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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Lethality, time to death, histopathology, body temperature, food intake, body weights, and white blood counts were measured in male Fischer-344 rats before and after administration of T-2 toxin to rats by nasal, oral, dermal, and parenteral routes. Potency as measured by LD ₅₀ values (mg/kg) at 24 hr, from greatest to least, were intramuscular (0.47) > intranasal (0.56) > subcutaneous (0.58) > intravenous (1.17) > oral (2.29) > intraperitoneal (2.44) > dermal [in dimethylsulfoxide (DMSO)] (2.56) > dermal (in ethanol) (5.81 at 10 days). Mean			

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time to death (MTD) was less than 24 hr in all instances, except by dermal (in ethanol) exposure, which was nearly one (1) week. MTD changed little from lower to higher doses. At lower doses by the dermal (in ethanol) route, a minor increase in body temperature occurred, but at higher lethal doses by parenteral routes, hypothermia was the rule. Reduction in food intake was immediate and lasted for 4-5 days post T-2 exposure. By 15 days postexposure, body weights remained lower than controls, but the rate of weight gained had returned substantially toward normal. An initial increase in total white blood count occurred within hours, with subsequent reduction in neutrophil, lymphocyte, and platelet count by 48 hr. No change in hemoglobin or hematocrit occurred over 48 hr. Listlessness, ruffled fur, hyperexcitability to external stimuli, and diarrhea were regularly observed within hours of most routes of exposure and within days of dermal exposure (in ethanol). Histopathology demonstrated damage to a broad array of organs and tissues with marked changes in rapidly dividing cells, such as the intestine and lymphatic system, including the thymus. In conclusion, T-2 toxin by dermal and parenteral routes exerted changes in behavior (activity, food intake), body temperature, and hematologic parameters with substantial histologic evidence of toxicity to rapidly dividing cells. Onset of action was within hours and recovery occurred over weeks in surviving animals.

CLINICAL AND HEMATOLOGIC EFFECTS
OF T-2 TOXIN IN RATS

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David L. Bunner, Harold A. Neufeld, Lucas H. Brennecke,
Yvette G. Campbell, Richard E. Dinterman, and Joseph G. Pelosi



US Army Medical Research Institute of Infectious Diseases
Fort Detrick, Frederick, MD 21701-5011

Running Title: Effects of T-2 Toxin in Rats

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense.

Correspondence: Colonel David L. Bunner, M.D.
Chief, Pathophysiology Division
US Army Medical Research Institute of
Infectious Diseases
Fort Detrick
Frederick, Maryland 21701-5011
Phone: (301)663-7181

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Lethality, time to death, histopathology, body temperature, food intake, body weights, and white blood counts were measured in male Fischer-344 rats before and after administration of T-2 toxin to rats by nasal, oral, dermal, and parenteral routes. Potency as measured by LD₅₀ values (mg/kg) at 24 hr, from greatest to least, were intramuscular (0.47) > intranasal (0.56) > subcutaneous (0.58) > intravenous (1.17) > oral (2.29) > intraperitoneal (2.44) > dermal [in dimethylsulfoxide (DMSO)] (2.56) > dermal (in ethanol) (5.81 at 10 days). Mean time to death (MTD) was less than 24 hr in all instances, except by dermal (in ethanol) exposure, which was nearly one (1) week. MTD changed little from lower to higher doses. At lower doses by the dermal (in ethanol) route, a minor increase in body temperature occurred, but at higher lethal doses by parenteral routes, hypothermia was the rule. Reduction in food intake was immediate and lasted for 4-5 days post T-2 exposure. By 15 days postexposure, body weights remained lower than controls, but the rate of weight gained had returned substantially toward normal. An initial increase in total white blood count occurred within hours, with subsequent reduction in neutrophil, lymphocyte, and platelet count by 48 hr. No change in hemoglobin or hematocrit occurred over 48 hr. Listlessness, ruffled fur, hyperexcitability to external stimuli, and diarrhea were regularly observed within hours of most routes of exposure and within days of dermal exposure (in ethanol). Histopathology demonstrated damage to a broad array of organs and tissues with marked changes in rapidly dividing cells, such as the intestine and lymphatic system, including the thymus. In conclusion, T-2 toxin by dermal and parenteral routes exerted changes in behavior (activity, food intake), body

temperature, and hematologic parameters with substantial histologic evidence of toxicity to rapidly dividing cells. Onset of action was within hours and recovery occurred over weeks in surviving animals.

INTRODUCTION

In 1946, Brian and McCowan described significant problems with dermal reactions experienced by laboratory workers isolating a new group of fusarial toxins. This publication appeared during the peak (1942-1947) of reported problems with toxic alimentary aleukia in Russia, when over 10% of the population of Orenberg in the USSR, were fatally affected (Ueno, 1980). Bamburg (Bamburg et al., 1969) first reported T-2 toxin in 1968. Reports of bean hull poisoning (Ueno et al., 1972a) and discovery of T-2 in moldy corn (Hsu et al., 1972) were soon followed by evidence that T-2 was the likely agent of toxic alimentary aleukia (Ueno et al., 1972b). Trichothecenes again gained some notoriety when it was suggested that they were being used as warfare agents used in Southeast Asia (Haig, 1982).

