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REVIEW ARTICLE

T-2 MYCOTOXIN INDUCED TOXICITY: A REVIEW

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ABSTRACT

T-2 toxin is a member of trichothecene mycotoxin. The major toxic effect of T-2 toxin is that it inhibit protein synthesis which is followed by a secondary disruption of DNA and RNA synthesis. T-2 toxin affects the actively first through skin and it causes heamatotoxicity, neurotoxicity, reproductive toxicity, genotoxicity and it can decrease antibody levels, immunoglobolines and certain other humoral factors. In addition, in this review article discussed about outbreaks of T-2 toxin and its biosynthesis, toxicokinetics regulatory matters related to its use as a potential warfare and treatment.

INTRODUCTION

The Trichothecenes (TCT) are metabolites of Fusarium, Myrothecium, Trichothecium, Trichoderma, Cephalosporium, Cylindrocarpon and Stachybotrys species (Ueno, 1989; Buck and Cote, 1991). Till now they are 148 TCT have been isolated from fungal cultures and plants in that 83 non- macrocyclic and 65 macrocyclic (Drove, 1988) (Figure 1). Fusarium grow in 32^0C but toxin production is highest in < 20ºC temperature therefore TCT are grow at cool climates particularly when grain harvest have been delayed into the winter months, or infected grain has been stored in cold conditions (Jordan *et al*., 2002). Fusarium fungi are natural producers of TCT which are commonly occurring in soil and it sporulate both in soil and plant material. Some of the fusarium species are also plant pathogens causing different plant diseases and it may reduce the crop yield (Snijders and Perkowski, 1990; Mesterhazy *et al*., 1999; Eriksen, 2003). Fusarium species produces different mycotoxins depending on the substrate and growth conditions They are zearalenone, deoxynivalenol (DON), diacetoxyscirpenol (DAS), and T-2 toxin may produced by *F. sporotrichioides*, *F. graminearum* and certain other species of fungi (Biberstein and Zee, 1990). The TCT are all non-volatile, low-molecular-weight sesquiterpene epoxides, and can be further classified according to the presence or absence of characteristic functional groups Shown in Figure 2.

1.Type A: functional group other than a ketone at C8 position (e.g.; T-2, HT-2, DAS);

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2. Type B: carbonyl functions at C8 position (e.g.; DON, NIV, FUS-X, 3-acetyl-deoxynivalenol,
15-acetyl-deoxynivalenol);
3. Type C: second epoxide group at C7, 8 or C9, 10; (e.g.; crotocin and baccharin);
4. Type D: macrocyclic ring system between C4 and C15 with two ester linkages (e.g.; satratoxin G, H, roridin A and verrucarin A) (Sudakin, 2003; Rocha, 2005; Koch, 2004; Pestka, 2007)

T-2 toxin

T-2 toxin and HT-2 toxin are mycotoxins of the group trichothecene type A produced by fungi of the fusarium genus (F. acuminatum, F. poae and F. sporotrichioides) which are mainly found in various cereal crops (wheat, maize, barley, oats) and processed grains (malt, bear and breed) (Eriksen GS, Alexander J). T-2 is nonvolatile and resistant to UV and temperature, it can be inactivated by heating at 200 °C to 210 °C for 30 min to 40 min, or by soaking in sodium hypochlorite - sodium hydroxide solution for at least four hours. Some bacteria and moulds have the ability to transform and detoxify T-2 toxin (Shima *et al*., 1997). T-2 toxin have been used as a biological weapon, it can be delivered via food or water sources, as well as, via droplets, aerosols, or smoke from various dispersal systems and exploding munitions (Michael, 2013.). Chemically T-2 toxin is tetracyclic sesquiterpenoid with 12, 13 epoxytrichothec-9-ene ring system (Swanson *et al*., 1998), with hydroxyl (OH) group at the C-3 position, acetyloxy (-$OCOCH_3$) groups at C-4 and C-15 positions, atom of hydrogen at C-7 position and an ester linked isovaleryl

[$OCOCH_2CH(CH_3)_2$] group at the C-8 position (Swanson *et al*., 1998). The toxicity can be reduced by cleavage of esters demonstrated in different cell culture experiments (Oldham *et al*., 1980).

