CURRENT AWARENESS DOCUMENT

TRICHOTHECENE-TYPE, LYSERGIC ACID RELATED AND OTHER MICROBIOAL CARCINOGENS OF DIVERSE CHEMICAL STRUCTURES

CARCINOGENICITY AND STRUCTURE ACTIVITY RELATIONSHIPS. OTHER BIOLOGICAL PROPERTIES. METABOLISM. ENVIRONMENTAL SIGNIFICANCE.

Prepared by:

David Y. Lai, Ph.D.

Yin-Tak Woo, Ph.D., D.A.B.T.

JRB Associates/
Science Applications
International Corporation
8400 Westpark Drive
McLean, Virginia 22102

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EPA Project Officer and Scientific Editor

Joseph C. Arcos, D.Sc.

Extradivisional Scientific Editor

Mary F. Argus, Ph.D.

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5.3.1.4 Trichothecene-type, Lysergic Acid Related and Other Microbial Carcinogens of Diverse Chemical Structures.

5.3.1.4.1 Fusarium Toxins.

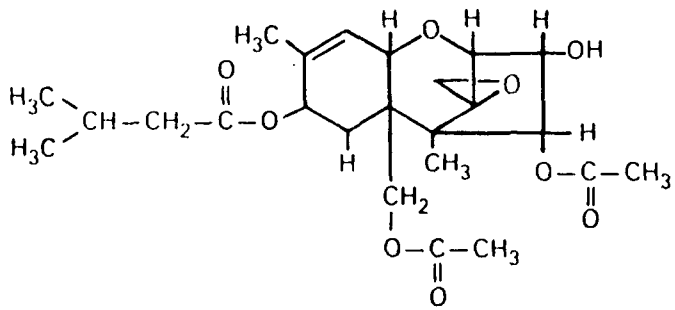
Various species of Fusarium are, among other fungi, commonly found in moldy cereal grains and are associated with numerous outbreaks of mycotoxicosis in humans and livestock throughout the globe. The natural occurrence, chemistry, toxicity and biological effects of several metabolites elaborated by Fusarium and related fungi have been extensively studied and reviewed (1-5).

Chemically, T-2 toxin (T_2-trichothecene; fusariotoxine T2; isariotoxin) and fusarenon X (3,7,15-trihydroxy-4-acetoxy-8-oxo-12,13-epoxy-Δ^9-trichothecene) (see Table XXIV), two of the Fusarium toxins which have been tested for carcinogenicity, belong to the group trichothecenes. The trichothecenes are a complex group of sesquiterpenoids containing the tricyclic trichothecane skeleton. More than forty trichothecenes have been isolated as metabolites of various fungi. All of these naturally occurring compounds contain an olefinic double bond at the 9,10 position and an epoxy group at the 12,13 position of the trichothecene nucleus. They are generally colorless, crystalline, optically active and soluble in polar organic solvents. The esters of the compounds are saponified in alkali solutions; in strong mineral acids the 12,13 epoxide is opened. Zearalenone (also known as F-2 toxin), a resorcyclic acid lactone (see Table XXIV) is another Fusarium toxin that has been assayed for carcinogenicity. Some physicochemical properties of T-2 toxin, fusarenon X and zearalenone are compiled in Table XXV.

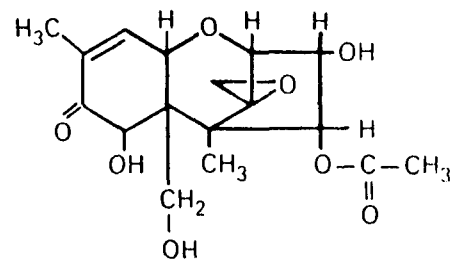
Toxicity. Like many other trichothecenes, T-2 toxin and fusarenon X are highly toxic to mammals. The characteristic pathological changes are "radiomimetic" type lesions to actively dividing cells of the gastrointestinal

Table XXIV

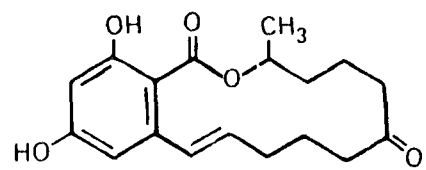
Fusarium Toxins Which Have Been Tested for Carcinogenic Activity



T-2 Toxin



Fusarenon X



Zearalenone

Table XXV
Physicochemical Properties of Some *Fusarium* Toxins[a]

Toxin	Physical form	m.p.	Optical rotation	Solubility
T-2 toxin	Colorless needles	151-152°C	$[\alpha]_D^{26} = +15^\circ$	Soluble in acetone, acetonitrile, chloroform, diethyl ether, ethyl acetate and dichloromethane
Fusarenon X	Colorless bipyramide crystals	91-92°C	$[\alpha]_D^{25} = +58^\circ$	Soluble in chloroform, ethyl acetate, methanol and water; insoluble in *n*-hexane and *n*-pentane
Zearalenone	Colorless crystals	164-165°C	$[\alpha]_{546}^{25} = -170.5^\circ$	At 25°C, soluble in acetone, slightly soluble in ethanol, methanol and dichloromethane; sparingly soluble in acetonitrile, benzene, *n*-hexane and water

[a]Summarized from IARC Monographs, Vol. 31, 1983.