There have been a number of studies documenting the chronic toxicity of T-2 (Hayes and Schiefer, 1980; Hsu et al., 1972; Kotsonis et al., 1975; Lutsky et al., 1978; Rukmini et al., 1980; Schoenthal et al., 1979). Most describe an illness related to bone marrow suppression and lymphatic injury with death frequently associated with sepsis. Chan, et al. (1984) reported data on lethality and biochemical changes in rats and rabbits after acute exposure.

The best known mechanism of action of T-2 is the inhibition of protein synthesis (Cannon et al., 1982; Rosenstein and LaFarge-Fayssinet, 1983; Thompson and Wannemacher, 1984; Wei et al., 1974), although effects on mitochondrial function have been suggested as well (Pace, 1983). Reports on human toxicity of another trichothecene, diacetyoxyscirpenol, came from trials

as an anticancer agent (Desimone et al., 1979; Diggs et al., 1978; Murphy et al., 1978; Yap et al., 1979) and documented the frequent occurrence of bone marrow injury, emesis, hypotension, and altered central nervous system function.

This study focused on acute toxicity after single dose administration of T-2 toxin in rats by oral, parenteral, dermal, and intranasal routes of administration. LD₅₀ data, mean time to death, food consumption, weight gain, body temperature changes, limited clinical observations, and hematologic effects were assessed.

METHODS

T-2 toxin: T-2 toxin was obtained from Calbiochem, (San Diego, Calif.), in a crystalline form at a purity of 99% as determined by thin layer chromatography and mass spectrometry.

Rats: Rats were male Fischer-344 strain obtained from Charles River, (Wilmington, Mass.) The rats weighed 150-175 g upon arrival and were kept until they weighed 200 g or more.

Study design. All rats, including the controls, were offered food ad lib both before and after toxin administration. At time 0, all groups were given the toxin or vehicle alone (control) by the following routes: im, iv, (dorsal penile vein), sc, ip, intranasal (in), oral (or) or dermal (derm). For the or, in, and iv routes, rats were anesthetized with xylazine hydrochloride, 5 mg/kg, and ketamine hydrochloride, 50 mg/kg. Dermal exposure used either dimethylsulfoxide (DMSO) or ethanol as the vehicle and was applied to a 1-cm² area of skin. Rats exposed by the derm route did not have barriers applied to prevent oral intake. Shaving, followed by use of a depilatory (Surgex, Cooper Lab, Geneva, Switzerland) preceded toxin application. Other routes used a

solution of water, ethanol, and glycerol in a 5:2:3 ratio in a total volume of 0.1 ml. Each time point for the white blood cell counts and platelet studies represented 6 animals, although less than 6 frequently remained in the treated groups because of deaths. Temperatures were taken with a digital rectal probe (Markson Model 565, Delmar, Calif.). Time points for collection of temperature, food consumption, and body weight data are noted on the graphics. After euthanasia of the rats in a CO₂ chamber, blood collection was collected from the open chest cavity with heparinized syringes. Time points for the blood collection were at 0, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and 48 hr. White blood counts and platelet counts were done by standard laboratory procedures by a Coulter Model ZBI (Coulter Electronics, Hialeah, Fla.) and a J.T. Baker Model MK4HC Particle Counter (Baker Instruments, Allentown, Penn).

LD₅₀ values were calculated by probit analysis (Finney 1971) by SAS computer program to evaluate lethality studies at multiple dosages.

RESULTS

Lethality: LD₅₀ values by all routes varied tenfold ranging from 0.47 mg/kg to 5.81 mg/kg. The highest potencies were seen by im, in, and sc routes, with intermediate potencies seen by iv, or, ip and derm (in DMSO) routes. The lowest potency was seen after dermal administration with ethanol as the solvent. (Table 1).

Time to death: Once lethal levels were reached, increasing doses made little if any difference in accelerating MTD (Table 2). By all routes except dermal in ethanol, MTD was consistently less than 24 hr (9-18 hr). Mean time to death after dermal exposure in ethanol was approximately 6 days.

Food consumption and body weight: Following dermal exposure, a prompt drop in food consumption was observed and remained near zero for 4 days, with

recovery over the next few days (Fig. 1). A similar but earlier response (not shown) was seen after parenteral exposure to T-2 toxin. Although the rate of weight gain had returned to near normal by 2 weeks postexposure, a catch up to normal weight had not occurred. Lower doses caused lesser weight losses and more transient periods of food refusal. At high doses with complete food refusal, the rate of weight loss was comparable to but not in excess of starvation.

Dermal effects: When T-2 in ethanol was applied to the depilated skin, erythema began in less than 24 hr, and full thickness necrosis resulted within 3 days after higher doses. If the animal survived, healing took place over several weeks. When T-2 in DMSO was applied, only mild erythema occurred. The rats behavior did not suggest any significant local discomfort; i.e., no rubbing, scratching, or chewing of lesions occurred.