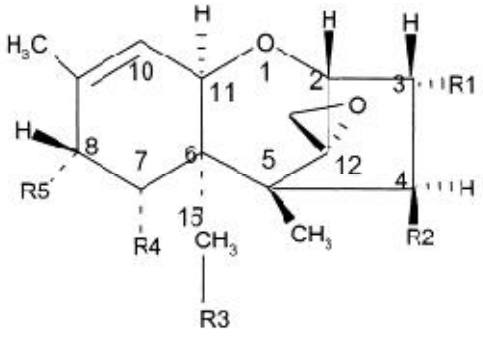

Figure 1. General chemical structure of trichothecenes (Cavret *et al.*, 2006)

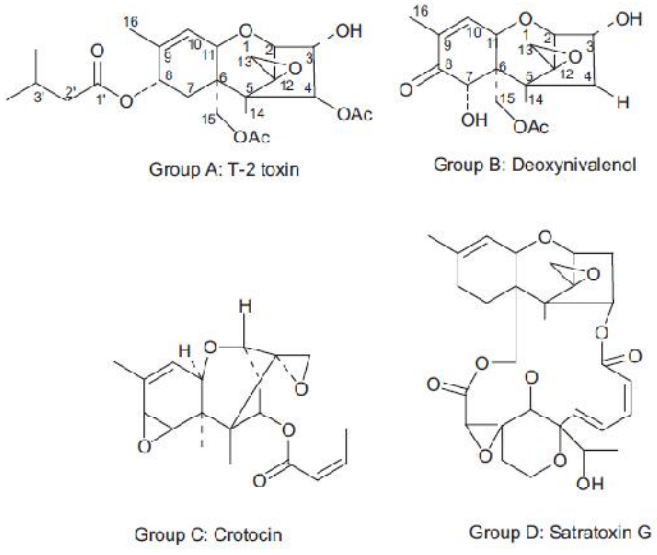

Figure 2. Chemical structure of trichothecenes with examples of groups A, B, C and D (Wu *et al.*, 2010)

T-2 toxin mode of action

T-2 toxin inhibit synthesis of DNA and RNA both in vivo (0.75 mg/kg bw single or multiple doses) and invitro (> 0.1-1 ng/ml) (Rosenstein and Lafarge-Frayssinet, 1983; reviewed in WHO, 1990). T-2 toxin inhibits protein synthesis in the initiation phase, by binding of 60 S ribosomal subunit, and inhibited the activity of peptidyl transferase. It is reported in invitro 0.01 ng/ml in suspensions of rat hepatocytes gave 75 % inhibition and in invivo from bone marrow, spleen and thymus 0.75 mg/kg bw single dose in mice.(Rosenstein and Lafarge-Frayssinet, 1983; Feinberg and McLaughlin, 1989; Thompson and Wannemachter,1990; WHO 1990). T-2 toxin causes cellular damage in cell membrane changes in the phospholipid turnover in bovine platelets and haemolysis of erythrocytes in invitro at 0.4 pg/ml concentration(Bunner and Morris, 1988; Grandoni,1992; Rizzo, 1992). T-2 toxin caused apoptosis both in invitro (HL-60 cells, 264.7 cells 10 ng/ml and Jurkat cells, 10 μM) (Ueno *et al*., 1995; Yang *et al*., 2000) and invivo (10 mg/ kg bw) in thymic splenic, lymphocytes and bone marrow intestinal epithelial crypt cells of mice (Li *et al*., 1997; Shinozuka *et al*., 1998).T-2 toxin metabolites such as T-2 triol and T-2 tetraol can activate the c-Jun N-terminal kinase 1 (JNK1) and p38MAPK. It has been suggested that trichothecenes trigger a ribotoxic stress response causing the activation of MAP kinases (Shifrin and Anderson, 1999). Such activation may signal both cell survival or induce cell death that is apoptosis. Haematopoietic progenitor cells sensitive target for T-2/HT-2 toxin both invitro_and invivo (Parent-Massin and Parchment, 1998). T-2 toxin also inhibits the mitochondrial electron transport chain by inhibiting yeast succinic dehydrogenase (Khachatourians, 1990) and it inhibited gap-junctional intercellular communication in Chinese Hamster V79 cells (IARC, 1993).

