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Comparison of Acute Oral Toxicity of Cannabinoids in Rats, Dogs and Monkeys[1,2]

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Comparison of Acute Oral Toxicity of Cannabinoids in Rats, Dogs and Monkeys. THOMPSON, G. R., ROSENKRANTZ, H., SCHAEPPI, U. H., AND BRAUDE, M. C. (1973). *Toxicol. Appl. Pharmacol.* **25**, 363–372. For preclinical toxicologic evaluation, Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-THC, and *Cannabis* extract were administered po to rats, dogs and monkeys as solutions in either absolute ethanol, sesame oil, or sesame oil with 2.5–9.0% ethanol. All three compounds were significantly more potent in female than in male Wistar-Lewis and Fischer rats. However, within the dosage range of 225–3600 mg/kg, Δ^9-THC and Δ^8-THC produced the same lethality, while both isomers were approximately twice as potent as the *Cannabis* extract. Death due to all three compounds consistently occurred between 36 and 72 hr after treatment regardless of the dose level or sex of the rats. Mortality in rats apparently resulted from severe hypothermia and other central effects. Toxicity was characterized by severe hypothermia, bradypnea, rapid weight loss, inactivity, wide stance, ataxia, muscle tremors, and prostration. Rats treated with equimolar amounts of tetrahydrocannabinol from the three compounds exhibited equivalent diversities and severities of clinical signs. In dogs and monkeys, single oral doses of Δ^9-THC and Δ^8-THC between 3000 and 9000/mg/kg were nonlethal. Predominant toxic signs in dogs included drowsiness, ataxia, prostration, anesthesia, tremors, mild hypothermia, salivation, emesis, and anorexia. Toxic signs in monkeys included hyperreactivity to stimuli, lethargy, drowsiness, characteristic huddled posture, slow movements, abnormal eating procedures and sedation. Histopathologic alterations did not occur in either dogs or monkeys.

Various forms of marihuana preparations have been used and abused for nearly 5000 years and presently may be consumed by 200 to 300 million people throughout the world (Grinspoon, 1969; Mechoulam, 1970; Rossi, 1970). Despite this historical and widespread use, attempts to define the mechanism of action and detrimental effects in animals and man have only recently been fruitful. Many of the pharmacologic and toxicologic data previously reported for marihuana were obtained in studies utilizing

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crude extracts obtained by a variety of procedures, or unnatural synthetic materials (Walton *et al.*, 1938; Adams, 1942; Adams *et al.*, 1945; Loewe, 1946; Wolstenholme and Knight, 1965). Consequently, comparison and evaluation of these data is difficult. Precise systematic delineation of toxicologic and pharmacologic effects has been possible only since the isolation and identification of Δ^9-THC as the major active component (Gaoni and Mechoulam, 1964) and Δ^8-THC as a minor active constituent in *Cannabis* (Hively *et al.*, 1966). At equivalent doses, other cannabinoids are psychotomimetically inactive (Mechoulam, 1970; Mechoulam *et al.*, 1970). The acute and subacute toxicities of Δ^9-THC administered to rodents were only recently reported (Phillips *et al.*, 1971a,b; Dewey *et al.*, 1972), as was the acute toxicity induced by Δ^8-THC (Thompson *et al.*, 1971a; Dewey *et al.*, 1972). The present study compares the acute oral toxicity of Δ^9-tetrahydrocannabinol (Δ^9-THC) and Δ^8-THC to that of a crude marihuana extract (CME) in three phylogenetically different species (rats, dogs, and monkeys). In addition, the acute toxicity of Δ^9-THC was determined in two rat strains to evaluate strain differences in susceptibility.