Rectal temperature: Mild but definite increases in temperature occurred by several routes best exemplified by the dermal route (in ethanol) in Fig. 2. Doses of T-2 that proved to be lethal, induced hypothermia as can be seen in Fig. 3. Survivors, however, had only minimal reduction in temperature.

Clinical observations: Listlessness, ruffled fur, and hyperexcitability began within a few hours of parenteral administration and within a few days of dermal exposure in ethanol. Recovery took several days. No seizures were noted. Diarrhea began in 8-12 hr and resolved over several days.

Hematologic responses: Total white blood counts, as well as neutrophil and lymphocyte counts, generally increased during the first 12 hr but were more pronounced during certain experiments. Fig. 4 displays this response. Mild, but probably real reductions in lymphocyte and neutrophil counts were

ordinarily present at 48 hr. Platelet counts were modestly reduced as well by 48 hr in this species. No change in hemoglobin or hematocrit occurred over 48 hr.

Pathology: Regardless of the route of administration, systemic histopathologic lesions associated with T-2 toxin were similar, the most prominent being cellular necrosis of the most rapidly dividing cells of the gastrointestinal tract, and all lymphoid tissues. Local changes at sites of toxin injection were also characterized by necrosis of all cellular elements. The severity of the necrosis, both local and systemic, was dose-dependent.

Lymphoid necrosis, while observed in rats as early as 8 hr postinjection, was most severe in rats dying or killed in the 12-24 hr postinjection period. Lymphoid tissues showing the most severe changes were the gut-associated lymphoid tissues (G.A.L.T.) of the small and large intestines. Rats in low-dose groups tended to show necrosis principally in the center of the lymphoid nodules, while those in the higher dose groups showed a more uniformly severe necrosis of the nodules. There was diffuse necrosis of lymphocytes within the lamina propria of the intestinal mucosa. G.A.L.T. necrosis was not affected by route of toxin administration.

Splenic lymphoid necrosis was seen in both organized (white pulp) and free lymphocytes (red pulp). Like the G.A.L.T., centers of the lymphatic nodules appeared to be affected first in rats from lower dose groups. In higher dose groups, lymphocytes throughout the white pulp were necrotic. No reticular cells in either the red or the white pulp showed any necrosis.

Lymph nodes showed a similar pattern of lymphoid necrosis in that B-cell areas were more severely affected than T-cell areas, especially in the lower dose groups. Not all lymph nodes, however, were uniformly affected. While

lymph nodes within the peritoneal and thoracic cavity showed marked necrosis of lymphocytes, peripheral lymph nodes were less severely affected.

Lymphocytes comprising the thymus and bronchiole-associated lymphoid tissue (B.A.L.T.) showed marked lymphoid necrosis, but the lesions were usually less severe than those in the G.A.L.T., spleen, and mesenteric lymph nodes.

Severity of the intestinal, glandular, epithelium, necrosis was dose-dependent and varied with time of death. The earliest lesions were pyknosis and karyorrhexis of glandular cells, and often entire intestinal glands were necrotic, while overlying surface epithelial cells showed little or no change. In rats dying at 18-24 hr, a larger amount of surface epithelium was missing, probably due to the failure to replace the normal turnover of epithelial cells. Small and large intestinal necrosis was of equal severity. Although congested capillaries were not an uncommon finding, very little hemorrhage was present.

In the stomach, the areas of cell division within the gastric mucosa showed necrosis only in the highest doses by all routes. In those rats dosed via gastric tube, there was modest superficial necrosis and sloughing of the glandular mucosa and marked cellular swelling of the stratified squamous epithelial cells lining the non-glandular stomach.

Liver lesions were found in the higher dose groups by all routes of administration and consisted of randomly scattered, variably-sized foci of hepatocellular coagulative necrosis. Inflammatory cells were rarely found to be associated with these necrotic foci.

Renal lesions were mild, even in the high dose groups, and consisted of multifocal proximal tubular epithelial necrosis. Only a small percentage of the tubules were so affected. No glomerular changes were noted.

Local lesions were noted by all of the routes of toxin administration except ip and iv. By both sc and im injections, the severity of the lesions was dose-dependent and consisted of necrosis of all cellular and connective tissue elements in the immediate area, including small blood vessels. There was a resultant moderate amount of hemorrhage and edema. Intranasal administration resulted in nasal cavity changes, consisting of epithelial necrosis and sloughing, congestion and dilatation of submucosal venous sinuses, and marked hemorrhage.

DISCUSSION

Lethality: If one considers the actual amount and timing of absorbed toxin, the lethality of T-2 by routes tested are very comparable (Wannemacher et al., 1985). The relatively high LD₅₀ of T-2 in ethanol by the dermal route testifies to the slow absorption by this route in ethanol. As expected, this contrasts sharply to T-2 in DMSO by the dermal route, since we know that DMSO frequently helps accelerate absorption of medicinals. The use of depilatories can alter the skin as a barrier and may have contributed to the relatively low dermal LD₅₀. Neither was a physical barrier used to prevent oral ingestion in these early studies, which retrospectively may have made the lethality by dermal exposure nearer that for oral LD₅₀'s. Certainly the rats did exhibit some nasal irritation, probably from direct contamination by the T-2 applied to the skin and transferred by their grooming. Lethality by nasal instillation could have been due to local injury, since rats are obligate nasal breathers.