Out break of T-2 toxin

T-2 mycotoxin on human affected by accidental ingestion of moldy wheat or corn (Locasto, 2001). In the period 1931-47, a human disease known alimentary toxic aleukia (ATA) occurred in the USSR that was suggested to be related to the presence of toxic Fusarium species in moldy over- wintered grain (WHO, 1990). Scabby grain toxicosis is a disease from T-2 toxin it causes both humans and animals, that reported from Japan and Korea during 1946- 63. The commonest clinical symptoms were nausea, vomiting, diarrhea and abdominal pain. (JECFA, 2001).The consumption of bread made from flour that had become moldy in storage following unseasoned rains in the wheatwhich is contaminated by fusarium. Of the 224 persons investigated on a random sample, 97 were affected with symptoms including abdominal pain (100%), throat irritation (63%) diarrhea (39%), blood in stools (5%) and vomiting (7%). In 12 out of 24 samples of refined wheat flour used in the preparation of bread, the following mycotoxins were found: T-2 toxin (0.55–0.8 mg/kg) it was reported in Kashmir, India, in 1987(Bhat *et al*., 1987, 1989).

T-2 toxin used as abiological warfare agent in Laos during the Vietnam war first time. Other reports uses of T-2 toxin as a biological weapon by Soviet forces against Kampuchea (1979-81) and Afghanistan (1979-81). The air attacks in Laos have been described as “yellow rain” and consisted of a shower of sticky, yellow liquid that sounded like rain as it fell from the sky (Haig, 1982).

Dietary intake

T-2 toxin cause skin, eye and gastrointestinal problems for humans when delivered at low doses, and cause severe eye irritation, corneal damage, impaired vision in macrogram (Ueno, 1989; Wannemacher and Wiener, 1997). Skin visication has been observed when exposed to yellow rain (Seagrave, 1981; Ember, 1984; Ueno, 1989). T-2 toxin is about 400 fold more potent (50 ng Vs 20 μg) than mustard in producing skin injury (Bunner *et al*., 1985). In cow gastroenteritis, intestinal hemorrhages, bloody feces, enteritis, and abdominal and ruminal ulcers were observed at a level of 0.64 ppm for 20 days (Mirocha *et al*., 1976, Petrie *et al*., 1977). Anorexia and gastroenteritis were noted at 0.44 mg/kg pure T-2 toxin for 15 days (Weaver *et al*., 1980).

In calves, necrosis of the lips, beak and oral mucosa and enteritis, which are caused by T-2 toxin approximating 4 to 10 ppm (Biberstein and Zee, 1990). Some evidence of mild enteritis with loose feces was observed in 0.08- 0.6 mg T-2 toxin/ kg b.wt. orally for 30 days (Pier *et al*., 1976). In pigs 4 or 8 mg/ kg b.wt, through intravenous administration of T-2 toxin resulted in increased plasma concentrations of epinephrine, norepinephrine, thromboxane B_2 and 6- keto-prostaglandin F (Lorenzana *et al*., 1985, WHO, 1990). In high dose persistent vomiting, watery diarrhea, abdominal straining, cold extremities, coma and death are observed at low concentration at 0.5 ppm cause a reduction in feed intake in pigs (Rafai *et al*., 1995).Chickens are more sensitive to T-2 toxin. Broiler chickens fed graded concentrations of 1-16 ppm of T-2 toxin for 3 weeks developed an abnormal positioning of the wings, hysteroid seizures and impaired righting reflex and at 4ppm causing growth retardation (Wyatt *et al*., 1973a, chi *et al*., 1977a Leeson *et al*., 1995). 2.5 ppm T-2 toxin showed Altered feathering, depression, necrosis of the oral and oesophegeal mucosa and visible atrophy of lymphoid organs. In laying hens egg production and shell thickness were significantly decreased at 8 ppm T-2 toxin and lesions were observed from the second week in hens fed 4 and 8 ppm (Chi *et al*., 1977c; Leeson *et al*., 1995).In Turkey poults Oral lesions and decreased size of thymus were reported at 10 ppm T-2 toxin (Richard *et al*., 1978). Duckling are sensitive to T-2 toxins (Leeson *et al*., 1995). necrotizing upper alimentary tract lesions, oral and esophageal lesions, ulcerative proventriculitis, and severe depletion of the lymphoid tissues were developed in Young Mallard ducks fed diets containing 20-30 ppm pure T-2 toxin for 2-3 weeks (Hayes and Wobeser, 1983).