tract, spleen, bone marrow, lymph nodes, thymus, ovary and testes (6, 7). Common symptoms in the trichothecene poisoning of humans and farm animals are skin irritation, nausea, vomiting, neural disturbance, leukopenia and anemia (2, 8-10). Table XXVI summarizes the LD_{50} values of T-2 toxin and fusarenon X in the rat, mouse and guinea pig. Structure-activity studies showed that reductive or hydrolytic opening of the 12,13-epoxide group results in loss of the toxicity and biological activities of these compounds; hydrogenation of the 9,10 double bond also lead to decreased toxicity in HeLa cells and hamster kidney cells (4). Zearalenone is a non-steroidal estrogenic compound exhibiting physiological and biochemical activities similar to the known carcinogen, diethylstilbestrol. In experimental and field animals, zearalenone causes atrophy of the seminal vesicles and testes, uterine wall edema and epithelial metaplasia in the cervix and vagina (cited in ref. 11).

Mutagenicity. The mutagenic and related genotoxic potential of T-2 toxin, fusarenon X and zearalenone have been investigated in a few assay systems (Table XXVII). Several investigators (12-14, 16-18) found no mutagenic activity of these three Fusarium toxins in various strains of Salmonella typhimurium with or without microsomal activation. T-2 toxin and fusarenon X were also negative in a rec assay using mutant and parent strains of Bacillus subtilis (19). Similarly, T-2 toxin and zearalenone did not cause higher frequencies of mitotic crossing-over to the ade 2 locus of Saccharomyces cerevisiae strain D3 (13). However, Nagao and coworkers (15) have reported positive mutagenic effects of fusarenon X on strains TA100 and TA98 of S. typhimurium in the absence of S-9 mix. This toxin also induced "petite" mutations in the yeast assay (20) and caused clastogenic damage in mouse lymphocytes (23), Chinese hamster V79-E cells (21) and HeLa cells (24). Similarly, T-2 toxin has been demonstrated to induce high incidences of

Table XXVI
Acute Toxicity of Some *Fusarium* Toxins

Toxin[a]	Species and route	LD_{50} (mg/kg)	Reference
T-2 toxin	Rat, oral	5.2	(2)
	Mouse, oral	10.5	(2)
	i.p.	5.2	(2)
	Guinea pig, oral	3.0	(8)
Fusarenon X	Rat, oral	4.4	(2)
	Mouse, oral	4.5	(2)
	s.c.	4.2	(2)
	i.p.	3.4	(2)
	i.v.	3.4	(2)
	Guinea pig, oral	4.4	(2)
	i.p.	< 0.5	(2)

[a]See Table XXIV for structural formulas.

Table XXVII
Mutagenic and Related Genotoxic Effects of Some *Fusarium* Toxins[a]

Toxin[b]	*Salmonella typhimurium*	*Bacillus subtilis*	*Saccharomyces cerevisiae*	Chromosomal aberration	Unscheduled DNA synthesis
T-2 toxin	- (12-14)	- (19)	- (13)	+ (21,22)	+ (25)
Fusarenon X	- (12) + (15)	- (19)	+ (20)	+ (21,23,24)	n.t.
Zearalenone	- (12-14, 16-18)	+ (16,19)	- (13)	n.t.	n.t.

[a] "+" = positive; "-" = negative; n.t. = not tested; numbers in parentheses are references.

[b] See Table XXIV for structural formulas.

chromatid aberrations in V79-E cells (21) and bone marrow cells (22) of the Chinese hamster. Treatment of human fibroblasts with T-2 toxin was reported to result in increased unscheduled DNA synthesis (25). In the B. subtilis rec assay, zearalenone exhibited a positive effect (16, 19).

Teratogenicity. T-2 toxin is teratogenic in the mouse. Gross malformations involving the tail, limbs, ribs and vertebrae, exencephaly, open eyes and retarded jaws were found in fetuses from female mice intraperitoneally injected with 0.5, 1.0 or 1.5 mg/kg T-2 toxin on day 9, 10 or 11 of gestation (26, 27). Fusarenon X, on the other hand, showed no teratogenic effects in DDD mice when the animals were treated with the toxin at doses of 0.6-1.6 mg/kg or 10-20 ppm during pregnancy (28). Ruddick and associates (29) treated groups of 10 pregnant rats with 1, 5, or 10 mg/kg zearalenone by gavage on days 6 through 15 of gestation; various skeletal abnormalities, in a dose-dependent fashion, were observed in the offspring. Infertility, fetal resorption, reduced litter size, and fetal malformations have also been reported in pigs fed zearalenone in the diet (30).

Carcinogenicity. Table XXVIII summarizes the carcinogenicity studies on T-2 toxin, fusarenon X and zearalenone.

