

Effects of T-2 Mycotoxin on Gastrointestinal Tissues: A Review of *in vivo* and *in vitro* Models

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Abstract. T-2 mycotoxin, a trichothecene, is the principal toxic component of *Fusarium* sp. Agricultural products and food are frequently contaminated with this toxin. Various animal models have been used to determine its metabolic fate, rate of excretion, and distribution. A modulation effect on cell-mediated immunity and alterations in gastrointestinal propulsion have been demonstrated. The toxin has been shown to produce some similar pathologic alterations in various animal species studied. The consistent alteration appears to mainly affect mitotic cells of the gastrointestinal tract and the lymphoid system. A host of bioassay systems are now being used as alternative methods to the use of animals for testing of the mycotoxin. These tests may accurately assess and define the role of the subject-toxin interactions following consumption of T-2 mycotoxin contaminated food sources.

T-2 mycotoxin, as observed above with *in vivo* and *in vitro* models, promotes a chemically-induced change in structure and function of affected gastrointestinal cells from a transient and reversible aberration in a single enzymatic reaction to cell death. Regardless of the end point measured, the toxic response brought about in cells appears to involve the interactions of virtually all subcellular processes—membrane transport and permeability, chemical metabolism, DNA function, and energy production/expenditure—as cells attempt to maintain their functional integrity while disposing of the toxicant. The variation in the quality of the toxic response with dose suggests that more cellular processes are perturbed as the chemical dose is increased.

sporium, *Fusarium*, *Myrothecium*, *Stachybotrys*, *Trichoderma*, *Trichothecium*, and *Verticimonosporium*. They are chemically related by the tetracyclic 12, 13-epoxytrichothec-9-ene skeleton (Ueno 1983; Bamberg and Strong 1971). Currently, more than 45 kinds of derivatives have been detected from the metabolites of various species of fungi. These compounds have been isolated and identified, and shown to possess cytotoxic and phytotoxic activities (Ueno 1984). Some of these compounds have been reported as associated with human and animal mycotoxicoses (Lutsky *et al.* 1978; Schoental *et al.* 1979).

T-2 mycotoxin (4 β ,15-diacetoxy-3 α -hydroxy-8 α [(3-methylbutyryl)oxy]-12,13-epoxytrichothec-9-ene) is one of the most potent of the trichothecene mycotoxins. It is the principal biologically active fungal metabolite produced by *Fusarium* sp. The mycotoxin causes a well-documented toxicosis in a variety of animals after both experimental and natural exposures. The toxicosis, which is associated with cellular injury in multiple organ systems, causes an assortment of clinical signs. This toxin and its metabolites have been reported as possible constituents of "yellow rain," a chemical biological warfare agent exploited in South East Asia (Holden 1982; Mirocha *et al.* 1982, 1983; Robert and Rosen 1982; Robinson 1982). Because T-2 mycotoxin is of apparent commercial importance to the chemical industry, there is a need for obtaining additional experimental toxicological information. Presently there is a substantial amount of information available in the literature on the occurrence and identification of T-2 mycotoxin in food residues. However, there is a lack of information on T-2 mycotoxin specially addressing gastrointestinal complications and pathology. An attempt is made here to consolidate such information while describing *in vivo* and *in vitro* models. Efforts were

Trichothecenes are sesquiterpenoid mycotoxins produced by fungal strains of the genera *Cephalo-*

Table 1. Background information on T-2 mycotoxin^{ab}

Fungal sources	<i>Fusarium sporotrichioides</i> ; <i>F. tricinctum</i> , <i>F. culmorum</i> (<i>F. roseum</i>), <i>F. solani</i> , <i>F.</i> <i>poae</i> , <i>Trichoderma lignorum</i>
Molecular formula	C ₂₄ H ₃₄ O ₆ : %C, 62.33; %H, 6.54; %O, 31.13
Molecular weight	466.2193
Form	crystals, mp 151–152 C
Solubility	2.58 g in 100 ml ethanol; [α] _D ²⁰ + 15°C
Lethal dose ₅₀	4.0 mg/kg in rats and pigs
Toxicity	cytotoxic, dermatotoxic, emetic, immunosuppressive, phytotoxic
Symptoms	causes blisters, necrosis of tissue, dizziness, nausea, vomiting, diarrhea, hemorrhaging, may result in death
Occurrence	found in moldy corn and mixed feed associated with outbreaks of the hemorrhagic syndrome in cattle and pigs

^a Reference Sources: The Merck Index (1983, Windholz M, Budavari S, Blumetti RF, Ottebein ES; eds, 10th Ed, Merck Co Inc, Rahway, NJ, p 1400), Handbook of Toxic Fungal Metabolites (1981, Cole RJ, Cox RH; eds, Academic Press Inc, New York, NY, pp 185–186), and Mycotoxicology (1987, Marasas WFO, Nelson PE; eds, Penn State Univ Press, University Park, Pa, pp 43–44)

^b Toxin is also referred to as fusariotoxin T-2, insariotoxin, and T-2 toxin

made to eliminate reported field cases where only circumstantial evidence implicated T-2 mycotoxin consumption.