Mean time to death: By most routes the range of the time to death was relatively narrow, with high doses showing lethality in 8-10 hr. This was even true by dermal application in DMSO. Lower effective doses and lower mortality were associated at times with much later deaths. For example, after

dermal application in ethanol, deaths occurred as late as one week after initial exposure. The general appearance of the rats at the time of death, whether early or late, was quite similar, with listlessness, ruffled fur, and ultimately an inability to ambulate, at least suggesting that the nature of death was similar for both early and late deaths.

Food consumption and body weight: After higher doses within the LD₅₀ range, food consumption took 4-7 days to return to normal. Lower doses did, however, show a more transient decrease in food intake. The onset of the reduced food consumption was apparent within hours after parenteral administration. Desimone et al. (1979) found that, in human anticancer trials, diacetoxyscirpenol at 3 mg/m² (approximately 0.07 mg/kg) induced nearly universal nausea or vomiting. Clear documentation of how T-2 induces nausea or loss of appetite has not been accomplished, but a central origin is possible.

Rectal temperature: Hypothermia is an ominous sign in that it is associated with a high mortality and may be related to the onset of shock. Of some note, the human trials with diacetoxyscirpenol described fever as a very regular occurrence (Diggs et al., 1978). Lower doses, noted particularly by the dermal route in ethanol, induced low grade fever at times in rats as well. Whether this is mediated centrally by direct effects of T-2, or by indirect effects of vasomotor nature or mediator release is not known.

Dermal injury: The observation that T-2 in DMSO has almost no local toxicity when applied to skin, implies that the persistent local presence of T-2 is required for the responses of erythema, edema, and necrosis. An interesting contrast, though, is the apparent absence of cytolethality of T-2

in cell cultures (Thompson and Wannemacher, 1983). This finding suggests that T-2 does require a local host response of some sort to induce the abnormalities.

Systemic tissue injury: The mild suppression of lymphocytes and platelets combined with lymphatic and intestinal epithelial injury testify to the radiomimetic nature of T-2. The findings are also quite compatible with earlier published studies of subacute or chronic exposure to T-2 that cause severe bone marrow suppression and could easily be associated with lessened host resistance and resultant sepsis.

In conclusion, the acute toxicity of T-2 toxin helps to describe the role of T-2 in natural outbreaks of T-2 exposure in alimentary toxic aleukia and animal exposures with food refusal. Much information regarding the cellular and systemic pathophysiology is needed to improve our understanding of the nature of its in vivo toxicity. Although inhibition of protein synthesis is undoubtedly a principle action of T-2 toxin, its role in lethality and local tissue injury in vivo and the role of secondarily generated mediators needs to be clarified.

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LEGENDS

FIG. 1. Food consumption (g/day) and body weight (g) plotted over 15-day period after dermal (in ethanol) exposure to T-2 toxin.

0---0 (control)

●---● (2 mg/kg T-2)

■---■ (8mg/kg T-2)

FIG. 2. Rectal temperature over 10-day period after dermal exposure to 4 mg/kg T-2 toxin in ethanol (●---●) and control (0---0).

FIG. 3. Rectal temperature over 24-hr period after T-2 toxin by im route (0.55 mg/kg) control (0---0), all treated (■---■), survivors only (●---●), nonsurvivors (x---x).

FIG. 4. Total white blood cell, neutrophil, lymphocyte and platelet counts after 0.3 mg/kg T-2 toxin given im