In 1972, a Japanese group led by Saito were the first to note, in rats and mice chronically fed rice moldy with Fusarium nivale and F. graminearum, several unusual tumors not seen in control animals (cited in ref. 32). However, subsequent bioassay studies with T-2 toxin did not reveal any neoplasms in Wistar rats given the toxin in the feed at levels of 10 or 15 ppm for 12 months (32). Similarly, Marasas et al. (31) failed to detect tumors in Holtzman rats or rainbow trout fed low doses (5 or 15 ppm to the rats and 200 or 400 ppb for the trout) of T-2 toxin for 8-12 months. Also, topical appli-

Table XXVIII
Carcinogenicity of Some *Fusarium* Toxins

Toxin[a]	Species and strain	Principal organs affected and route	Reference
T-2 toxin	Trout, rainbow	None; oral	(31)
	Rat, Holtzman	None; oral	(31)
	Rat, Wistar	None; oral	(32)
	Rat, Wistar-Porton	Pancreas, gastrointestinal tract, brain and mammary gland; oral	(33)
	Rat, unspecified	Hematopoietic tissues; topical	*Cited in* ref. 23
	Mouse, unspecified	None; topical	(31)
	Mouse, DDD	Multiple sites[b]; oral	(32)
Fusarenon X	Rat, Donryu	Liver, lung[b]; s.c. Liver[b]; oral Multiple sites[c,d]; oral	(34) (34) (32, 35)
	Mouse, DDD	Hematopoietic tissue[b]; s.c.	(34)
Zearalenone	Rat, Fischer 344/N	None; oral	(11)
	Mouse, $B6C3F_1$	Liver, pituitary; oral	(11)

[a]See Table XXIV for structural formulas.

[b]Low tumor incidence. Not considered by the authors to be a significant carcinogenic effect.

[c]Tumor incidence not significantly higher than that of controls.

[d]High mortality of the treated animals.

cation of T-2 toxin to mouse skin did not initiate tumorigenesis (31). Ohtsubo and Saito (32) administered to groups of 16 to 22 female DDD mice 0, 10 or 15 ppm T-2 toxin in the feed for 12 months. One animal with adenocarcinoma of the glandular stomach, one animal with angiosarcoma of the uterus, one animal with thymoma and two animals with hepatocellular carcinoma were found among the 10 treated mice surviving for 15 months. Although such neoplasms were not seen in the controls, the findings were not considered by the authors (32) to be attributable to the compounds, because of the low incidences.

The first indication for the carcinogenicity of T-2 toxin came from the studies of Schoental et al. (33) in 1979. These authors noted the carcinogenic effects of T-2 toxin in groups of Wistar-Porton rats that survived for 12 to 27.5 months following the first of 3-8 monthly doses of the toxin (0.2-4 mg/kg body weight), given intragastrically; significant incidences of benign and malignant tumors of the pancreas, stomach, duodenum, brain and mammary gland were found in the treated animals. The results have suggested to Schoental and coworkers (33) that the T-2 toxin is a "versatile carcinogen" for the rat. Unpublished data of Lafarge-Frayssinet et al. (23) also indicate that this fungal metabolite is carcinogenic toward the rat, inducing leukemia in animals painted with the toxin on the skin of the back for an extented period of time. Moreover, Lindenfelser et al. (36) observed a weak promoting effect of T-2 toxin in skin tumorigenesis by 7,12-dimethylbenz[a]anthracene in CD-1 mice.

The carcinogenic potential of fusarenon X has been tested in rats and mice by Saito and associates (32, 34, 35). In one experiment, a group of 20 male Donryu rats was administered fusarenon X (0.4 mg/kg body weight) by gavage weekly for 50 weeks. One of the 16 animals that survived 50 weeks bore

a hepatoma; no tumors were seen in 10 controls. In another experiment, 18 rats of the same strain were given weekly s.c. injections of fusarenon X (0.4 mg/kg body weight) for 22 weeks. Of 14 treated animals surviving for more than 52 weeks, one developed a hepatoma and one had an epidermoid tumor of the lung. Again, none of the 10 controls bore any neoplasms (32, 34). In a more recent study, which involved feeding groups of 25-52 Donryu rats with 3.5 or 7.0 ppm fusarenon X in the diet for 1 or 2 years, tumors of various organs were observed. However, the tumor incidences were not significantly higher than those of the controls. The high mortality of the treated animals in the study renders it difficult to evaluate the carcinogenicity of this toxin (32, 35). When two groups of 16 or 18 male DDD mice were given weekly s.c. injections of fusarenon X (2.5 mg/kg body weight) for 10 or 20 weeks, one case of leukemia (not seen in 25 controls) occurred in 13 of the mice that survived the treatment. Again, because of the low tumor incidence and low survival rate of the treated animals, it was uncertain to the authors (34) whether the neoplasms were indeed induced by fusarenon X.

Schoental (37) has suspected that zearalenone may be the dietary component that contributes to the high incidence of spontaneous tumors in some laboratory animals in the United States. Under the bioassay conditions of the U.S. National Toxicology Program, zearalenone is indeed carcinogenic in $B6C3F_1$ mice but not carcinogenic for F344/N rats (11). Groups of 50 F344/N rats and 50 $B6C3F_1$ mice of each sex were given either a control diet or a diet containing low dose (25 ppm for rats; 50 ppm for mice) or high dose (50 ppm for rats, 100 ppm for mice) of zearalenone for 103 weeks. No chemical-related increase in tumor incidence was found in the rats killed 1-3 weeks after the last treatment. However, increased incidences of hepatocellular adenomas were seen in female low-dose mice (2/49) and female high-dose mice (7/49) as compared

with the controls (0/50). Moreover, the incidences of pituitary adenomas in high-dose mice (6/44 for males; 13/42 for females) were significantly higher than those of the controls (0/40 for males; 3/46 for females).