T-2 Mycotoxin

Environmental Occurrence and Metabolism

T-2 mycotoxin is found as a contaminant of various agricultural products (Gareis *et al.* 1985; Szathmary 1983; Vesonder 1983). General information concerning properties of the mycotoxin are given in Table 1. It has been found in corn, barley, and mixed feeds in the U.S. and Canada at concentrations as high as 25 ppm (Vesonder 1983). *In vivo* studies on the fate of T-2 mycotoxin in laboratory animals, poultry, and livestock have demonstrated that the parent compound is rapidly cleared from body fluids and tissues (Chi *et al.* 1978; Matsumoto *et al.* 1978; Pace *et al.* 1985; Robison *et al.* 1979).

T-2 mycotoxin, and other trichothecenes, in pigs and chickens are rapidly metabolized to various compounds and eliminated primarily through the bile into the gastrointestinal tract, and excreta (Bauer *et al.* 1985; Visconti and Mirocha 1985; Yoshizawa *et al.* 1981), and secondarily in vomitus (Bauer *et al.* 1985). T-2 mycotoxin is metabolized

to several hydrolyzed products, including HT-2 mycotoxin and T-2 tetraol, and hydroxylated compounds like 3'-hydroxy HT-2 toxin (TC-3) and 3'-hydroxy T-2 toxin (TC-1) (Matsumoto *et al.* 1978; Visconti and Mirocha 1985; Yoshizawa *et al.* 1982). In bile, T-2 mycotoxin metabolites have been identified as TC-3, 3'-hydroxy-7-hydroxy HT-2 mycotoxin (TC-6), and the glucuronide form of T-2 triol (Gareis *et al.* 1986; Roush *et al.* 1985). Also deepoxidation products such as 3'-hydroxy-depoxy HT-mycotoxin, 3'-hydroxy-depoxy T-2 triol, and deepoxy T-2 tetraol have been isolated from excreta of rats intubated intragastrically with TC-3 and T-2 tetraol (Yoshizawa *et al.* 1985). It has been suggested that T-2 mycotoxin is degraded by microorganisms of the large intestine of rats by first deacetylation to HT-2 toxin followed by the reduction of 12,13-epoxy group to deepoxy HT-2 mycotoxin (Conrady-Lorch *et al.* 1986; Ishii *et al.* 1986).

Acute Toxicity

Man and domestic animals can be seriously affected by trichothecene mycotoxins (Ciegler 1979; Hayes 1980a, 1980b; Hsu *et al.* 1972; Joffe 1971; Petrie *et al.* 1977; Yagen and Joffe 1976). A disease, alimentary toxic aleukia, which reportedly killed thousands in the Soviet Union (Joffe 1971), was apparently caused by eating bread made from wheat infested with *Fusarium*. "Moldy corn disease" of domestic animals is caused by ingestion of corn infested with fungi producing T-2 mycotoxin (Hsu *et al.* 1972; Petrie *et al.* 1977). Intoxication with T-2 mycotoxin results in weight loss due to diarrhea and emesis, and inflammations with hematological changes and destruction of bone marrow (Bamburg and Strong 1971; Hayes and Schiefer 1980b; Marasas *et al.* 1969). Low concentrations of the toxin fed to livestock and poultry have been reported to cause diarrhea and feed refusal; perioral, pharyngeal, and intestinal irritations; some hemorrhaging and lowered immunity; and infertility (Hoerr *et al.* 1982; Hsu *et al.* 1972; Palyusik and Koplík-Kovacs 1975; Rafai and Tuboly 1982; Speers *et al.* 1977; Weaver *et al.* 1977). The toxin caused inhibition of rat liver mitochondrial electron transfer (Pace 1983), and lipid peroxidation (Tsuchida *et al.* 1984).

Lethal dose (LD) values for T-2 mycotoxin administered by various routes to vertebrates are shown in Table 2. The acute LD₅₀ obtained varied between 1.0 and 14 mg·kg⁻¹, there being little difference between the various routes in any given species (Fairhurst *et al.* 1987). In guinea pigs, the inhaled LD₅₀ of T-2 corresponding to an LC₅₀

Table 2. Lethal dose (LD₅₀) values of T-2 mycotoxin administered by various routes to vertebrates

Route	Vertebrate/LD ₅₀ values in mg · kg ⁻¹				
	Guinea pig	Mouse	Rat	Pig	Pigeon
Respiratory	3.3–4.3 ^a	—	—	—	—
Oral	3.0–4.0 ^b	—	—	5.0 ^c	—
Intragastric	5.3 ^d	~9.6 ^d	~7.0 ^d	—	—
Intramuscular	1.0 ^e	—	—	—	—
Intraperitoneal	—	14.0 ^d	0.9–1.3 ^{df}	—	—
Intravenous	1.0–2.0 ^d	11.0 ^d	0.9 ^d	3.0 ^e	—
Subcutaneous	1.0–2.0 ^a	6.4–8.0 ^d	~2.0 ^d	—	—
Sublingual	—	—	—	—	1.7 ^d

^a Reference Source: Marrs *et al.* 1986

^b Reference Source: De Nicola *et al.* 1978

^c Reference Source: Robison *et al.* 1979

^d Reference Source: Fairhurst *et al.* 1987

^e Reference Source: Pace *et al.* 1985

^f Reference Source: Martin *et al.* 1986

^g Reference Sources: Beasley *et al.* 1986; Weaver *et al.* 1978a

(lethal concentration × time) of 5749 mg min m⁻³ is between 3.25 and 4.33 mg·kg⁻¹. This is about twice the subcutaneous LD₅₀ of the same sample of T-2 mycotoxin used by Marrs *et al.* (1986). One explanation for this would be that approximately 50% of the inhaled dose of aerosol was retained. The oral LD₅₀ observed by De Nicola *et al.* (1978) was very similar to the inhaled LD₅₀ observed by Marrs *et al.* (1986).