METHODS

All rats used in these studies were housed 2 or 3 per galvanized steel cage (10 × 7 × 7 in.), 60 cages per rack, with both food and water available ad libitum. Pilot mortality studies with Δ^9-THC administered orally were performed with young adult Wistar-Lewis rats (Batelle Memorial) approximately 150 g each and 6–8 weeks old. These animals received single injections of 1.0 ml/100 g body weight with the compound dissolved in a solution of 10% ethanol in sesame oil. Five to 10 male or female rats per dose level received 225–1800 mg/kg with the doses spaced at a log interval of 0.3. In subsequent studies, male and female Fischer rats (Charles River, approximately 100 g and 6 weeks old) were randomly divided into groups of 10 rats each for treatment and orally intubated with Δ^9- or Δ^8-THC dissolved in 2.5–9.0% ethanol in sesame oil, or Δ^9-THC or CME dissolved in 100% sesame oil.[6] The ethanol was initially included in the vehicle to facilitate solubilization of the cannabinoids, but improved techniques eventually allowed use of only sesame oil as the vehicle (Rosenkrantz *et al.*, 1972). The doses for Δ^9- and Δ^8-THC in Fischer rats ranged from 225 to 3600 mg/kg and for CME they ranged from 625 to 7500 mg/kg. The CME dosages were 3-fold greater to account for the approximate 30% cannabinoid content of CME. Injected volumes in Fischer rats ranged from 1.0 to 2.0 ml/100 g. In all cases, control rats were similarly treated with the maximum volume of vehicle administered to drug-treated rats.

All rats were checked at least twice each day throughout the 7-day observation period to see whether mortality had occurred. Statistical evaluation of median lethal doses (LD50) was performed by the method of Litchfield and Wilcoxon (1949). In addition, physiological and behavioral changes were recorded daily.

Rhesus monkeys (2.7–4.7 kg and 2.5–3.5 years old) and beagle dogs (6–13 kg and 7–10 months old) were housed individually in galvanized steel cages. Monkeys were fed Purina monkey biscuits supplemented with apples twice each day, while dogs received Kibbled Biscuits (Mother Hubbard) supplemented with canned beef once

[6] All three compounds used in these studies were graciously supplied by Dr. John A. Scigliano, National Institute of Mental Health, and stored at −10°C under nitrogen.

each day. Water was available ad libitum to all animals. Ambient temperature in the dog and monkey quarters was maintained between 23 and 26°C. Both dogs and monkeys were conditioned to the laboratory environment for at least 4 weeks prior to clearance for treatment with single doses of 65.6 (dogs only), 131.3, 262.5, 525, 1050 (monkeys only) or 2000 mg/kg Δ^9-THC or Δ^8-THC, or 5000 mg/kg CME. One female and 1 male in each species was treated at each dose level. The compounds were administered as solutions in 9% ethanol in sesame oil or in absolute ethanol, and injection volumes ranged from 0.5 to 3.0 ml/kg. All animals were given the drug by intubation with a No. 20 French catheter. Prior to withdrawal, the catheter was flushed with 3.0 ml of sesame oil which was sufficient to displace the total volume of the tubing. Immediately after treatment, each animal was returned to its cage and subsequent observations for behavioral changes or any other signs were made at 15-min intervals for the duration of the treatment day and daily thereafter for 7 days.

RESULTS

Acute Toxicity in Rats

LD50 values for rats treated orally with single doses of Δ^9-THC, Δ^8-THC or CME and observed for 7 days are compared in Table 1. The LD50 values for female rats were consistently lower than those for the corresponding male groups; significant sex differences ($p < 0.05$) were observed for rats treated with Δ^9- and Δ^8-THC administered as solutions in 2.5% ethanol in sesame oil or CME dissolved in sesame oil. The LD50 values for Wistar-Lewis rats were consistently less than those observed in Fischer rats treated with Δ^9-THC of similar purity and formulation. However, only the male