toxin is rapidly metabolized by deacetylation, hydroxylation glucoronide conjugation and de-epoxidation (Johnsen *et al*., 1988). The main biotransformation pathway of T-2 toxin is deacetylation of the C- 4 acetyl group with isolated microsomes from liver, kidney and spleen of various animals.This reaction is catalysed by a non- specific carboxyestrase in several tissues, mainly in the liver, but also blood plasma (Johnson *et al*., 1988).

Biosynthesis of T-2

Biosynthesis of Fusarium trichothecenes begins with the cyclization of farnesyl pyrophosphate, a primary metabolic intermediate, to form trichodiene. The terpene cyclase trichodiene synthase (Tri5) catalyzes this reaction and encodes for the gene TRI5. Trichodiene undergoes a series of oxygenations catalyzed by a cytochrome P^{450} monooxygenase encoded by TRI4. TRI4 controls the addition of four oxygens at C-2, C-3, C-11, and the C-12, C-13-epoxide to form the intermediate isotrichotriol. Tri3 encodes a transacetylase that converts 15-decalonectrin to calonectrin, and Tri4 encodes a cytochrome P-450 monooxygenase that converts trichodiene to an as yet uncharacterized oxygenated product. Tri3, Tri4, and Tri5 are clustered within a 9-kb region of the F. sporotrichioides genome. Tri6 gene encodes a transcriptional factor required for pathway gene expression. Tri3 gene encodes an acetyl-CoA-dependent acetyltransferase that acetylates the C-15 hydroxyl of 15-decalonectrin. Tri101 encodes isotrichodermol 3-o-acetyltransferase.