Administering T-2 mycotoxin to the skin of mice has been reported to cause histological changes in the duodenum (Schiefer and Hancock 1984). These duodenal changes might be caused by either a generalized radiomimetic effect and/or by biliary excretion of the biologically active toxicant (Marrs *et al.* 1986). Cell damage is reported to result from the inhibitory effects of the toxin on protein and DNA synthesis (Ueno *et al.* 1973, Agrelo and Schoental 1980, Rosenstein and Lafarge-Frayssinet 1983). Exposure of rats to T-2 mycotoxin resulted in an intestinal decrease in protein and an increase in RNA concentrations (Suneja *et al.* 1983, 1984). The decrease in protein might indicate either a decrease in synthesis or an increase in degradation. The increase in RNA content has not been explained.

In *in vitro* studies, the cytotoxic effects of T-2 mycotoxin in eukaryotic cells are correlated with inhibition of protein, by blockage of polypeptide chain initiation (Cannon *et al.* 1976; Cundliffe *et al.* 1974), and DNA syntheses (Di Ninno *et al.* 1985; McLaughlin *et al.* 1977; Melmed *et al.* 1985; Ueno *et al.* 1973). T-2 mycotoxin markedly inhibits growth of human carcinoma and mouse leukemia cells (Perlman *et al.* 1969), with cell differentiation asso-

ciated with cytotoxicity of the toxin (Samara *et al.* 1987).

Distribution

Tritium-labeled T-2 mycotoxin administered intramuscularly to guinea pigs was observed to be distributed in all tissues within 30 min (Pace *et al.* 1985). The concentration of radiolabeled toxin rapidly declined, with no measurable long-term accumulation. In general, the early time (12 to 24 hr) distribution patterns of the guinea pig seem to parallel the distributions reported in chickens (Chi *et al.* 1978; Yoshizawa *et al.* 1980) and pigs (Robison *et al.* 1979).

Tritium-labeled T-2 mycotoxin and its metabolites rapidly distribute to tissues of orally dosed mice with maximum levels reached within 30 min, declining thereafter to non-detectable levels by 72 hr (Matsumoto *et al.* 1978). Radiolabeled products were eliminated (feces to urine, 3:1) over a 72-hr time period.

The time-dependent progression of peak radioactivity from guinea pig bile (12 hr) to large intestine (24 hr) to feces (4 days) suggests that metabolites undergo enterohepatic circulation (Pace *et al.* 1985). The slow elimination of radioactivity from the intestine might account for the reported histopathological lesions in the gastrointestinal tract of rodents (Brennecke and Neufeld 1982). These studies suggest that enteric absorbants, such as charcoal, may be of some benefit in the treatment of T-2 mycotoxin intoxication (Pace *et al.* 1985). Clays such as smectite are able to protect mice

against T-2 mycotoxin-induced disturbances of gastrointestinal transit (Fioramonti *et al.* 1987).

Following intravenous administration of tritium-labelled T-2 mycotoxin to swine, the radioactivity accumulated in the greatest amounts in the ileum, followed by the jejunum and duodenum, stomach and large intestine (Corley *et al.* 1986). The distribution of radioactivity in the gastrointestinal tract is assumed to be primarily from the bile, with some contribution from blood flow to areas of the intestine (Corley *et al.* 1985).

Biointeractions with Heavy Metals

The effect of varying dietary levels of zinc has been evaluated in mice fed T-2 mycotoxin (Chanin *et al.* 1984). Zinc retention in stomach and liver was enhanced by T-2 mycotoxin, whereas lungs and small intestines showed interactive effects. The dependence of the T-2 mycotoxin absorptive effect on zinc status is especially interesting. The mechanisms of this interaction could be the result of differences in such areas as transit time, transport inhibition, mucosal surface area, and gut permeability. T-2 mycotoxin appears to interfere with zinc homeostasis at the level of gastrointestinal tissues by enhancing zinc absorption in zinc-replete mice and decreasing zinc absorption in zinc-deficient mice. Alternatively, it did not appear to influence the rate of zinc excretion from the body following absorption. A possible mechanism for this interaction is the formation of a zinc-T-2 mycotoxin complex which could upset the homeostatic mechanisms of the gastrointestinal tract for zinc. The gastrointestinal tract is probably the major organ involved in the control of zinc status (Beach *et al.* 1980; Cousins 1982; Fraker *et al.* 1977, 1982; Miranda *et al.* 1982) but any implication of a zinc-T-2 mycotoxin complex upsetting this control is entirely speculative and is not supported by any evidence in the literature (Chanin *et al.* 1984).