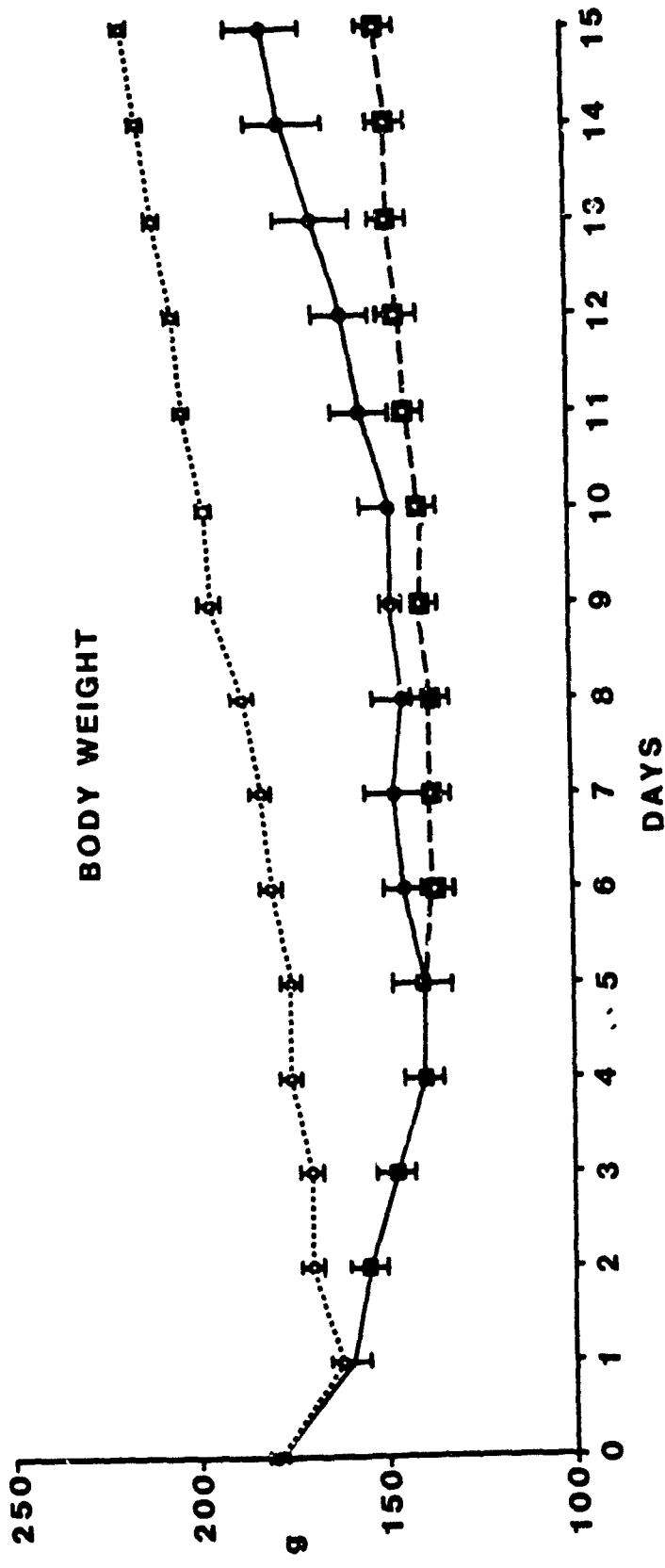
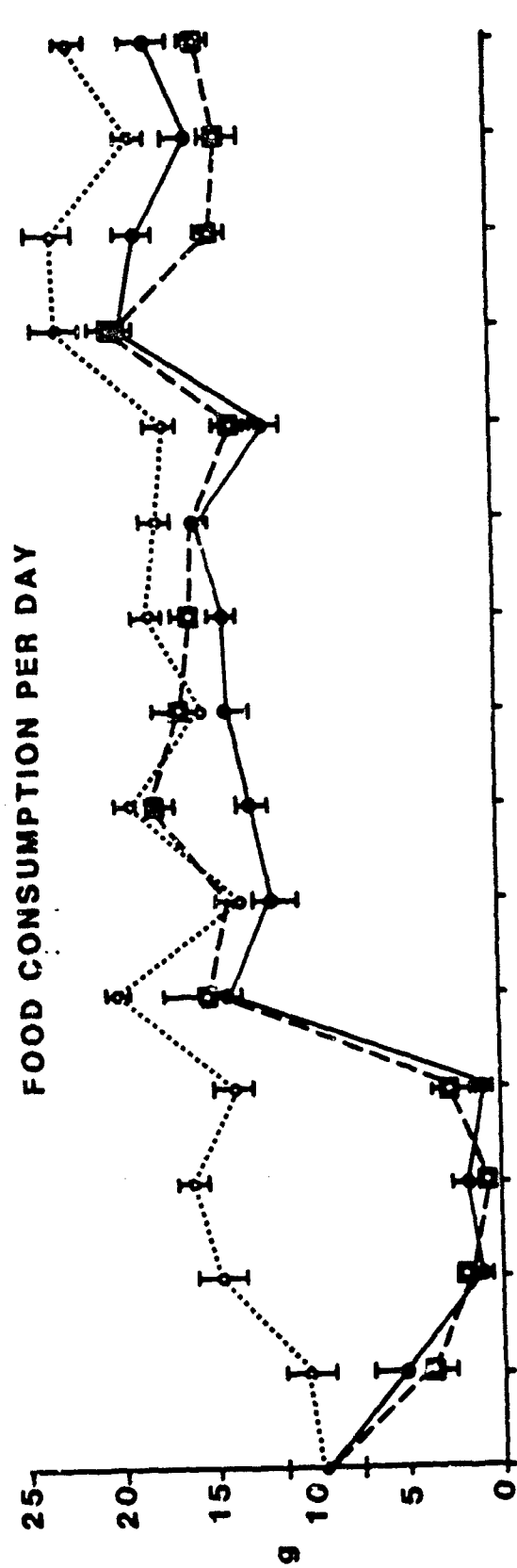
0---0 (control) ●---● (0.3 mg/kg T-2)

