice was 77 mg/kg via intraperitoneal injection. In 1983, the Canadian government recommended the "level of concern" to 2.0 ppm of vomitoxin in wheat grains products for adult human consumption, and 1.0 ppm for infant foods. The Food and Drug Administration of the United State is expected to issue an advisory opinion that a "level of concern" of 1 ppm be set for vomitoxin in finished wheat products for human consumption. FDA will also advice that "a level of concern" of 2 ppm be established on wheat as it enters the milling process.

Toxicological data on nivalenol revealed that a LD_{50} of 4.1 mg/kg for male adult mice via intraperitoneal injection, and new borne mice were about ten times higher that adult in their susceptibility to the trichothecenes. In this respect, "the level of concern" of nivalenol should be much lower than that of deoxynivalenol (=vomitoxin).

Summary

(1) Trichothecene mycotoxins composed from more than 60 kinds of chemically closed derivatives, and produced by various species of fungi and a higher plant.

(2) No direct evidences that the trichothecenes induced the acute and subacute toxicoses in human and animals, but several approaches from mycology, toxicology, pathology, and epidemiology strongly supported that ATA, red-mold toxicosis, stachybotryotoxicosis, moldy corm toxicosis, and vomiting and refusal of feed are caused by the uptake

of trichothecenes contaminated in cereal grains and feedstuffs.

(3)There are several hypothesis that etiologically unknown diseases such as peragra, esophageal cancer, and others, are caused by the trichothecenes.

(4)In Canada, the United States, and Europe, vomitoxin (=deoxynivalenol) is highly contaminated in wheat, barley and corn, and in Japan both vomitoxin and nivalenol are the major contaminant in cereal grains and their products.

(5)It is very hard to eliminate the trichothecenes from cereal grains by milling and other food processing.

(6)Governmental control of the contamination of trichothecenes is urgently requested for protection of human health from hazardous trichothecene mycotoxins.

(7)International co-operation system in regards to the information on analytical methods, supply of standard trichothecenes, taxonomy of trichothecene-producing fungi, and toxicological data, should be set up.

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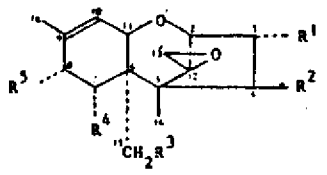
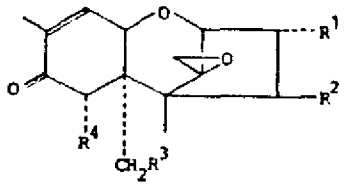


Name	R^1	R^2	R^3	R^4	R^5
Trichodermol	H	OH	H	H	H
Trichodermin	H	OAc	H	H	H
Verrucarol	H	OH	OH	H	H
Calonectrin	OAc	H	OAc	H	H
Scirpentriol	OH	OH	OH	H	H
4-Acetoxyscirpenol	OH	OAc	OH	H	H
15-Acetoxyscirpenol	OH	OH	OAc	H	H
Diacetoxyscirpenol	OH	OAc	OAc	H	H
T-2 tetraol	OH	OH	OH	H	OH
Neosolaniol	OH	OAc	OAc	H	OH
8-Acetylneosolaniol	OH	OAc	OAc	H	OAc
HT-2 toxin	OH	OH	OAc	H	$OCOCH_2CH(CH_3)_2$
T-2 toxin	OH	OAc	OAc	H	$OCOCH_2CH(CH_3)_2$
7-Hydroxydiacetoxy-scirpenol	OH	OAc	OAc	OH	H
7,8-Dihydroxy-diacetoxyscirpenol	OH	OAc	OAc	OH	OH

Fig. 1-1 The chemical structure of some trichothecenes containing a substituent other than a ketone at C-8 (type A).



Name	R^1	R^2	R^3	R^4
Trichothecolone	H	OH	H	H
Trichothecin	H	$OCOCH{=}CHCH_3$	H	H
Deoxynivalenol	OH	H	OH	OH
3-Acetyldeoxynivalenol	OAc	H	OH	OH
3,15-Diacetyldeoxynivalenol	OAc	H	OAc	OH
Nivalenol	OH	OH	OH	OH
Fusarenon-X	OH	OAc	OH	OH
Diacetylnivalenol	OH	OAc	OAc	OH

Fig. 1-2 The chemical structure of some trichothecenes containing a ketone at C-8 (type B).

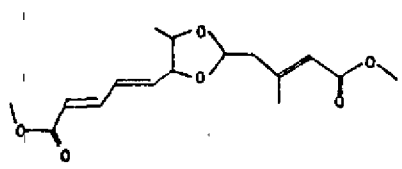
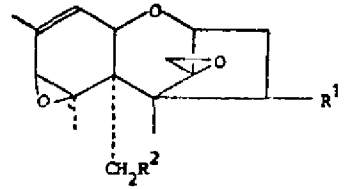
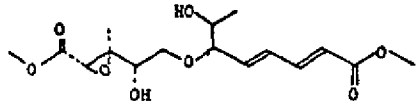
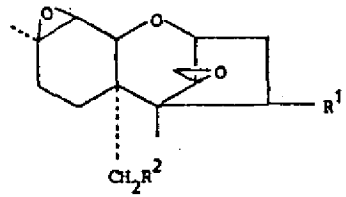
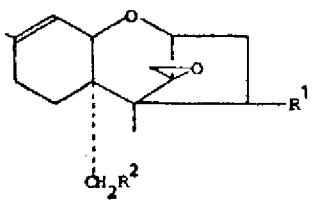
Name	R^2	R^1
Crotocin	H	$-OCOCH=CHCH_3$
7α,8α-Epoxyroridin H		
Baccharin		

Fig. 1-3 The chemical structure of some trichothecenes containing a second epoxide ring at C-7,8 or C-9,10 (type C).



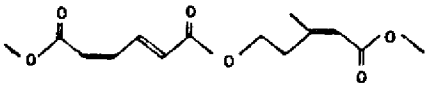
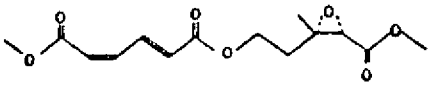
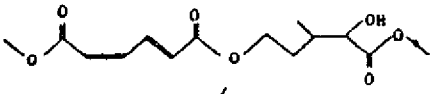
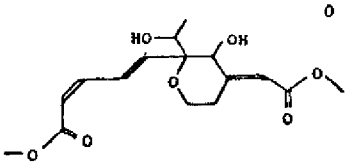
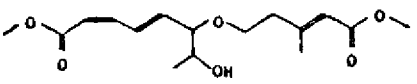
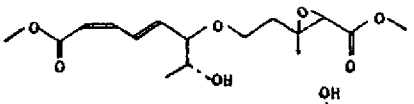
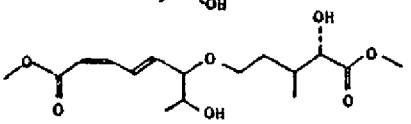
Name	R^2	R^1
Roridin A		
Roridin D		
Roridin		
Satratoxin H		
Verrucarin A		
Verrucarin B		
Verrucarin J		

Fig. 1-4 The chemical structure of some trichothecenes containing a macrocyclic ring between C-4 and C-15 (type D).

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