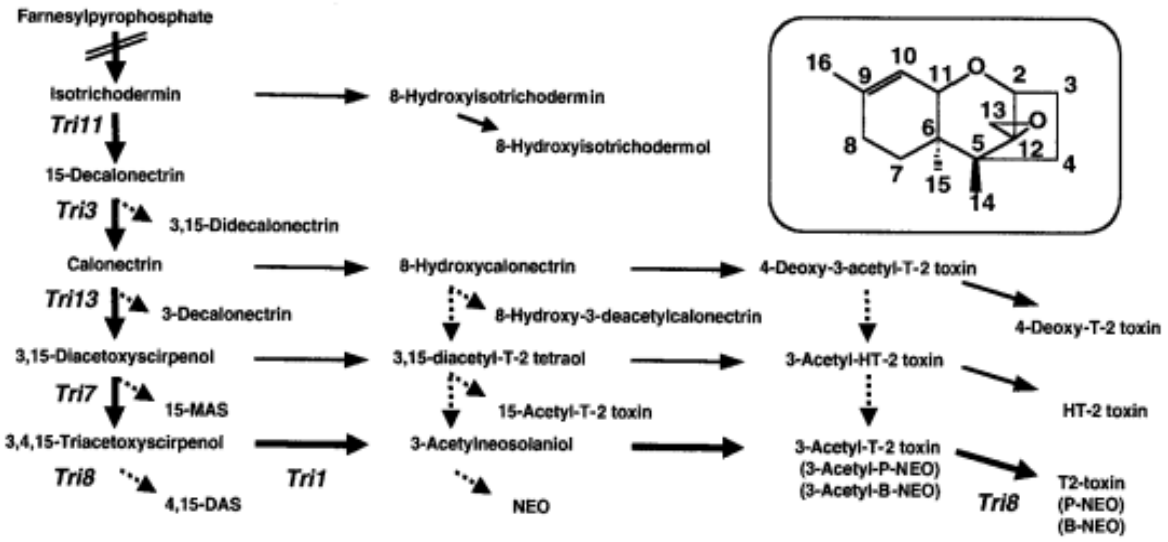

Figure 3. Biosynthesis of T-2 (Meek *et al.*, 2003)

Toxicokinetics

T-2 toxin toxicity does not depending on metabolic activation (Wannemacher and Wiener, 1997). It is readily metabolized by mammalian gut microflora to several metabolites, and it is rapidly absorbed after ingestion in most animal species and it is distributed in the organism with little or no accumulation in any specific organ or tissue (WHO, 1990; SCF, 2001). T-2

Tri10 acts upstream of the cluster encoded transcription factor TRI6 is necessary for full expression of both the other trichothecene genes and the genes for the primary metabolic pathway that precedes the trichothecene biosynthetic pathway, as well as for wild-type levels of trichothecene self-protection. We further suggest the presence of a regulatory loop where Tri6 is not required for the transcription of Tri10 but is required to limit the expression of Tri10 (Figure 3).

Occurrence of T-2 mycotoxin

In united kingdom (UK) from the period of 2001-2005 T-2 toxin occurrence was reported in wheat, barley and oats by Edwards (2009a,b,c).A total of 289 samples of wheat products (n=130), oat products (n = 98) and rye products (n=61) were identified in grain-milling factories in Germany (Gottschalk *et al*., 2009). T-2 toxin analysis was undertaken in Spanish with 75 wheat-based bread and 75 pasta samples, 27 wheat flakes, 71 maize snacks ,72 sweet corn. The maximum concentration of T-2 toxin found were 67.9µg/kg in wheat based bread, 4.9 µg/kg in pasta, 70 µg/kg maize snacks and 256 µg/kg in sweet corn (Gonzáles-Osnaya *et al*., 2011, Cano-Sancho *et al*., 2011). In Europeon origin T-2 toxin was detected by nearly in 40% of cereal samples The highest concentrations were found in maize (mean concentration 0.8 µg/kg and maximum concentration 8.4 µg/kg) and in oats or oat-based products (mean concentration 34 µg/kg and maximum concentration 266 µg/kg) this was reported by Biselli and Hummert (2005).

Under the project of Scientific Cooperation(SCOOP) eight European countries collected 3,490 samples for the detection of T-2 toxin of all the samples, 20% were positive, estimated intakes of T-2 toxins in the European diet is described in Table 1. The maximum concentration found were 2-160 µg/kg in Denmark, 1.7- 280 µg/kg in Finland, France, Italy, Norway and in Portugal (Schothorst and van Egmond, 2004). Intake of T-2 from grains in Norway is described in Table 2.

Toxicity of T-2 mycotoxin

Acute toxicity

Acute effects of T-2 toxin were previously considered by the JECFA (FAO/WHO, 2001) and the SCF (SCF, 2001) concluding that T-2 toxin has acute toxicity. T-2 toxin has acute toxicity, with oral exposure to 0.06 - 10 mg/kg bw in various species. The effects observed include non-specific symptoms like weight loss, feed refusal, dermatitis, vomiting , diarrhoea, haemorrhages and necrosis of the epithelium of stomach and intestine, bone marrow, spleen, testis and ovary in

Table 1. Estimated intakes of T-2 toxins in the European diet (WHO, 1985)