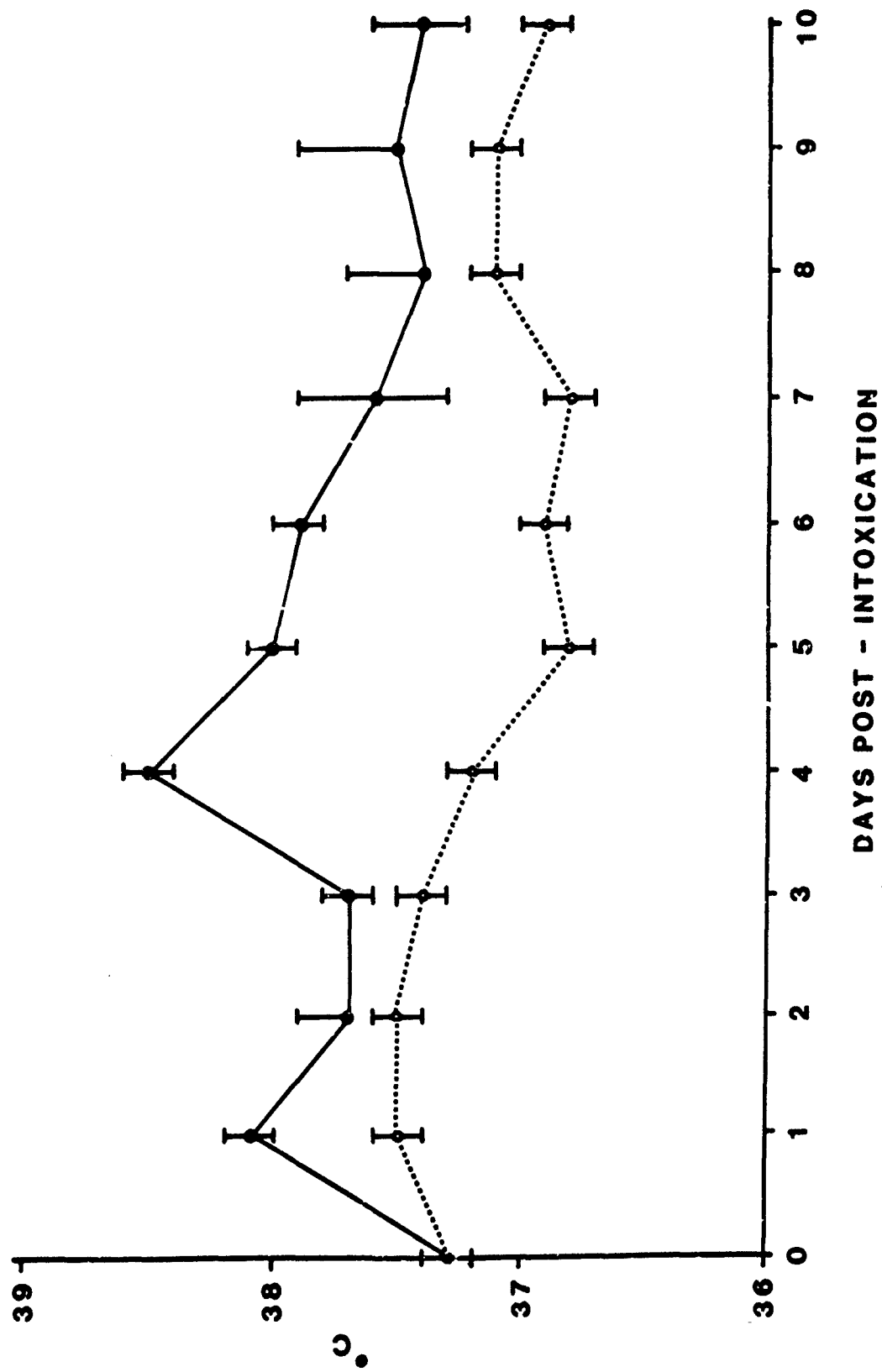
Table 1. LD₂₀, 50, 80 at 24 hr in mg/kg with 95%
confidence limits ()