TABLE 1

7-DAY MEDIAN LETHAL DOSE VALUES FOR Δ^9-THC, Δ^8-THC AND CME ADMINISTERED ORALLY TO RATS

Compound	% Purity	Vehicle	Rat strain	LD50[a] Male	LD50[a] Female
Δ^9-THC	90%	2.5% EtOH in SO	Wistar-Lewis	1160 (850–1580)[b]	860 (640–1160)
	90%	2.5% EtOH in SO	Fischer	1910 (1390–2680)	1040 (820–1320)
	96%	Sesame oil	Fischer	1015[b] (780–1320)	800 (630–1010)
Δ^8-THC	99%	2.5% EtOH in SO	Fischer	1980 (1580–2470)	860 (680–1090)
CME	as defined[c]	Sesame oil	Fischer	3300 (2480–4390)	1380 (950–2020)

[a] Method of Litchfield and Wilcoxon. Slopes of all lines did not deviate significantly from parallelism ($p < 0.05$).

[b] 95% confidence interval.

[c] CME contained 25–32% Δ^9-THC, 2% Δ^8-THC, 2.9% cannabidiol, 3.5% cannabinol and 4% ethanol.

Wistar-Lewis rats exhibited significantly different mortality values ($p < 0.05$). Median lethal doses in Fischer rats treated with Δ^9-THC dissolved in sesame oil were also consistently less than those obtained when the compound was dissolved in 2.5% ethanol in sesame oil, but this apparent potency difference probably resulted from the different purity values for the two Δ^9-THC lots used in these formulations. Comparison of lethal potencies for the three compounds indicated that Δ^9- and Δ^8-THC administered in 2.5% ethanol in sesame oil were equipotent, but the purity of Δ^8-THC was approximately 9% greater than the purity of Δ^9-THC. The purest Δ^9-THC was significantly more potent in male Fischer rats than was Δ^8-THC, but female rats were equally affected by both agents. CME was significantly less potent on a mg/kg basis than both Δ^9- and Δ^8-THC, but the potencies of all three compounds were approximately equivalent on the basis of tetrahydrocannabinol content.

The temporal pattern of rat deaths indicated that all three compounds induced mortalities by similar mechanisms since nearly all deaths occurred during the interval 36–72 hr after treatment (Table 2). Of 373 total deaths in male and female Wistar-Lewis and Fischer rats treated with Δ^9-THC, Δ^8-THC or CME administered in 2.5–9% ethanol in sesame oil or sesame oil alone, 353 mortalities (95%) occurred 36–72 hr after treatment. None of the vehicle control rats died. Therefore, despite the sex-related *potency* differences for all three compounds and the strain potency difference observed for Δ^9-THC, the *temporal* pattern of mortality in rats was not sex-related and was not affected by the rat strain, compound or vehicle.

TABLE 2

TEMPORAL PATTERN OF RAT MORTALITY AFTER ORAL ADMINISTRATION OF Δ^9-THC, Δ^8-THC AND CME[a]

		Day in study						
Compound	Sex	1	2	3	4	5	6	7
Δ^9-THC	M	0	48	26	5	1	1	1
	F	1	71	22	4	0	0	0
Δ^8-THC	M	1	38	19	1	0	0	0
	F	1	59	20	2	0	0	0
CME	M	0	20	1	0	0	0	0
	F	2	29	0	0	0	0	0
Total deaths		5	265	88	12	1	1	1

[a] Includes all rat deaths regardless of vehicle, dose or rat strain.

Comparison of the temporal mortality pattern with changes in body weight, rectal temperature and respiratory rate indicated that rat mortality was apparently related to the severe hypothermia and other central effects (Fig. 1). Body weights in rats that succumbed to treatment and in rats that survived decreased approximately 10%, probably as a result of anorexia, but both groups gradually recovered to pretreatment weight values and the recovery phase in rats that eventually died commenced during the interval of maximum mortality. Respiratory rates were most severely affected by

treatment and decreased from a pretreatment mean of 175/min to a minimum of 68/min for rats that eventually died and 104/min for the survivors. However, maximal bradypnea in both groups occurred 3 hr post-treatment with progressive recovery thereafter. Respiratory rates in eventual survivors were normal by 48 hr post-treatment, the time of maximum mortality, while respiratory rates were still decreased by 30% at this time in rats that eventually succumbed to treatment. Hypothermia in survivors was also maximal at 3 hr post-treatment and rectal temperatures in these rats were normal