Modulation of Cell-Mediated Immunity

T-2 mycotoxin is immunosuppressive and depresses T- and B-lymphocyte mitogen responses (Buening *et al.* 1982; Friend *et al.* 1983; Rafai and Tuboly 1982), prolongs skin graft rejection time (Rosenstein *et al.* 1979), and is cytotoxic to lymphocytes and rapidly dividing cells (Hayes *et al.* 1980a; Lafarge-Frayssinet *et al.* 1981; Saito *et al.* 1969). Recently, it has been reported that mice pretreated with T-2 mycotoxin had alterations of their

cell-mediated immunity. The treated animals show an increased resistance to listeriosis that apparently is associated with increased migration/activation of macrophage effector cells (Corrier *et al.* 1987; Ziprin *et al.* 1987a, 1987b). Administration of polymyxin E to these mice markedly reduced the gram-negative intestinal microflora but did not eliminate the toxin-induced resistance to listeriosis. Enhancement of selective aspects of host immunity has been reported to accompany depletion of subpopulations of short-lived suppressor T-lymphocytes following treatment with T-2 mycotoxin (Masuko *et al.* 1977). The depletion of a subpopulation of short-lived lymphocytes that exert a suppressive influence on macrophage activation is one mechanism whereby T-2 mycotoxin may concurrently induce lymphoid necrosis, modulate macrophage-lymphocyte interaction, and enhance macrophage phagocytosis (Corrier *et al.* 1987). The toxin has been reported to inhibit chemotaxis, phagocytosis, and to generate chemiluminescence in granulocytes. The toxin apparently does not affect the morphology of cells, but may cause perturbation of cell membranes (Niyo *et al.* 1988a, Gyongassy-Issa and Khachatourians 1984, Yarom *et al.* 1984a, 1984b).

Effect on Gastrointestinal Propulsion

Among the physiological disturbances induced by T-2 mycotoxin administration, the toxin stimulates gastrointestinal propulsion that affects the rate of digesta transit and, apparently, the absorption of nutrients (Sarr *et al.* 1980). Shortly after orally dosing mice with the toxin (concentration one-tenth the LD₅₀ daily for 4 days; Ueno 1984), an increase in gastrointestinal propulsion was observed for 4 days.

The mechanisms involved in the stimulation of gastrointestinal propulsion by T-2 mycotoxin are unknown but a speculative hypothesis involving prostaglandins may be postulated because T-2 mycotoxin has been found to increase the release of prostaglandins and related eicosanoids within the brain (Shohami and Feuerstein 1986). Prostaglandins are known to act peripherally to accelerate gastric emptying and small intestine transit (Ruwart and Rush 1984), and to stimulate intestinal motility (Fargeas *et al.* 1984). Disturbances of gastrointestinal motility by T-2 mycotoxin may be in part due to changes in mesenteric blood flow (Lundeen *et al.* 1986; Siren and Feuerstein 1986). Another trichothecene, fusarenon-X, has been found to increase small intestinal propulsion and to inhibit spontaneous peristalsis (Matsuoka *et al.* 1979). This

finding has been attributed to an increase in intestinal fluid secretion evidenced by a leakage of plasma contents into the intestinal lumen (Matsuoka and Kubota 1981). A similar mechanism may be postulated to explain the increase in small intestinal propulsion observed following T-2 mycotoxin administration to mice (Fioramonti *et al.* 1987).

Clinical Symptoms

Predominant clinical features of subchronic trichothecene intoxication in humans (Goodwin *et al.* 1978) and animals (Wyatt *et al.* 1973) include signs of impaired central nervous system (CNS) function, such as retarded reflexes and general depression with coma (Martin *et al.* 1986). In animals, dietary and intragastrically administered T-2 mycotoxin produces loss of righting reflex, and meningeal vaso-congestion (Schoental *et al.* 1979; Wyatt *et al.* 1973). Whether or not the CNS represents a primary or secondary site of T-2 toxicant action is not known. It is generally acknowledged that T-2 mycotoxin affects multiple tissue target sites with predominant lesions occurring in the gastrointestinal, lymphoid, and cardiovascular systems (Bamburg 1983; Ueno 1977). The toxin impairs regulatory aspects of neuronal nucleic acid metabolism at the transcriptional-translational level (Doebler *et al.* 1984; Yanagihara 1974), and in this regard seems to exert direct action(s) on the CNS (Martin *et al.* 1986). Trichothecenes, in general, appear to target mitotic cells of the intestinal tract and lymphoid tissues (Otokawa 1983).

Experimental administration of either culture preparations of *Fusarium* or purified T-2 mycotoxin, by various routes, produces the clinical picture of intoxication in rabbits (Gentry and Cooper 1981), cats (Lutsky *et al.* 1978), rats, and monkeys (Rukimini *et al.* 1980; Schoental and Joffe 1974; Schoental *et al.* 1979; Wilson *et al.* 1982). Intoxication consists of a multisystem syndrome that is often rapidly fatal and dominated by hemorrhagic diathesis, leucopenia, and sepsis (Yarom *et al.* 1984b). The cytotoxic effects of trichothecenes are correlated with their ability to inhibit protein and DNA synthesis in eukaryotic cells (Di Ninno *et al.* 1985; McLaughlin *et al.* 1977; Melmed *et al.* 1985), and to affect cell membrane functions (Samara *et al.* 1987), inhibit platelet aggregation (Yarom *et al.* 1984a), induce hemolysis of human red blood cells (Segal *et al.* 1983), and inhibit phagocytosis and chemotaxis in polymorphonuclear cells (Niyo *et al.* 1988a, Yarom *et al.* 1984b).