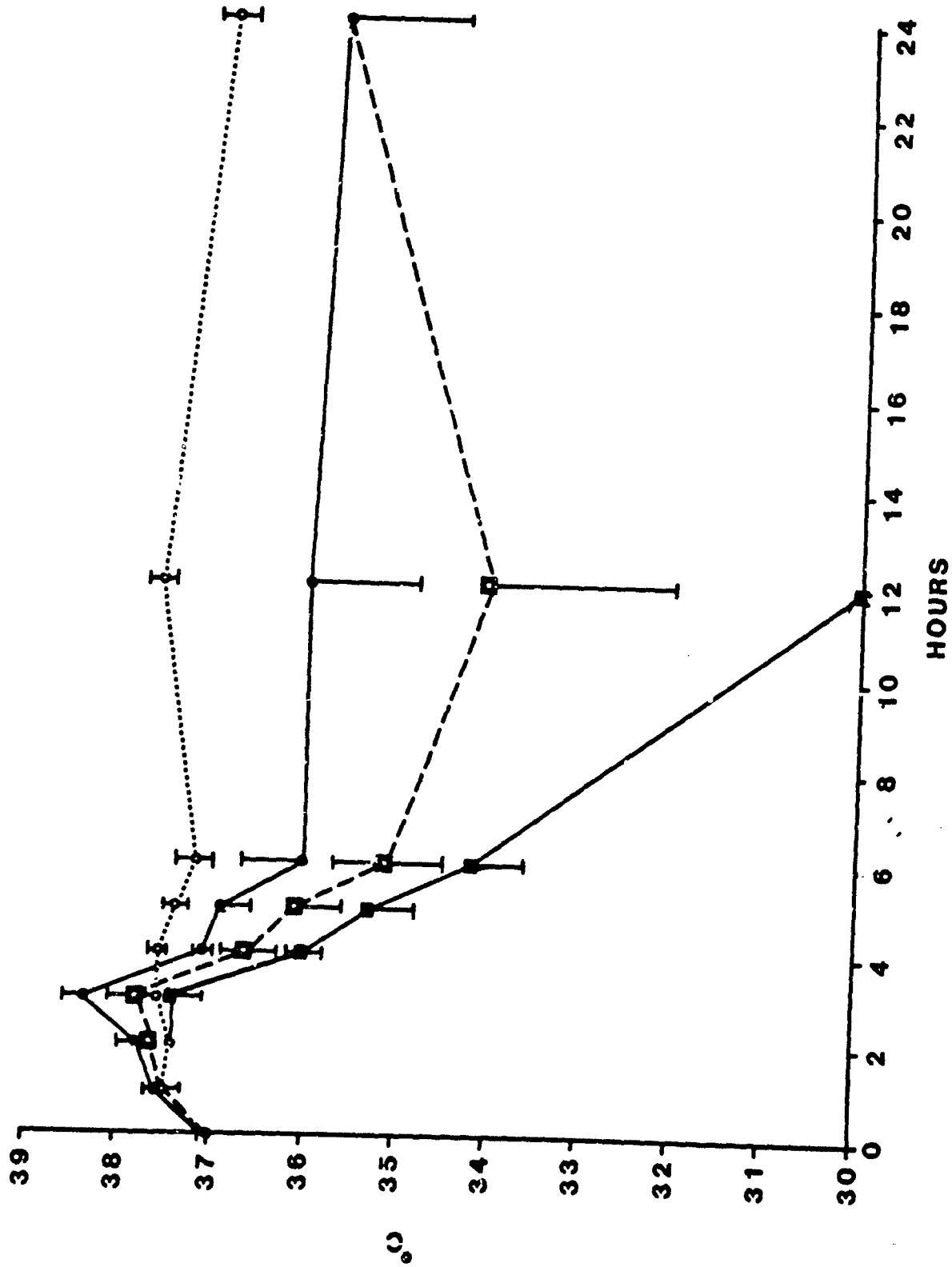
Route	Solvent	LD ₂₀	LD ₅₀	LD ₈₀
Intramuscular	Ethanol	0.38	0.47	.56
	(.22-.43)	(.40-.52)	(.51-.69)	
Intranasal	Ethanol	0.37	0.56	.74
	(.12-.48)	(.44-.65)	(.64-.94)	
Subcutaneous	Ethanol	0.45	0.58	0.71
	(.33-.52)	(.52-.65)	(.65-.83)	
Intravenous	Ethanol	0.98	1.17	1.36
	glycerol & water	(.79-1.12)	(1.05-1.47)	(1.20-1.93)
Oral	Ethanol	1.70	2.29	2.88
	(0.1-2.19)	(1.65-2.98)	(2.47-4.17)	
Intraperineal	Ethanol	1.65	2.44	3.23
	(.68-2.24)	(1.87-3.58)	(2.85-5.41)	
Dermal	DMSO	2.13	2.56	3.01
	(0.92-2.49)	(2.16-3.39)	(2.63-4.99)	
Dermal	Ethanol	3.61	5.81	8.02
	(Calculated at 10 days)	(.30-5.05)	(4.31-8.45)	(6.34-13.83)