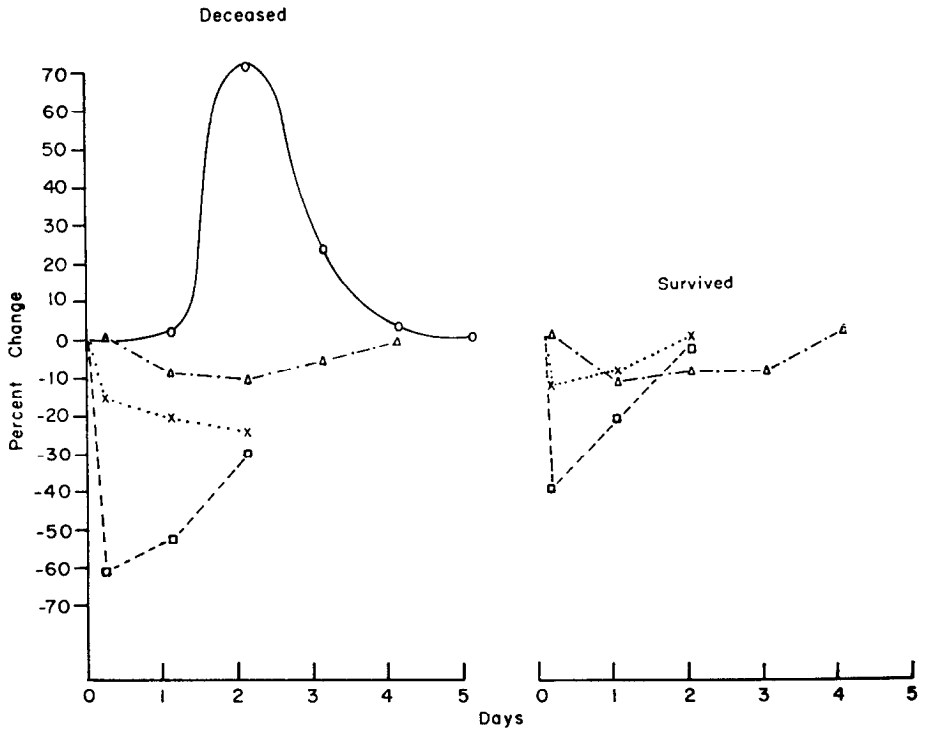

FIG. 1. Comparison of temporal patterns for mortality and physiological changes in rats treated orally with Δ^9-THC, Δ^8-THC and CME. Each point represents a mean for at least 13–237 individual rats and includes all rats regardless of compound, dose, vehicle, rat strain, or sex. ○——○, Deaths; ×···×, rectal temperature; □---□, respiration rate; △-·-·-·-△, body weight.

at 48 hr. In rats that succumbed to treatment, however, mean rectal temperatures progressively decreased from 37.7 to 28.6°C by 48 hr post-treatment which coincided with the peak of the incidence of mortality. Fifty percent of the rats that eventually died exhibited rectal temperatures between 26 and 28°C in an ambient environment that was 23–26°C.[7]

Additional clinical changes in rats were generally of low incidence and minor significance. Within 15 min after treatment with any of the compounds, rats commenced

[7] Sofia reported in an article that was published subsequent to the acceptance of this manuscript (*Eur. J. Pharmacol.* **2**, 139–142, 1972), that mice treated ip with Δ^9-THC and housed individually exhibited a greater incidence of mortality than did mice that were housed in aggregates. His observations could be explained by accentuated hypothermia in mice housed individually.

frequent urination; lacrimation and dose-related weight loss were evident 24 hr post-treatment. Maximal body weight loss in Wistar-Lewis rats (15%) occurred at 24 hr while Fischer rats exhibited a maximum loss (20%) at 48 hr post-treatment. The severity of weight loss followed a pattern $\Delta^9 > \text{CME} > \Delta^8$ and recovery was completed by day 6 for all three compounds.