Metabolism and Mechanism of Action. In vivo (38) and in vitro (39-41) metabolic studies in mammals have shown that T-2 toxin is deacetylated at the C-4 position to give HT-2 toxin which is then converted to 4-deacetylneosolaniol, after hydrolytic removal of the isovaleric acid moiety at the C-8 position. Further deacetylation at the C-6 methylol side chain yields T-2 tetraol. A microsomal esterase responsible for the deacetylation has been found in the liver and brain of rats and in the liver, kidney, brain and spleen of rabbits (40). Deacetylation of fusarenon X at the C-4 position by liver esterase of rats and rabbits leads to nivalenol (42). Pharmacokinetic studies indicate that T-2 toxin (38) and fusarenon X (20) are rapidly metabolized and cleared from the body with short retention in the tissues and body fluids. Zearalenone is reduced to α- and β-isomers of zearalenol by hepatic 3 α-hydroxysteroid dehydrogenase (43, 44). Both free and conjugated (glucuronic and sulfate) forms of the parent compound and the metabolites are excreted in the urine and feces; the extent of formation and excretion of the metabolites varies with the animal species. In humans, the predominant metabolites in the urine are glucuronide conjugates of zearalenone and α-zearalenol (43). The metabolic half-life of zearalenone in the rat is reduced by increased dietary protein (45).

The mechanism of carcinogenic action of Fusarium toxins is not known. It is generally believed, however, that T-2 toxin and fusarenon X probably do not require metabolic activation to exert their biological effects (see refs. 4, 23, 33). Owing to the presence of an epoxide grouping in their molecules, they react readily with physiologically important thiol-containing enzymes,

such as creatine phosphokinase, and lactate and alcohol dehydrogenases. Like many other trichothecenes, T-2 toxin and fusarenon X bind to and disaggregate polyribosomes, and are potent inhibitors of protein and DNA synthesis in eukaryotes (see ref. 4). T-2 toxin has been reported to induce single strand breaks in DNA of lymphoid cells but not of liver cells of mice (23). The fact that T-2 toxin is reactive toward thiol groups and that liver cytosol contains glutathione transferase capable of catalyzing the conjugation of the trichothecene was suggested as the reason for the absence of effect of T-2 toxin in hepatic tissue. Fusarenon X affects membrane function and the uptake of phosphate in Tetrahymena (46). Zearalenone mimics the physiological and molecular action of the known carcinogen, diethylstilbestrol. It has been shown to promote cellular proliferation and enhance the rate of protein, DNA and RNA synthesis in uterus of mice and rats. Zearalenone, as well as its metabolites, α- and β-zearalenol, compete with estradiol for cytoplasmic and nuclear estrogen receptor sites in uterus tissue. It is possible that this estrogenic mycotoxin might act as an epigenetic carcinogen, perturbing gene expression by interacting with nuclear estrogen receptors.

Environmental Significance. T-2 toxin, fusarenon X and zearalenone are produced by a large number of Fusarium species (see Table XXIX) which infect various agricultural commodities such as corn, wheat, oat, barley, sorghum, straw, hay and mixed feed. These fungi occur most commonly in the midwestern United States, Canada, Russia, eastern Europe, Finland and northern Japan, where temperatures are low and moisture contents are high during harvest and storage seasons. Sporadic outbreaks of mycotoxicosis in humans and farm animals attributed to moldy food contaminated by Fusarium species have been recorded worldwide. There is evidence showing that T-2 toxin is responsible for the "Alimentary Toxic Aleukia (ATA)" syndrome, a fatal epidemic which

Table XXIX
Some *Fusarium* Toxins and the Fungi of Origin[a]

Compound	Fungi of origin
T-2 toxin	*Fusarium tricinctum*; *F. poae*; *F. roseum*; *F. solani*; *F. semitectum*; *F. lateritium*; *F. rigidosum*; *F. equiseti*; *Trichothecium viride*; *T. lignorum*
Fusarenon X	*Fusarium nivale*; *F. episphaeria*; *F. oxysporum*; *Gibberella zeae* (*F. roseum graminearum*)
Zearalenone	*Gibberella zeae* (*Fusarium roseum graminearum*); *F. culmorum*; *F. equiseti*; *F. gibbosum*; *F. lateritium*; *F. moniliforme*; *F. tricinctum*; *F. avenaceum*; *F. roseum*

[a]Summarized from IARC Monographs, Vol. 31, 1983.

affected over 10% of the population in Orenburg, USSR, between 1942 and 1947. This fungal metabolite has also been implicated in the moldy corn poisoning of poultry, pigs and cattle in the United States and Canada (see refs. 1, 4). Organisms such as F. solani which produce T-2 toxin were detected in moldy bean hulls that caused poisoning of horses in northern Japan for the past several decades. Fusarenon X and nivalenol isolated from F. nivals are believed to be associated with "red mold disease" which affected humans, horses and sheep in Japan (see ref. 4). Apparently unaware of the carcinogenic potential of Fusarium graminearum, which contains fusarenon X and zearalenone and has been implicated to be carcinogenic itself (see "Carcinogenicity" Section), two British food manufacturers have recently planned to produce various "myco-protein" foods from this fungus (47).

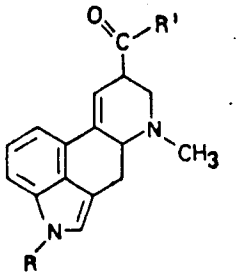
5.3.1.4.2 Ergot Alkaloids.