Animal Models

Laboratory Animals

The T-2 mycotoxin LD₅₀ values for laboratory animals are shown in Table 2. In rats, mice and guinea pigs the toxin values fell between 1 and 14 mg·kg⁻¹. The mouse was less sensitive than either the rat or guinea pig (Fairhurst *et al.* 1987). In rats, the toxin caused mucosal ulcerations, disruption of the lamina propria, and lymphocytolysis throughout Peyer's patches in follicular and parafollicular areas. Nuclear debris was frequently present. In the small intestine dead and dying lymphoid cells were seen in the lamina propria. The most severely affected segment seemed to be the duodenum. Disruption of duodenal Peyer's patches by the toxin may be significant in that this may represent interference in buildup of local antigen-specific immune responses (Enders *et al.* 1987). The colon was practically unaffected by such changes but nuclear debris was seen in the gastric mucosa (Fairhurst *et al.* 1987).

In mice, 10 ppm of T-2 mycotoxin in the diet is capable of inducing stomatitis, dermatitis, gastric mucosal hyperplasia, necrosis of the intestinal mucosa (Hayes 1979), and necrosis of splenic follicles. After about 3 weeks on a T-2 mycotoxin diet, mice are apparently able to overcome the suppression of the hematopoietic system, and erythroid hyperplasia occurs in the spleen and bone marrow (Hayes *et al.* 1980). A zone-specific necrosis of the adrenal cortex has also been seen in females but not males (Thurman *et al.* 1986). In mice, both lymphoid protein and DNA synthesis are inhibited by T-2 mycotoxin (Rosenstein and Lafarge-Frayssinet 1983). Gastric emptying and small intestinal transit were significantly accelerated after T-2 mycotoxin administration to mice (Fioramonti *et al.* 1987).

Mice given trichothecenes experimentally either by injection or by ingestion had pyknosis and karyorrhexis of the cryptal epithelial cells of the small intestine along with a marked edema and swelling of the intestinal villi with inflammatory cells infiltrating the lamina propria. The intestinal mucosa became necrotic and ulcerated. Necrosis of lymphoid cells in the intestinal lymphoid nodules was also reported. The toxin produced cellular necrosis in the thymus, especially in the cortical area, and in the germinal centers of the spleen. Bone marrow necrosis mimicked that seen with radiation damage, and the hematopoietic cells in these areas were pyknotic and karyorrhexic (Carlton and Szezech 1978; Ueno 1983).

Severe transmural intestinal necrosis was limited to mice given a single lethal dose of diacetoxyscir-

penol (DAS) and may be the cause of death. Septicemia or endotoxemia or both may have resulted and caused the shock-like state of the animals before death (Conner *et al.* 1986). The lowest dose of DAS that produced overt morphologic injury to the intestinal epithelium was 10 mg/kg, given intraperitoneally. At this dosage, damage was limited to multifocal necrosis of crypt epithelium. Thus, the intestine was slightly less sensitive to DAS than are the lymphohematopoietic organs. When the toxin was administered (10 mg/kg) to mice via either gastric gavage or intraperitoneal injection, multifocal necrosis of intestinal epithelium occurred that was attributable to causing death.

Guinea pigs exposed to T-2 mycotoxin at an inhalation dose of 4,424 to 6,510 mg min m⁻³, over an exposure time ranging from 22.5 to 75 min, showed petechial hemorrhages of the gastric mucosa. Animals from the highest dose had small mucosal hemorrhages in the jejunum, ileum and colon (Marrs *et al.* 1986). Microscopically, the small intestine was observed to have dead and dying lymphoid cells throughout the lamina propria, together with macrophages containing nuclear debris. Foci of nuclear debris were found in and around the columnar epithelium and at the bases of the crypts. Small zones of mucosal necrosis and ulceration were observed at the bases of the crypts in severely affected sections. All other organs examined were histologically normal but changes such as lymphocytolysis were seen in the lymphoid tissue of the lungs and adjacent to the pancreas and stomach in the decedents (De Nicola *et al.* 1978; Marrs *et al.* 1986). Changes in the lymphoid system have been shown to occur in many species other than the guinea-pig. These species include mice (Hayes *et al.* 1980), chickens (Bitay *et al.* 1981), cats (Lutsky and Mor 1981) and non-human primates (Jagadeesen *et al.* 1982). Guinea pigs intubated with a single LD₅₀ (1.0-2.0 mg/kg) of T-2 mycotoxin have hyperemia of the stomach mucosa and uterus (Mir-ocha 1983).

Rabbits responded like other laboratory species with dermal trichothecene application producing intense irritation and necrosis of the epidermis and adnexal structures (Carlton and Szezech 1978). Rabbits given 0.5 mg T-2 mycotoxin/kg/day developed leucopenia, and showed lowered concentrations of serum alkaline phosphatase and serum sorbitol dehydrogenase, and a lowered antibody response to *Aspergillus fumigatus* (Niyo *et al.* 1988b). Ingestion of the toxin caused lymphocyte necrosis and/or lymphoid depletion in ileal Peyer's patches and mesenteric/jejunal lymph nodes. Gastric mucosal hyperemia, hemorrhage, and superfi-

cial mucosal necrosis were observed in the rabbits (Niyo *et al.* 1988b).