Behavioral changes in rats were similar for all three compounds and consistently indicated depression. Typically, depression in rats progressed from inactivity to prostration and death if intoxication was sufficiently severe. Prostrate rats seldom lost their righting reflex and could frequently be aroused by tactile and auditory stimulation. Nearly all treated rats exhibited a peculiar tendency to assume a wide stance with all four limbs abnormally spread and firmly grasped the cage floor when handled. The behavioral sequence in rats treated with Δ^9-THC, Δ^8-THC or CME was unaffected by the rat strain or dosage. However, as the dose was increased the onset of initial behavioral changes was decreased, the duration of effect was increased and a greater percentage of rats exhibited the more severe behavioral changes. In addition, female rats showed a slightly faster onset of behavioral effects than did male rats. Depressant signs persisted for 5 days after single oral treatment of rats.

Preliminary histopathologic evaluation of tissues from a few rats treated with large doses revealed that most lesions were only mild or moderate in severity regardless of the compound (Table 3). Major organs were generally unaffected, and this probably contributed to the low level of toxicity in this species.

TABLE 3

SUMMARY OF HISTOPATHOLOGIC CHANGES OBSERVED IN FISCHER RATS TREATED WITH SINGLE ORAL DOSES OF Δ^9-THC, Δ^8-THC OR CME

Compound	Δ^9-THC	Δ^8-THC	CME
Dose (mg/kg)	3600	2700	5400
No. animals	5	3	2
Spleen, hypocellularity	++[a]	++	+
Lung, congestion	++	+	
pneumonitis	++		
Thymus, congestion	++	+	
hemorrhage	+++	++	
Adrenal, congestion		++	

[a] Severity rating: (+) slight, borderline control; + mild; ++ moderate; +++ severe; ++++ very severe, (maximal).

Acute Toxicity in Beagles

Mortality resulting from systemic toxicity was not observed in dogs treated orally with 65.6 to 3000 mg/kg Δ^9- or Δ^8-THC except for 1 of 3 dogs treated with 525 mg/kg Δ^9-THC that succumbed 45 min after treatment as a result of compound aspiration and subsequent respiratory arrest. In addition, 1 dog treated with 5000 mg/kg CME died 15 min after treatment also as a result of compound aspiration. Histopathologic changes in both deceased dogs were restricted to hemorrhagic edema in the lungs, and

compound was observed in the bronchial tree of both animals. Consequently, these deaths were not attributed to systemic intoxication.

Clinical changes in dogs were most prominent in those animals treated with Δ^9-THC, A 50% incidence of mydriasis and a 67% incidence of salivation were the initial clinical changes induced by Δ^9-THC within 20 and 60 min, respectively, but these effects did not occur in dogs treated with Δ^8-THC or CME. Emesis and vocalization occurred between 1 and 14 hr after treatment in 7/12 dogs treated with Δ^9-THC, 2/8 dogs treated with Δ^8-THC and 1/1 dog treated with CME. Anorexia was observed 18–24 hr after treatment only in 4/12 dogs treated with Δ^9-THC. Only one-third of all treated dogs exhibited rectal temperatures that were less than 38°C as compared to a mean control value for 20 dogs of 38.3 $\pm$ 0.1 (SE).

The sequence of behavioral changes in dogs was similar for all three compounds and indicative of depression. Depression in dogs generally paralleled the initial effects in rats, but anesthesia, tremors, muscle spasms and clonic-tonic convulsions with opisthotonos occurred in 25–40% of the prostrate dogs. The incidences of prostration and tremors were greater in dogs treated with Δ^8-THC, but convulsions were most prevalent after treatment with Δ^9-THC. Despite the severity of these behavioral effects, all dogs recovered within 24 hr after a single oral dose except for the 2 that died as a result of compound aspiration.