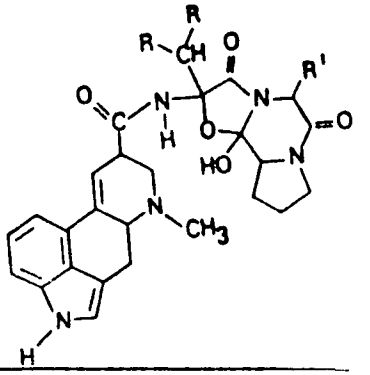
Ergot is the sclerotium of the fungus Claviceps purpurea which grows on many grasses and some grains, particularly rye. It contains many alkaloids belonging chemically to various amides of lysergic acid (see Table XXX). The most prominent constituents of ergot alkaloids are ergotamine, ergocristine, ergokryptine, ergocornine, ergosine, ergometrine and their respective isomers ergotaminine, ergocristinine, ergokryptinine, ergocorninine, ergosinine and ergometrinine. Dihydroergotoxine is a mixture (1:1:1) of the dihydrogenated derivatives (saturation of the double bond between C-9 and C-10) of ergocristine, ergokryptine and ergocornine.

Ergot alkaloids are known to cause contraction of smooth muscle, particularly of the blood vessels and the uterus. Therefore, many of them or their dihydrogenated derivatives (less toxic and having fewer side effects) have been used in obstetrics as a uterine stimulant and for the relief of migraine

Table XXX

Chemical Formulas and Cytogenetic Effects of Some Ergot Alkaloids and Derivatives





Compound	R	R'	Cytogenetic effect[b]
Lysergic acid	-H	-OH	
Lysergide (LDS)	-H	$-N-(C_2H_5)_2$	+ (48)
Methysergide	$-CH_3$	$-N(H)-CH(CH_2CH_3)CH_2OH$	+ (49-51)
Ergometrine[a]	-H	$-N(H)-CH(CH_3)CH_2OH$	+ (48)

Compound	R	R'	Cytogenetic effect[b]
Ergotamine[a]	-H	$-CH_2-C_6H_5$	+ (49, 50)
Ergocristine[a]	$-CH_3$	$-CH_2-C_6H_5$	
Ergokryptine[a]	$-CH_3$	$-CH_2CH(CH_3)_2$	
Ergocornine[a]	$-CH_3$	$-CH(CH_3)_2$	
Ergosine[a]	-H	$-CH_2CH(CH_3)_2$	
Dihydroergo-toxine[c]			+ (49-51)

[a] Ergot alkaloids derived from Claviceps purpurea.

[b] Symbol: "+" = positive effect; numbers in parentheses are references.

[c] Representing a 1:1:1 mixture of the dihydro derivatives (saturation of the double bonds between C-9 and C-10) of ergocristine, ergokryptine and ergocornine.

headache. Acute toxic effects of ergot poisoning include diarrhea, thirst, tachycardia, confusion and coma. "Ergotism," the poisoning by chronic ingestion of rye contaminated with ergot, is characterized by CNS symptoms, gastrointestinal disturbances and necrosis of the extremities due to constriction of the musculature of arterioles.

The cytogenetic effects of ergot derivatives have been studied in several assay systems. Negative findings were reported for dihydroergotoxine, ergotamine and methysergide in the micronucleus test in the bone marrow of mice and Chinese hamsters (52). Chromosome damage was not detected either in bone marrow cells of mice or of hamsters exposed to the three compounds (53, 54). However, Roberts and Rand (49) found that, at high doses, dihydroergotoxine, ergotamine and methysergide induce chromosomal aberrations in human lymphocyte cultures in vitro. Albeit to a lesser extent, these ergot derivatives also produce chromosome damage in bone marrow cells of mice in vivo (50). Dihydroergotoxine and methysergide, but not ergotamine, exhibit weak dominant lethal effects in the mouse (51). Similarly, ergometrine and lysergide cause chromosomal abnormalities in human lymphocytes in vitro (48). The structures of ergot derivatives which display chromosome damaging properties are shown in Table XXX.

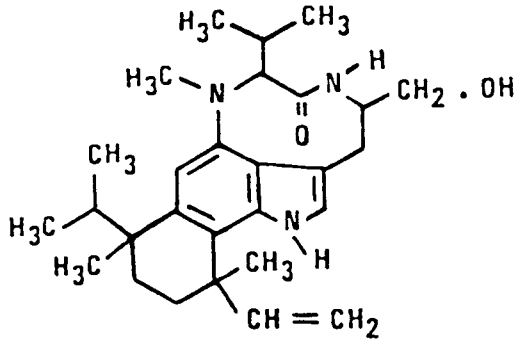
The teratogenic and carcinogenic activities of ergot alkaloids have not been evaluated. However, one of the ergot derivatives, lysergide, has been suspected to be a teratogen and carcinogen toward humans (55). In 1942, Nelson and coworkers (56) fed crude ergot to groups of Osborne-Mendel rats for 2 years and observed multiple tumors on the ears in 24% (9/38) of rats at a 2% dosage, and in 61% (23/28) of rats at a 5% dosage. The tumors were histologically identified as neurofibromas. There has been no other reports on the carcinogenicity of ergot alkaloids since; the exact component(s) of the crude ergot responsible for the tumor induction is still unknown.