The domestic cat appears to be highly susceptible to the radiomimetic effects of the trichothecene toxins. With this species, T-2 mycotoxin administered at 0.1-0.2 mg/kg causes major gross clinical signs in cats such as emesis, vomiting, diarrhea, anorexia, ataxia of the hind legs, discharge from the eyes, and ejection of hemorrhagic fluid (Cole and Cox, 1981; Sato *et al.* 1975). Consecutive administration of toxin at sublethal dosages caused a marked decrease in leucocytes. Necropsy showed extensive cellular damage in the bone marrow, intestine, spleen, and lymph nodes. Also evident were meningeal hemorrhaging of the brain, bleeding in the lungs, and vacuolic degeneration of renal tubules (Sato *et al.* 1975).

Birds

T-2 mycotoxin-induced feed refusal has been observed with pigeons (Kotsonis *et al.* 1975), similar to reports of trichothecene-induced food refusal observed in chickens (Kotsonis *et al.* 1975), swine (Weaver *et al.* 1978a), and cattle (Weaver *et al.* 1980). In pigeons, T-2 mycotoxin caused vomiting (Fairhurst *et al.* 1987; Kotsonis *et al.* 1975; Lutsky *et al.* 1978; Rukmini *et al.* 1980; Sato *et al.* 1975). The onset and duration of the vomiting were dose-related. Vomiting began as early as 10 min postexposure and persisted for as long as 4 hr. Damage to the gastrointestinal mucosa and nausea probably promotes the onset of the vomiting phenomenon (Fairhurst *et al.* 1987; Ueno 1977).

Chickens appear to be relatively resistant to the effects of T-2 mycotoxin, when the concentration in the feed does not exceed 5 ppm. Broilers fed toxin at 4-16 ppm for three weeks duration developed oral inflammatory lesions infected with bacteria. These oral bilateral necrotic lesions have also been observed in turkey poults, and are indicative of feed contaminated with trichothecenes. The trichothecenes, in general, appear to be detrimental to the immune system of birds, causing them to be more susceptible to infectious agents. The toxins cause a decrease in the cellularity of the bursa of Fabricius and general necrosis of other lymphoid sites. Turkeys are more susceptible to dietary T-2 mycotoxin than are chickens (Richard *et al.* 1978). Turkey poults develop chronic oral lesions when fed T-2 mycotoxin for an extended period of time. T-2 mycotoxin, and other trichothecenes, do not seem to alter the clotting mechanism of poultry,

however, leukopenia and anemia have been associated with chronic toxicoses (Mirocha 1983).

Cattle

When T-2 mycotoxin is present in the diet (50 ppm) of bovine species, for at least 15 days, there is no effect on target organs. The toxin apparently only causes congestion and edema to the gastrointestinal tract. The caustic nature of the toxin is neutralized and/or degraded in the rumen. However, the mycotoxin must remain intact for a period of time as it is secreted in the milk of treated-lactating animals (Weaver *et al.* 1977). In calves, orally given 0.32–0.46 mg/kg of T-2 mycotoxin, ulcerations develop in the abomasum and rumen, and an acute enteric response with bloody feces occurs (Pier *et al.* 1976; Weaver *et al.* 1977). The calves become inappetent, dehydrated and a slight to severe weight loss was observed respective to the toxin dose level. Clinicopathologic changes were restricted to the higher toxin dosages with increased prothrombin times and increased levels of serum glutamic oxalacetic transaminase (Pier *et al.* 1976). No apparent reduction in leukocyte count or bone marrow alterations were observed in toxin-treated calves. In cattle, intramuscularly injected with T-2 mycotoxin to circumvent the rumen, petechial hemorrhages of the gastrointestinal tract have been observed (Mirocha 1983).

Feeding cattle a T-2 mycotoxin-contaminated diet has been reported to cause intestinal necrosis that seems to be associated with altered release of lysosomal enzymes (Kosuri *et al.* 1970; Saito *et al.* 1969). However, this observation has not been seen with rats fed a diet containing T-2 mycotoxin (1.5 mg/kg body weight for 4 days; Suneja *et al.* 1984). These rats showed no altered release of either acid phosphatase or acid ribonuclease from lysosomes. With other toxins, such as aflatoxin B and luteoskyrin, they have been shown to alter the integrity of rat lysosomal membranes *in vivo* and *in vitro* (Pokrovskii *et al.* 1972, 1974; Tung *et al.* 1970).

Swine

Administration of lethal doses of T-2 mycotoxin, intravascularly to swine, caused congestion and hemorrhage in the stomach, small intestines (except the duodenum), and the large intestine (Beasley 1986; Weaver *et al.* 1978c). By either intravenous or subcutaneous route in swine, the toxin apparently causes necrosis of epithelial and

crypt cells of the jejunum and ileum (Marrs *et al.* 1986; Pang *et al.* 1987a, 1987b, 1987c; Weaver *et al.* 1978a). When sows are fed a diet containing T-2 mycotoxin (12 ppm), during breeding and gestation intervals, the sows in some cases show congestion and edema of the gastrointestinal mucosa and a decrease in reproductive efficiency (Kurtz 1981). When T-2 mycotoxin is given parenterally it produces abortion in the pregnant sow but no histopathologic lesions are detected in the placenta or the fetuses (Weaver *et al.* 1978b, 1978d). T-2 mycotoxin fed in the diet at the rate of 1, 2, 4, and 8 ppm to young swine, for eight weeks, promotes the occurrence of only small erosions of the oral cavity. Diacetoxyscirpenol (DAS) on the other hand when fed to swine, at similar concentrations to T-2 mycotoxin, promotes ulcerations and proliferative lesions in the buccal mucosa and proliferative lesions on the lingual surfaces of the oral cavity (Weaver *et al.* 1978b, 1987d).