Only 1 dog, treated with a single dose of 3000 mg/kg Δ^9-THC, was examined for histopathologic alterations, and no lesions were detected.

Acute Toxicity in Rhesus Monkeys

No deaths occurred in any of the 22 monkeys treated orally with 131.3–3150 mg/kg Δ^9- or Δ^8-THC or with 5000 mg/kg CME. In addition, clinical observations were of minor significance. Only 1 of 22 treated monkeys was hypothermic and none of the monkeys became prostrate. Emesis and anorexia were the only other clinical signs observed, and these occurred only in 4/12 monkeys treated with Δ^9-THC and never occurred later than 24 hr post-treatment.

Behavioral changes in monkeys were similar for the three compounds and generally indicated depression. However, initially a small percentage of treated monkeys exhibited a relatively short period of hyperactivity, hyperreactivity to visual, auditory and tactile stimuli, and aggressiveness. This phase was then followed by a period of inactivity characterized by lethargy, lack of coordination, imbalance, drowsiness and/or a characteristic huddled posture. This specific posture was exhibited by more than 90% of the treated monkeys. In each case, the monkeys assumed a sitting position, often facing the back of their cages, and buried their faces in their hands or between their knees. While sitting in this manner, the monkeys seldom showed any normal behavioral activity; 3/12 monkeys treated with Δ^9-THC and sitting in this posture held food in their cheek pouches without mastication for 24–48 hr. Monkeys which were immobile and in the huddled posture reacted to external stimuli with exceptionally slow movements; recovery was generally complete within 2 to 4 days. Only 1 monkey, treated with 1050 mg/kg Δ^9-THC, was examined for histopathologic changes, and no lesions occurred in this animal.

In an attempt to determine a lethal dose for Δ^9-THC, 3 additional monkeys were treated orally with 6000, 7000 or 9000 mg/kg. The large volumes (60–80 ml) required

to administer these massive doses were subdivided into three aliquots and given at 15-min intervals. Similar treatment of a control monkey with 80 ml of 100% sesame oil did not induce clinical or behavioral changes. All 3 treated monkeys survived these massive doses, and behavioral changes were generally similar to effects previously described. However, the onset was more rapid (10 min) and the duration of effects was more persistent (120 hr). In addition, 9000 mg/kg induced generalized anesthesia at 19 hr after the initial treatment, and 8–10 ml of the formulation was lost via the anus. This material was not associated with feces and contributed to a marked oily residue on the haircoat. None of these monkeys exhibited gross pathologic alterations at necropsy.

DISCUSSION

The oral route was utilized in the present study because standardized inhalation procedures or a suitable vehicle for intravenous administration were not available, and because *Cannabis* is predominantly consumed by ingestion in most countries other than the United States (Grinspoon, 1969). Large doses were necessary to establish the minimum lethal oral dose in each species and to produce the maximum biological effects. Although lethality did not occur in dogs and monkeys, evaluation of the severity of effects in all three species indicated that Δ^9-THC, Δ^8-THC and CME were approximately equipotent when compared on the basis of tetrahydrocannabinol content.