Toxin	Commodity	Weighted mean (µg/kg)	Consumption (g/person per day)	Intake			% total intake
				ng/person per day	µg/person per day	ng/kg bw per day	
T-2	Barley	4.6	20	91	0.09	1.5	20
	Maize	3.2	8.8	28	0.03	0.5	6
	Oats	21	2.0	42	0.04	0.7	2
	Rice	0.7	12	8	0.01	0.1	2
	Rye	0.2	1.5	0	0	0	0
	Wheat	1.6	180	280	0.28	4.7	63
	Total intake			450	0.45	7.6	100

Table 2. Intake of T-2 from grains in Norway (Norkost, 1997; Langseth, 2000)

Population group	Grain	Concentration of toxin (µg/kg	Body weight (kg)	Median consumption			95th percentile consumption		
				Grain (g/person per day)	Toxin intake		Grain (g/person per day)	Toxin intake	
					µg/person per day	µg/kg bw per day		µg/person per day	µg/kg bw per day
Males, females 6 years	Oats	21	23	6.2	0.13	0.006	26	0.54	0.02
	Rye	0.2	23	13	< 0.01	< 0.001	25	0.01	< 0.001
	Wheat	1.6	23	180	0.28	0.012	380	0.60	0.026
Males, females 10 years	Oats	21	35	8.2	0.17	0.0005	34	0.71	0.020
	Rye	0.2	35	16	< 0.01	< 0.001	32	0.01	< 0.001
	Wheat	1.6	35	230	0.37	0.010	490	0.79	0.022
Males 16–29 years	Oats	21	75	7.5	0.16	0.002	76	1.6	0.021
	Rye	0.2	75	15	< 0.01	< 0.001	31	0.01	< 0.001
	Wheat	1.6	75	280	0.44	0.006	700	1.1	0.015
Males 30–59 years	Oats	21	83	7.7	0.16	0.002	63	1.3	0.016
	Rye	0.2	83	14	< 0.01	< 0.001	28	0.01	< 0.001
	Wheat	1.6	83	240	0.38	0.005	570	0.91	0.011
Males 60–79 years	Oats	21	79	6.5	0.14	0.002	67	1.4	0.018
	Rye	0.2	79	13	< 0.01	< 0.001	25	0.01	< 0.001
	Wheat	1.6	79	190	0.31	0.004	720	1.2	0.015
Females 16–29 years	Oats	21	63	6.3	0.13	0.002	45	0.94	0.015
	Rye	0.2	63	11	< 0.01	< 0.001	19	< 0.01	< 0.001
	Wheat	1.6	63	190	0.31	0.005	440	0.71	0.011
Females 30–59 years	Oats	21	65	5.8	0.12	0.002	46	0.96	0.015
	Rye	0.2	65	10	< 0.01	< 0.001	18	< 0.01	< 0.001
	Wheat	1.6	65	170	0.28	0.004	390	0.62	0.010
Females 60–79 years	Oats	21	69	5.1	0.11	0.002	56	1.2	0.017
	Rye	0.2	69	10.0	< 0.01	< 0.001	17	< 0.01	< 0.001
	Wheat	1.6	69	160	0.25	0.004	360	0.58	0.008

cats, dogs, pigs and ducklings (WHO, 1990; IARC, 1993; Rafai *et al*., 1995a; Eriksen and Alexander, 1997). A primary target of toxicity is haematopoetic tissue i.a. in the bone marrow and toxicity of gastrointestinal epithelium it is observed in oral and parenteral exposure (DeNicola *et al*., 1978).T-2 toxin also disturb circulatory system and causes blood pressure and catecholamine elevation in pigs and rats (Bubien *et al*., 1989 and WHO, 1990). Due to the repeated exposure of T-2 toxin doses caused thickening of coronary arteries including myocardial changes. vacuolisation and swelling of endothelial cells, basement membrane changes and enlarged medial smooth muscle cellsthese symptoms was observed when 3mg of T-2 toxin/ kg bw injected to the rats (Yarom *et al*., 1986, 1987a,b).