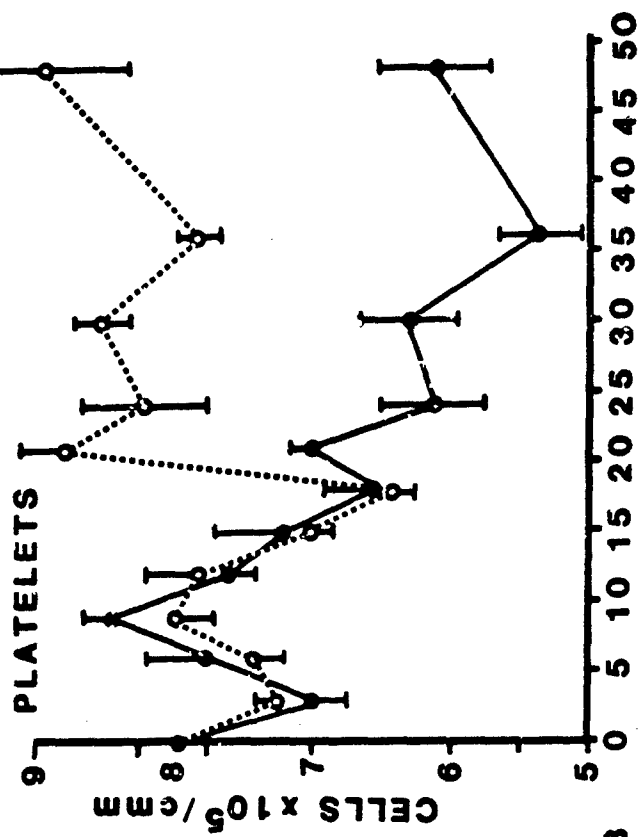
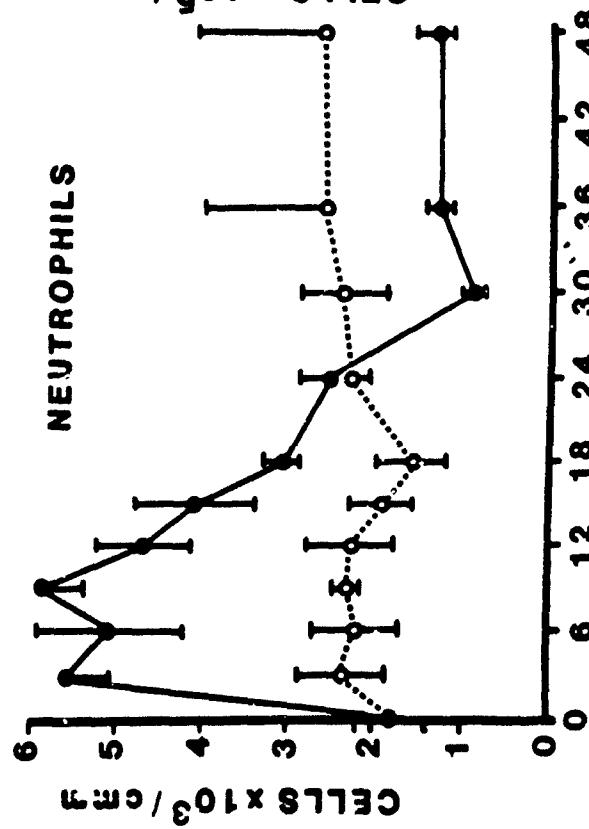
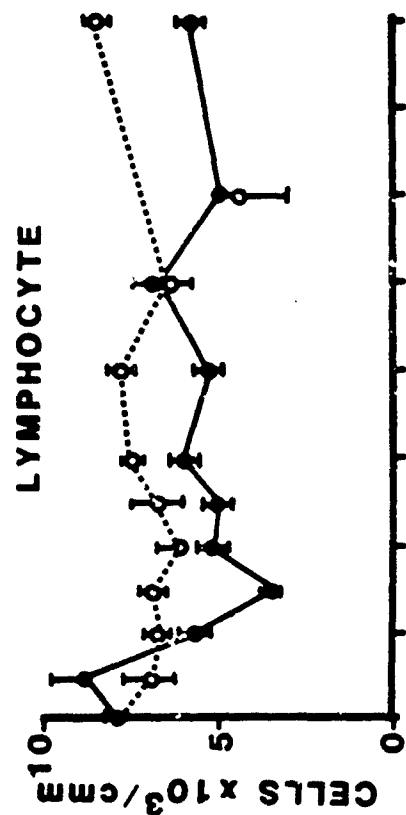
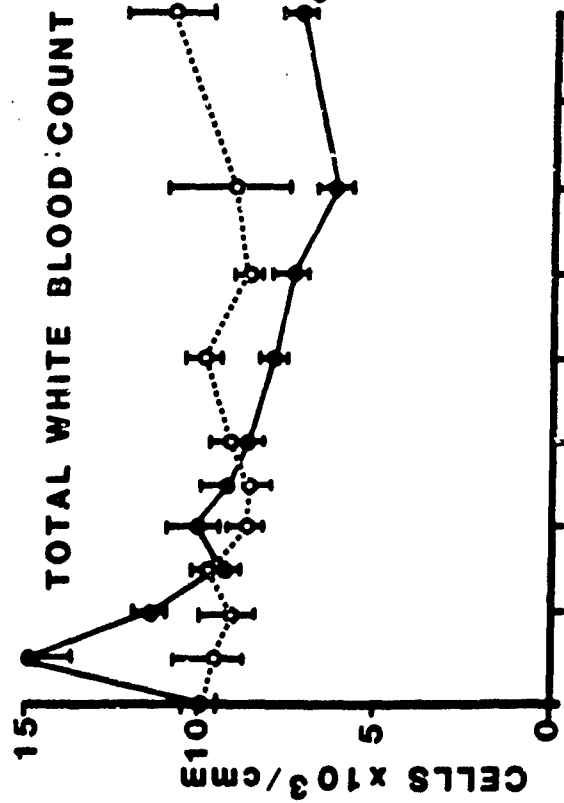
Table 2. Mean time to death after intramuscular T-2 toxin

T-2 toxin Dose, mg/kg	No. Deaths	Mean Time of Death, Hrs.		SEM
0.40	2/6	13.59	0.09	
0.50	5/6	11.19	0.86	
0.60	8/8	13.26	0.67	
0.70	8/8	11.15	0.58	
0.80	8/8	11.04	1.17	
0.94	8/8	13.00	0.21	
1.25	9/9	11.23	0.29	
1.89	10/10	10.38	0.42	
2.50	10/10	9.68	0.26	
3.13	8/8	11.33	0.29	









HOURS POST INOCULATION

END

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