5.3.1.4.3 Other Microbial Toxins.

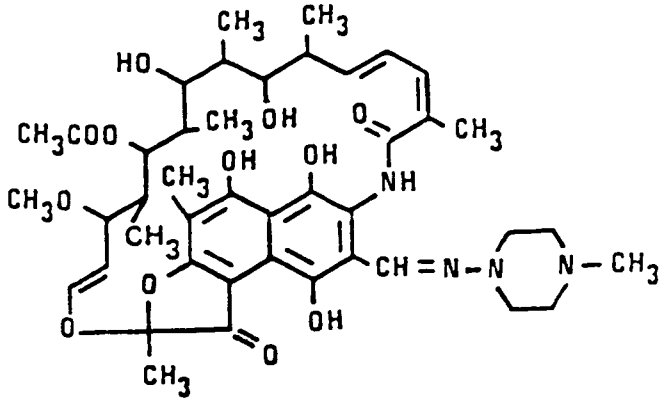
Although only a small number of microbial products have so far been discovered to be carcinogenic, it is doubtless that many more natural carcinogens among microbial metabolites will come to light if more of them are tested in proper bioassay systems for carcinogenicity. In fact, the genotoxic activity of a considerable number of mycotoxins has been shown in several short-term assays. Many of these mutagenic (and/or teratogenic) mycotoxins are structurally related to the aflatoxins, to rugulosin, luteoskyrin, fusarium X, T-2 toxin and other known carcinogens (see refs. 57-61). Recently, teleocidin, a product isolated from Streptomyces, and its hydrogenated derivative dihydroteleocidin B, have been demonstrated to be potent promotors of mouse skin carcinogenesis (62-64). Like many other tumorigenesis promotors, teleocidin blocks intercellular communication between Chinese hamster V79 cells (65). Rifampicin, a semi-synthetic derivative of rifamycin antibiotics produced by the fermentation of Streptomyces mediterranei, increases significantly the incidence of hepatomas in C3Hf female mice after oral administration (66). A single i.v. dose of 15 mg/kg marcellomycin, a new anthracycline antitumor antibiotic extracted from Actinosporangium sp. and structurally similar to adriamycin and daunomycin, induces mammary tumors in 9 of 20 female Sprague-Dawley rats (67). The structures of teleocidin, rifampicin and marcellomycin are shown in Table XXXI.

In 1965 Blank and coworkers (68) tested a series of fungal extracts for carcinogenic activity. Extracts of several species of fungi pathogenic for humans showed carcinogenic activity in Swiss Webster mice by subcutaneous injection. Increased incidences of sarcomas, leukemia and lung tumors were observed in mice that survived for 6 months following 3 weekly injections (for 4 weeks) of extracts of Candida albicans, Candida parapasilosis,

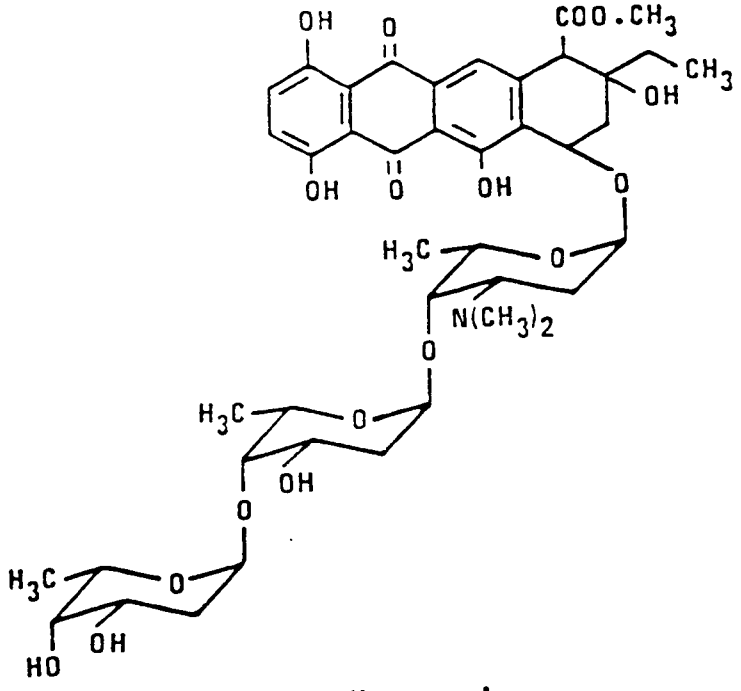
Table XXXI
Structural Formulas of Teleocidin, Rifampicin and Marcellomycin.



Teleocidin



Rifampicin



Marcellomycin

Scopulariopsis brevicaulis, Epidermophyton floccosum, Microsporum (3 species) or Trichophyton (6 species). The chemical nature of the extracts, however, has not been established.

As discussed in Section 5.2.1.3 of Volume IIIA, several hydrazo compounds present in the edible mushrooms Agaricus bisporus and Gyromitra esculenta are carcinogenic in rodents. Recent research has shown that 4-(hydroxymethyl)-benzenediazonium ion (tetrafluoroborate) present in Agaricus bisporus is also carcinogenic (69, 70), using mice as the test species.

Ethionine, the ethyl analog of the amino acid, methionine, is produced by Escherichia coli and by several other bacterial and fungal species (71). The hepatocarcinogenicity of ethionine was a topic in a previous volume of this series (see Section 5.2.1.5, Vol. IIIA).