Chronic toxicity

Dermal effects

T-2 toxin is a potent skin irritant it produces oedema, intradermal haemorrhage and necrosis of the skin. Individuals who were exposed to hay or hay dust contaminated with trichothecene-producing molds developed severe cutaneous irritations and working in large batches of fungal cultures from trichothecene-producing organisms, laboratory personnel suffered facial inflammation followed by desquamation of the skin and considerable local irritation. The hands of two laboratory workers were exposed to crude ethyl acetate extracts containing T-2 toxin (approximately 200 µg/ mL) when the extract accidently got inside their plastic gloves which causes skin irritation. Guinea pig is the most sensitive species. The effect on skin has been used as a biological assay for detection of trichothecenes. T-2 can be detected at 0.2 µg with a skin necrosis assay. The minimum effective amount needed to elicit irritation is much less. (reviewed in WHO, 1990). Hoerr FJ 2003 reported the depigmentation of the skin of the comb cyanosis and legs by inducing T-2 toxin and characterized it as necrohaemorrhagic dermatitis. 4 mg/kg to 16 mg/ kg of T-2 toxin causes the Very low feather quality and abnormal position of the wings were found in animal. kalantari H *et al*., 2004 reported that aloe vera and quince seed mucilage have the protective effect on dermal toxicity on rabbit skin. T-2 toxin-induced dermal toxicity in rabbit and its Healing effect by quince seed mucilage was reported by Hemmati, Ali Asghar, *et al*. (2012).

Immunotoxocity

The T-2 toxin target on immune system is bone marrow, lymph nodes, spleen, thymus and intestinal mucosa has been observed and it effects to both humoral and cellular immune resposes (FAO/WHO, 2001). T-2 toxin mostly immune toxic influence and T-cell mediated functions and delayed type hypersensitivity in experimental animals (Miller, 1986; Sharma, 1993). T-2 induces selective destruction of lymphoid progenitors (Holladay *et al*., 1993; Smith *et al*., 1994), inhibit IL-2 and IL-5 production by T-cells (Marin *et al*., 1996). T-2 toxin reduces MHC class II expression and directly induces antigen presentation (Blaylock *et al*., 1993). In addition it can destroy monocytes, granulocyte and erythrocyte colony forming cells (Parent *et al*., 1994; Rio *et al*., 1997) mainly by apoptosis (Ihara *et al*., 1997; Shinozuka *et al*., 1997). This is associated with hematopathological symptoms such as anaemia, leukopenia and bone marrow aplasia.

Neurotoxicity

Exposure of T-2 toxin changed the levels of neurotransmitters (dopamine, serotonin, tryptophan, 5-hydroxy-3 indoleacetic acid, 3,4-dihydroxyphenylacetic acid) in rat brain with 2-21 mg T-2 toxin /kg bw/day in diet (reviewed in WHO, 1990; MacDonald *et al*., 1988; Wang *et al*., 1993a). Apoptotic effect in fetal brain was observed in pregnant mice and rats which was exposed orally to 2-3 mg/kg b.w T-2 toxin (Ishigami *et al*., 1999, 2001; Sehata *et al*., 2003, 2004b). Exposure of T-2 toxin on mice to an LD50 dose of T-2 toxin, 5.94 mg/kg b.w. increases the ROS generation, lipid peroxidation, protein carbonyl content and changes the antioxidant enzymes in brain (Chaudary *et al*., 2010).

Genotoxicity

T-2 toxin was assayed in several invitro and invivo tests to check the genotoxicity. T-2 toxin does not showed the positive result in bacterial mutation assays. It produced single strand breaks in mouse lymphocytes, hepatocytes and Chromosomal damage was found in Chinese hamster V79 fibroblasts and human lymphocytes treated with T-2 toxin. Chromosomal aberration were also observed in Chinese hamster bone marrow after treatment with 1.7 mg/kg b.w. intra peretonialy in mice 0.1 mg/kg of feed. DNA single strand breaks were observed in mouse spleen and a weak effect was found in mouse thymus after intra peretonialy treatment (3 mg/kg b.w.) (FAO/WHO, 2001; SCF, 2001). In the earlier studies, DNA single strand breaks was seen invitro in spleen thymic lymphocytes and primary hepatocytes of BALB/c mice (FAO/WHO, 2001).