The parenteral administration of T-2 mycotoxin (LD₅₀, 1.21 mg/kg) and DAS (LD₅₀ 0.376 mg/kg) produces diarrhea and emesis, posterior paresis, and acute death. With injection of these toxins, some of the pigs were believed to die from endotoxic shock while others prolonged and showed acute necrosis in the germinal centers of the lymph nodes and spleen along with moderate necrosis of the hematopoietic elements of the bone marrow (Weaver *et al.* 1977, 1978a, 1981). The lesions produced by DAS were similar to those of T-2 mycotoxin but DAS produced much more pyknosis and karyorrhexis of lymphoid cells. Feed containing DAS (4 ppm) was refused by Swine (Weaver *et al.* 1978b, 1981). Feed containing T-2 mycotoxin concentrations greater than 12 ppm was refused by swine (Kurtz, 1981). Also, topical exposure of swine to a sublethal dose of T-2 mycotoxin, 15 mg/kg, can cause significant systemic effects on parameters such as body weight gain, rectal temperature, hematology, serum biochemistry, and cellular immune response (Pang *et al.* 1987b).

In vitro Bioassay Systems

In terms of mycotoxin identification, a bioassay system for demonstrating toxic effects is the ultimate tool in classification. They are necessary analytical adjuncts to chemical and other techniques, and serve as alternative methods to the use of animals for testing. They are necessary for determining the precise nature of the toxins' toxic properties (Acosta *et al.* 1985; Dagani 1983; Grisham and Smith 1984)). Bioassay systems serve as confirmatory evidence for the deleterious properties of

Table 3. *In vitro* bioassay systems used for detection of cytopathic effects of T-2 mycotoxin

Bioassay system	Effect observed	Sensitivity	Assay time
Human epidermal sheet	Penetration of skin surface ^a	79 ng/cm ²	days 2-4
Human fibroblasts	50% cells dead	0.003 ^b -0.9 µg/ml ^c	2-4
Human myeloid leukemic cells	100% cells dead	8 ng/m ^d	5
Human myeloid leukemic cells	Differentiation	2-4 ng/ml ^d	3-8
Mouse fibroblast cell line	50% cells dead	0.0001 µg/ml ^b	3-4
Pig intestinal explants	Cytopathic effects Inhibition of: —DNA/protein synthesis	1-3 µg/ml ^e	1-2
Rat intestinal sacs	Inhibition of: —glucose uptake —tryptophan uptake —lactase activity —sucrase activity	1.5 mg/kg ^f	45 min
Chick embryo	Lethality	0.01 µg/ml ^g	1

^a Reference Source: Kempainen *et al.* (1984)

^b Reference Source: Abbas *et al.* (1984)

^c Reference Source: Oldham *et al.* (1980)

^d Reference Source: Samara *et al.* (1987)

^e Reference Source: Williams and Hall (1987)

^f Reference Source: Suneja *et al.* (1984). T-2 mycotoxin was given daily, by oral gavage for four days

^g Reference Source: Veseley *et al.* (1982)

newly identified fungal metabolites and aid in the risk assessment of possible hazardous effects to animal populations. It is within this framework that bioassay systems are helpful in the diagnosis of mycotoxicoses. Examples of *in vitro* bioassay systems used for testing of T-2 mycotoxin are shown in Table 3.

Tissue and Cell Cultures

Trichothecenes have been found to be potent inducers of terminal differentiation using human leukemic cells as a bioassay system (Table 3). The lipophilic compounds T-2 mycotoxin, HT-2 mycotoxin, DAS, and acetyl T-2 mycotoxin have been reported to be effective in the range of 2-10 ng/ml; while the less lipophilic T-2 triol and scirpentriol are effective at higher concentrations (50-100 ng/ml). Also 9,10-epoxy T-2 mycotoxin and 9,10-dihydro T-2 mycotoxin, compounds missing the 9,10 double bond, were effective at 50-100 ng/ml. Roridin A, a macrocyclic trichothecene, has been found to be the most effective, inducing differentiation at concentrations as low as 0.3 ng/ml (Samara *et al.* 1987). The mechanism of induction of differentiation by these trichothecenes is apparently unknown.

The precise nature of the toxic action of 12,13-epoxytrichothecenes is still uncertain. T-2 mycotoxin as shown in Table 3 is toxic to mammalian cells in culture (Bodon and Zoldag 1974; Hsia *et al.* 1983), and has been reported to inhibit protein synthesis in animal cells *in vitro* (Cannon *et al.* 1976; Carter and Cannon 1977; McLaughlin *et al.* 1977; Ueno *et al.* 1973), and to inhibit DNA synthesis in Ehrlich ascites tumour cells without affecting RNA synthesis (Ueno and Fukushima 1968). The primary mechanism of trichothecene-induced cytotoxicity appears to be due to the ability of the toxin to bind to the 60 S subunit of the ribosomes causing the interference of the initiation of protein synthesis (McLaughlin *et al.* 1977).