REFERENCES TO SECTION 5.3.1.4

1. Ueno, Y.: Trichothecenes: Overview Address. In: "Mycotoxins in Human and Animal Health" (J.V. Rodericks, C.W. Hesseltine, and M.A. Mehlman, eds.), Pathotox, Park Forest South, Illinois, 1977, p. 189.
2. Sato, N. and Ueno, Y.: Comparative Toxicities of Trichothecenes. In: "Mycotoxins in Human and Animal Health" (J.V. Rodericks, C.W. Hesseltine, and M.A. Mehlman, eds.), Pathotox, Park Forest South, Illinois, 1977, p. 295.
3. Tamm, C.: Chemistry and Biosynthesis of Trichothecenes. In: "Mycotoxins in Human and Animal Health" (J.V. Rodericks, C.W. Hesseltine, and M.A. Mehlman, eds.), Pathotox, Park Forest South, Illinois, 1977, p. 209.
4. Busby, W.F. and Wogan, G.N.: Trichothecenes. In: "Mycotoxins and N-Nitroso Compounds: Environmental Risks" (R.C. Shank, ed.), Vol. II, CRC Press, Boca Raton, Florida, 1981, p. 30.
5. IARC: "Some Food Additives, Feed Additives and Naturally Occurring Substances," IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 31, International Agency for Research on Cancer, Lyon, 1983, 314 pp.
6. Ueno, Y., Ishii, K., Kanaeda, S., Tsunoda, H., Tanaka, T., and Enomoto, M.: Jpn. J. Exp. Med. 42, 187 (1972).
7. Lee, S., Beery, J.T., and Chu, F.S.: Toxicol. Appl. Pharmacol. 72, 228 (1984).
8. DeNicola, D.B., Rebar, A.H., Carlton, W.W., and Yagen, B.: Food Cosmet. Toxicol. 16, 601 (1978).
9. Hayes, M.A. and Schiefer, H.B.: Food Cosmet. Toxicol. 17, 611 (1979).

10. Rukmini, C., Prasad, J.S., and Rao, K.: Food Cosmet. Toxicol. 18, 267 (1980).

11. NTP: "Carcinogenesis Bioassay of Zearalenone in F344/N Rats and B6C3F$_1$ Mice (Feed Study)." National Toxicology Program, Technical Report Series No. 235, Research Triangle Park, North Carolina, 1982.

12. Ueno, Y., Kubota, K., Ito, T., and Nakamura, Y.: Cancer Res. 38, 536 (1978).

13. Kuczuk, M.H., Benson, P.M., Heath, H., and Hayes, A.W.: Mutat. Res. 53, 11 (1978).

14. Wehner, F.C., Marasas, W.F.U., and Thiel, P.G.: Appl. Environ. Microbiol. 35, 659 (1978).

15. Nagao, M., Honda, M., Hamasaki, T., Natori, S., Ueno, Y., Yamasaki, M., Seino, Y., Yahagi, T., and Sugimura, I.: Proc. Jpn. Assoc. Mycotoxicol. 3-4, 41 (1976).

16. Boutibonnes, P. and Loquet, C.: Int. Res. Commun. System Med. Sci. 7, 204 (1979).

17. Bartholomew, R. and Ryan, D.S.: Mutat. Res. 78, 317 (1980).

18. Ingerowski, G.H., Scheutwinkel-Reich, M., and Stan, H.-J.: Mutat. Res. 91, 93 (1981).

19. Ueno, Y. and Kubota, K.: Cancer Res. 36, 445 (1976).

20. Ueno, Y., Ueno, I., Iitoi, Y., Tsunoda, H., Enomoto, M., and Ohtsubo, K.: Jpn. J. Exp. Med. 41, 521 (1971).

21. Thust, R., Kneist, S., and Hühne, V.: Arch. Geschwülsforsch. 53, 9 (1983).

22. Norppa, H., Penttilä, M., Sorsa, M., Hintikka, E.-L., and Ilus, T.: Hereditas 93, 329 (1980).

23. Lafarge-Frayssinet, C., Decloitre, F., Mousset, S., Martin, M., and Frayssinet, C.: Mutat. Res. 88, 115 (1981).

24. Umeda, M., Yamamoto, T., and Saito, M.: Jpn. J. Exp. Med. 42, 527 (1972).

25. Oldham, J.W., Allred, L.E., Milo, G.E., Kindig, O., Capen, C.C.: Toxicol. Appl. Pharmacol. 52, 159 (1980).

26. Stanford, G.K., Hood, R.D., and Hayes, A.W.: Res. Commun. Chem. Pathol. Pharmacol. 10, 743 (1975).

27. Hood, R.D., Kuczuk, M.H., and Szczech, G.M.: Teratology 17, 25 (1978).

28. Ito, Y., Ohtsubo, K., and Saito, M.: Jpn. J. Exp. Med. 50, 167 (1980).

29. Ruddick, J.A., Scott, P.M., and Harwig, J.: Bull. Environ. Contam. Toxicol. 15, 678 (1976).

30. Chang, K., Kurtz, H.J., Mirocha, C.J.: Am. J. Vet. Res. 40, 1260 (1979).

31. Marasas, W.F.O., Bamburg, J.R., Smalley, E.B., Strong, F.M., Ragland, W.L., and Degurse, P.E.: Toxicol. Appl. Pharmacol. 15, 471 (1969).