Haematotoxicity

T-2 toxin induced haematotoxicty in vitro and invivo has been reported by JECFA, FAO/WHO, 2001 and SCF, 2001. The effect of T-2 toxin on red cell, leukocyte and platelet progenitor cells from mice, rats and humans in vitro have been investigated to check the cell proliferation, differentiation and cytotoxicity. After the exposure of T-2 toxin it resulted that 0.05-50 ng/ml can induce the cell toxicity (Dugyala *et al*., 1994; Lautraite *et al*.,1995,1996; Rio *et al*., 1997).Human circulating blood cells are less sensitive to T-2 than other progenitor blood cells. Haematopoietic tissue invitro is a target of toxicity in several animal species such as mice, rats, cats, rabbits and guinea-pigs.A single intramuscular injection of 0.65 mg T-2/kg bw can cause transient leukocytosis, prolongation of prothrombin time and a decrease in coagulation factors in cynomolgus monkeys (Cosgriff *et al*., 1986). Rukmini *et al*. (1980) showed that in rhesus monkeys weighing 2-3 kg given T-2 toxin 1 mg / kg bw/day for four days in milk by stomach tube then they observed skin haemorrhages, respiratory Failure, lung congestion Severe leukopenia as well as a decrease in haemoglobin concentration and platelet count.

Reproductive toxicity

In 2001 the SCF considered that reproductive toxicity was not critical effects from T-2 toxin (SCF, 2001). A NOAEL of 0.45

mg/kg b.w. per day was identified for embryotoxicity or fetotoxicity for CD-1 mice fed for two generations. The similar conclusion of the JECFA in 2001 was that for T-2 toxin No embryotoxicity or gross fetal malformations were seen at i.p. doses below 0.5 mg/kg b.w. per day (FAO/WHO, 2001). SCF 2001 reported that due to the the treatment of pregnant mice with an oral dose of 3 mg/kg b.w. of T-2 toxin on day 11 of gestation Some apoptosis was seen in embryos.

Carcinogenicity

IARC (IARC, 1993), the JECFA (FAO/WHO, 2001) and the SFC (SCF, 2001) was assessed for T-2 toxin carcinogenic properties. The IARC concluded that there were no data available on the carcinogenicity to humans of T-2toxins and that there was limited evidence in experimental animals for the carcinogenicity of T-2 toxin. The latter was based on the study of Schiefer *et al*. (1987), in which CD-1 mice were fed a semi-synthetic diet containing 0, 1,5 or 3.0 mg/kg T-2 toxin, for 16 months observed pulmonary and hepatic adenomas. Forestomach papillomas occurred in 5/35 mice after oral treatment with 0.1 mg T-2 toxin per kg bw per day (75 treatments, 3 times a week for 25 weeks).(SCF, 2001; WHO, 2001; Yang and Xia, 1988a) T-2 toxin in doses of 2 or 5 mg/kg in rat investigated hepatocarcinogenic properties.

Conclusion

Mycotoxines are toxic substances which is produced from various fungal species and it causes toxicity to both human and animals in many countries. T-2 toxin is one of the compound produced by several Fusarium species. The T-2 toxin occurrence reported worldwide and predominant in tropical and subtropical regions. T-2 toxin production due to the environmental factors like moist condition in grains. T-2 toxin induced oxidative stress causing DNA damage, and it produces edema, intradermal haemorrhage and necrosis of the skin. The T-2 toxin make it as a potentially viable biological warfare agent. In Laos (1975-81), Kampuchea (1979-81), and Afghanistan (1979-81) T-2 toxin has been used as a military conflicts in to produce lethal and nonlethal casualties. In Laos, 1000 in Kampuchea, and 3000 in Afghanistan more than 6300 deaths in have been attributed to yellow rain exposure (75). As genotoxicity and cytotoxicity data indicate that T-2 toxin is highly toxic, and as it is widespread in cereals and food, additional research of its toxic potential in animals and in humans is necessary.

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