Everted Jejunal Sacs

The effect of T-2 mycotoxin given by oral gavage on the intestinal transport system was examined by measuring the uptake of glucose and tryptophan using everted jejunal sacs (Table 3). Feeding of T-2 mycotoxin markedly decreased the uptake of glucose and tryptophan with respective differences over controls of: glucose, 549 µg absorbed/hr/g; and tryptophan, 279 µg absorbed/hr/g (Suneja *et al.*

1984). In addition, toxin-treated and non-treated intestinal segments were used as sources of mucosal layers for determining brush border sucrase and lactase activities. The toxin-treated segments showed lowered sucrase activity from 60 to 16 μg glucose liberated/10 min/mg protein; and lactase activity from 14 to 10 μg glucose liberated/10 min/mg protein. The toxin also inhibited $(\text{Na}^+ - \text{K}^+) - \text{ATPase}$ of the small intestinal mucosa from 2.6 to 2.1 μmoles phosphorus liberated/10 min/mg protein. (Suneja *et al.* 1984). With impairment of $(\text{Na}^+ - \text{K}^+) - \text{ATPase}$ there would be, presumably, a lack of maintenance of the Na^+ gradient across the intestinal epithelial cell, resulting in disruption of absorption of sugars and amino acids (Skou 1965). Apparently, the toxin does not interfere with intestinal alkaline phosphatase activity, an enzyme that is known to be localized in the microvillus membrane (Eichholz 1967). The toxin also does not alter the release of the lysosomal enzymes, acid phosphatase and acid ribonuclease (Suneja *et al.* 1984). In studies with rat intestinal mucosal homogenates, T-2 mycotoxin appears to interfere with incorporation of ^{14}C -leucine into protein, by about 15%. Intestinal mucosal protein content was reduced from 107 to 86 mg/g, indicating a significant loss of protein (Suneja *et al.* 1983).

The above results on glucose and tryptophan uptake and brush border enzymes suggest that exposure to T-2 mycotoxin induces changes in the functioning of the brush border membrane in the small intestine of rats (Suneja *et al.* 1984). The inhibition of the transport proteins by T-2 mycotoxin feeding could be due to their decreased synthesis or to direct interaction with the reactive site (epoxy group) of T-2 mycotoxin. Alkaline phosphatase, localized in the microvillus membrane, was not altered by T-2 mycotoxin suggesting that the toxin is more specific to the transport proteins (Eichholz 1967). Ueno and Matsumoto (1975) showed inhibition of SH-enzymes by prior incubation with T-2 mycotoxin *in vitro*, that could be prevented by dithiothreitol, suggesting a probable binding of epoxytrichothecenes with thiol residues of SH-enzyme proteins. The inhibition of sucrase, lactase and $(\text{Na}^+ - \text{K}^+) - \text{ATPase}$ may be due to the interaction of the reactive site of T-2 mycotoxin with the SH-group of enzyme proteins, with a concomitant reduction in glucose and tryptophan uptake.

Intestinal Ring Explants

Ring explants of porcine duodenum, jejunum, and ileum have been reported to take up methyl- ^3H thymidine over a four-day incubation period (Williams

et al. 1985). Incorporation of this DNA precursor was observed as a gradual and continuous process, indicative of DNA synthesis associated with transformation of primarily epithelial crypt cells within the explants (Browning and Trier 1969; Eastwood and Trier 1973). When similar ring explants were incubated with T-2 mycotoxin a decrease in uptake of radioactivity (about 90%) was observed. This decrease in radio-labeled thymidine incorporation to DNA by T-2 mycotoxin may not be due to direct inhibition of the appropriate polymerase or the accessory proteins necessary for replication, or damage to the DNA itself. T-2 mycotoxin may inhibit thymidine transport into the cells or damage membranes concomitant with cytotoxicity that indirectly inhibits the uptake of exogenous radio-labeled thymidine (Williams, unpublished data). Chemicals that interfere with cell metabolism are able to induce quantitative as well as qualitative alterations of nucleotide pools (Bianchi 1982).

T-2 mycotoxin incubated with the ring explants showed cytotoxicity effects to the gastrointestinal mucosa within 1 hr of T-2 mycotoxin exposure (Table 3). Necrosis of crypt epithelial cells, nuclear debris in the lamina propria, and loss of muscular retention were observed over a 48-hr incubation period. The most severely affected explants were the duodenum, followed by the jejunum, and ileum (Williams and Hall 1987). When a proteinaceous toxin (*Pasteurella multocida*, PM) was compared to T-2 mycotoxin in explants, exposed to a pseudorabies virus (swine pathogen, Gustafson 1986), the following results were obtained. The cultures were observed over a four day incubation period to be metabolically active synthesizing DNA and protein, showed mitotic figures with morphologic integrity retained, and showed cellular changes with virus-toxin. The PM toxin was not caustic to the intestinal mucosa and did not impair but enhanced pseudorabies virus replication, causing epithelial necrosis. The T-2 mycotoxin was caustic to the intestinal mucosa resulting in loss of epithelial cells, causing a loss of pseudorabies virus replication (Hall *et al.* 1987, Williams *et al.* 1987).

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