32. Ohtsubo, K. and Saito, M.: Chronic Effects of Trichothecene Toxins. In: "Mycotoxins in Human and Animal Health" (J.V. Rodericks, C.W. Hesseltine, and M.A. Mehlman, eds.), Pathotox, Park Forest South, Illinois, 1977, p. 255.

33. Schoental, R., Joffe, A.Z., and Yagen, B.: Cancer Res. 39, 2179 (1979).

34. Saito, M. and Ohtsubo, K.: Trichothecene Toxins of Fusarium Species. In: "Mycotoxins" (I.F.H. Purchase, ed.), Elsevier, Amsterdam, 1974, p. 263.

35. Saito, M., Horiuchi, T., Ohtsubo, K., Hatanaka, J., and Ueno, Y.: Jpn. J. Exp. Med. 50, 293 (1980).

36. Lindenfelser, L.A., Lillehoj, E.B., and Burmeister, H.R.: J. Natl. Cancer Inst. 52, 113 (1974).

37. Schoental, R.: Cancer Res. 34, 2419 (1974).

38. Matsumoto, H., Ito, T., and Ueno, Y.: Jpn. J. Exp. Med. 48, 393 (1978).

39. Ellison, R.A. and Kotsonis, F.N.: Appl. Microbiol. 27, 423 (1974).

40. Ohta, M., Ishii, K., and Ueno, Y.: J. Biochem. (Tokyo) 82, 1591 (1977).

41. Yoshizawa, T., Swanson, S.P., and Mirocha, C.J.: Appl. Environ. Microbiol. 40, 901 (1980).

42. Ohta, M., Matsumoto, H., Ishii, K., and Ueno, Y.: J. Biochem. (Tokyo) 84, 697 (1978).

43. Mirocha, C.J., Pathre, S.V., and Robison, T.S.: Food Cosmet. Toxicol. 19, 25 (1981).

44. Olsen, M., Pettersson, H., and Kiessling, K.H.: Acta Pharmacol. Toxicol. 48, 157 (1981).

45. Smith, T.K.: Fed. Proc. 41, 2828 (1982).

46. Chiba, J., Nakano, N., Morooka, N., Nakazawa, S., and Watanabe, Y.: Jpn. J. Med. Sci. Biol. 25, 291 (1972).

47. Anon.: Ind. Chem. News, p. 16, Nov. 1984.

48. Jarvik, L.F. and Kato, T.: Lancet 1, 250 (1968).

49. Roberts, G.T. and Rand, M.J.: Mutat. Res. 56, 59 (1977).

50. Roberts, G.T. and Rand, M.J.: Mutat. Res. 48, 205 (1977).

51. Roberts, G.T. and Rand, M.J.: Mutat. Res. 50, 317 (1978).

52. Matter, B.E. and Grauwiler, J.: Mutat. Res. 29, 198 (1975).

53. Sankers, D.V.S.: Clin. Res. 17, 318 (1969).

54. Matter, B.E.: J. Int. Med. Res. 4, 382 (1976).

55. Dishotsky, N.I., Longhman, W.D., Mogar, R.E., and Lipscomb, W.R.: Science 172, 431 (1971).

56. Nelson, A.A., Fitzhugh, O.G., Morris, H.J., and Calvery, H.O.: Cancer Res. 2, 11 (1942).

57. Reddy, C.S., Reddy, R.V., Chan, P.K., and Hayes, A.W.: J. Environ. Pathol. Toxicol. 4, 31 (1980).

58. Stark, A.-A.: Ann. Rev. Microbiol. 34, 235 (1980).

59. Shuin, T., Moriyama, M., Nishimura, R., Takai, S., and Umeda, M.: Gann 72, 197 (1981).

60. Moule, Y., Renauld, F., Darracq, N., and Douce, C.: Carcinogenesis 3, 211 (1982).

61. Pollock, G.A., DiSabatina, C.E., Heimsch, R.C., and Hilbelink, D.R.: Food Chem. Toxicol. 20, 899 (1982).

62. Fujiki, H., Mori, M., Nakayasu, M., Terada, M., Sugimura, T., and Moore, R.E.: Proc. Nat. Acad. Sci. (U.S.A.) 78, 3872 (1981).

63. Fujiki, H., Suganuma, M., Matsukura, N., Sugimura, T., and Takayama, S.: Carcinogenesis 3, 895 (1982).

64. Umezawa, K., Weinstein, I.B., Horowitz, A., Fujiki, H., Matsushima, T., and Sugimura, T.: Nature (London) 290, 411 (1981).

65. Jones, C.M., Trosko, J.E., Chang, C.-C., Fujiki, H., and Sugimura, T.: Gann 73, 874 (1982).

66. Della Porta, G., Cabral, J.R., and Rossi, L.: Toxicol. Appl. Pharmacol. 43, 293 (1978).

67. Westendorf, J., Marquardt, H., Ketkar, M.B., Mohr, U., and Marquardt, H.: Cancer Res. 43, 5248 (1983).

68. Blank, F., Chin, O., Just, G., Meranze, D.R., Shimkin, M.B., and Wieder, R.: Cancer Res. 28, 2276 (1968).

69. Toth, B., Patil, K., and Jae, H.-S.: Cancer Res. 41, 2444 (1981).

70. Toth, B., Nagel, D., and Ross, A.: Br. J. Cancer 46, 417 (1982).

71. Fisher, J.F. and Mallette, M.F.: J. Gen. Physiol. 45, 1 (1961).