The LD50 values for Δ^9-THC administered to two rat strains in the present study were somewhat larger than previously reported by Phillips *et al.* (1971a), and this discrepancy probably resulted from certain differences in the protocols. For example, the Δ^9-THC utilized in their study assayed at >99% purity while the maximum purity of our Δ^9-THC was 96%, and data in the present study indicated that small differences in compound purity resulted in considerable potency differences. In addition, the previous study used male Holtzman rats and potency differences for Wistar-Lewis and Fischer rat strains in our present study indicate that the greater sensitivity of Holtzman rats to Δ^9-THC may have resulted from a strain difference in absorption, distribution, biotransformation or excretion of the compound. The vehicle in the previous study was 10% Tween® 80 in saline. Wistar-Lewis rats treated orally with 3.0 ml/100 g of 10% Tween 80 in saline for 3 days exhibited severe toxic signs and mortality occurred (Rosenkrantz *et al.*, 1972). Even though this dosage was approximately three times the acute dose used in the previous mortality studies with Δ^9-THC, the possibility of potentiation or synergism between smaller doses of 10% Tween 80 in saline and Δ^9-THC should not be underestimated. A similar circumstance may surround the 2.5% ethanol–sesame oil vehicle used in the present study, but others have found that the higher the dose of Δ^9-THC, the greater the suppression of ethanolic effects (Forney, 1971). The influence of vehicle is accentuated when bovine serum albumin (BSA) is used as a suspending vehicle (Dewey *et al.*, 1972). The poor release of Δ^9-THC or Δ^8-THC from BSA resulted in an oral LD50 in male Sprague-Dawley rats that was >2000 mg/kg.

The temporal patterns of rat deaths also differed in various studies. Holtzman rats died between 10 and 36 hr after treatment (Phillips *et al.*, 1971a) while Sprague-Dawley

rats died between 72 and 120 hr after dosing (Dewey *et al.*, 1972). In the present study using Wistar-Lewis and Fischer rats, mortality consistently occurred between 36 and 72 hr after treatment. These slight differences probably resulted from differences in pharmacokinetics for the three vehicles. Nevertheless, all three studies indicate that relatively large doses of cannabinoids are required to induce rat lethality and there is a delay of 1 to 3 days before death occurs.

Maximal decrements in rectal temperatures of rats, dogs and monkeys correlated with the severity of toxicity in each species. Rats exhibited severe hypothermia, 50% of the animals that eventually died showing temperatures between 26° and 28°C. Only one-third of the treated dogs exhibited rectal temperatures that were less than 38°C. A few dogs exhibited protracted prostration, but none died from systemic toxicity. Hypothermia was present in only 1 of 22 treated monkeys, and none of the monkeys became prostrate or died. Therefore, the degree of hypothermia may serve as a useful indicator of the severity of intoxication with *Cannabis* derivatives.

Oral administration of cannabinoids to rats, dogs and monkeys consistently produced depression analogous to that observed previously in these and other species (Isbell *et al.*, 1967; Scheckel *et al.*, 1968; Irwin, 1969; Grunfeld and Edery, 1969; Phillips *et al.*, 1971a), and the sequence of behavioral changes in the present study was similar for all three compounds in each of the three species. The onset of behavioral signs consistently followed the pattern $\Delta^9 < \Delta^8 <$ CME, while the duration of effect followed a pattern of $\Delta^9 > \Delta^8 >$ CME. Furthermore, the time of onset was similar in all three species for a particular compound, but the duration of depression followed a pattern of rat > monkey > dog. Depression in all three species was manifested as inactivity, drowsiness and lack of coordination, but species-specific reactions were observed as previously described.

Thompson *et al.* (1971b) previously reported neurotoxicity in rats treated with Δ^9-THC, Δ^8-THC and CME for 119 days, and behavioral changes in the chronic studies differed substantially from effects observed in the present study. Depression predominated after acute treatments and for the first 7 to 10 days in the chronic study, but additional treatment with the three cannabinoids in the chronic toxicity studies produced hyperactivity, fighting, tremors and clonic convulsions. Consequently, acute toxicity studies did not predict the hyperactivity phase observed in chronic studies, but the similarity of responses for the three cannabinoids in the present study is in agreement with the similarity of effects for these compounds in the chronic studies. Therefore, both acute and chronic toxicity studies indicated that the biological activity of the crude marihuana extract resulted from the Δ^9- and Δ^8-THC contained therein as previously reported (Gaoni and Mechoulam, 1964; Hively *et al.*, 1966; Isbell *et al.*, 1967), and the potencies of the two active isomers were approximately equivalent.

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