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Behavioral Effects of Prolonged Administration of Δ^9-Tetrahydrocannabinol in the Rat

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Abstract. Rats treated chronically with Δ^9-tetrahydrocannabinol (THC, daily oral dose 20 mg/kg) were examined for residual effects on a variety of behaviors following a 1–4-month drug-free period. Learning a 12-arm radial maze and a differential reinforcement of low-rate responding (DRL-20) task was significantly retarded in THC-treated animals, although performance reached control levels by the end of testing. Learning two-way shuttle box avoidance was slightly facilitated in the drug-treated subjects. In open field tests THC-treated rats displayed an initial hypoactivity, followed by hyperactivity, but these changes were not significant. Most of the effects of THC resemble, but are weaker than those of chronic treatment with cannabis extract in a dose containing the same amount of THC. The findings are discussed in terms of the role of other constituents of cannabis that may add to, or potentiate the effects of THC itself.

Key words: Chronic THC – Learning – Activity – Rat – Shuttle box – Open field – Radial maze – DRL-20 operant behavior

Previous studies from our laboratory have shown that prolonged administration of a crude extract of *Cannabis sativa* to rats can produce a variety of behavioral changes that are demonstrable months after the end of the drug administration period. For example, rats that are intubated daily for 3 or 6 months with cannabis extract show hyperactivity in the open field (Stiglick and Kalant 1982b), facilitation of two-way shuttle-box avoidance (A. Stiglick, M. Llewellyn and H. Kalant, unpublished observations), and learning impairment on the Hebb-Williams maze (Fehr et al. 1976), radial-arm maze (Stiglick and Kalant 1982a) and a differential reinforcement of low-rate responding (DRL-20) bar-pressing task (Stiglick and Kalant 1982b). These effects are observed 1–6 months after the last intubation.

In all of our previous experiments the cannabis extract was adjusted to provide a dose of 20 mg/kg Δ^9-tetrahydrocannabinol (THC) with variable amounts of cannabinol (CBN), cannabidiol (CBD), and other constituents. THC is the major psychoactive component of natural cannabis material (Mechoulam 1970; Hollister 1974). However, other cannabinoids have been reported to enhance certain effects of THC (e.g., Fernandes et al. 1974). The purpose of the present study was, therefore, to investigate the residual effects of the same dose of THC (20 mg/kg), given for 3 months followed by a 1-month drug-free period, to determine whether the residual effects of cannabis extract are entirely attributable to THC content. THC-treated subjects were tested in the same procedures in which residual effects of cannabis extract had been demonstrated previously, i.e., the radial-arm maze, open field, and DRL-20. In addition, two-way shuttle-box avoidance learning was also studied, as in the unpublished studies with cannabis extract mentioned above, to define further the possible nature of the residual effects.

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Materials and Methods

The subjects were 33 male Wistar rats weighing 120–130 g (approximately 40 days of age) at the beginning of drug treatment. They were housed individually, exposed to a 12-h light-dark cycle (lights on 7 AM) and given free access to both food and water until they had attained a weight of 320–330 g. They were maintained at this weight by the procedure described by Stiglick and Kalant (1982a). The animals were always fed at the end of the day, following treatment or behavioral testing, to ensure that they were adequately motivated for tests involving food reward.

THC. An ethanolic solution of THC was obtained from the Department of National Health and Welfare, Ottawa. Gas-liquid chromatography analysis showed that the THC was 99% pure, containing negligible quantities of CBN and CBD. For intubation the ethanol was evaporated under reduced pressure at 40° C, and the residue was dissolved in olive oil to give a concentration of 10 mg THC/ml solution. The same supply of olive oil served as the control substance for vehicle-treated animals. New solutions were prepared from stock every 1–2 weeks.

Intubation Procedure. The rats were randomly assigned to either the THC group ($N = 17$), which received daily gavage at a dose of 20 mg THC/kg body weight, or the vehicle group ($N = 16$), which was given an equivalent volume of olive oil. All subjects received their respective treatments for 90 days, followed by a drug-free period of 34 days without tests. Subsequent behavioral tests were then conducted over the next 109 days using a testing schedule that was very similar to that used in previous experiments (Stiglick and Kalant 1982a, b).

Radial-Arm Maze Tests. The apparatus, procedure, dependent measures and statistical treatment have been described

previously for another experiment (Stiglick and Kalant 1982a, experiment 3). The apparatus consisted of a round centre platform elevated above the floor, with 12 radiating arms attached to it at equal distances from each other. Each arm contained a small well at the end that served as a food cup for a 45 mg Noyes pellet.

Testing was carried out between days 34–68 after the last intubation. On each test day a rat was introduced individually into the middle of the centre platform. Each test was terminated after 12 min or earlier when the animal obtained each of the 12 food pellets in the maze. Each animal was tested on Monday, Wednesday and Friday or on Tuesday, Thursday and Saturday for 5 weeks (15 sessions).

The mean numbers of 'correct' and 'error' scores on each test day were used as measures of learning ability. Correct responses were defined as the number of arms entered only once in the first 12 entries made. Erros were defined by the number of arms that a rat entered more than once. In addition, a criterion of 'almost perfect' performance was used as an overall measure of learning ability. An animal reached this criterion on the first day it achieved a correct score of 11/12.

The number of 'perseverative' responses and general activity levels were also assessed each day to determine if related changes in behavior were produced by the drug treatment (Stiglick and Kalant 1982a).

Open Field. The apparatus consisted of a roughly circular arena marked off into 19 equal hexagons (Stiglick and Kalant 1982b, for details of apparatus and procedures). For each test an animal was placed individually into the arena for exactly 7 min with a single Noyes pellet placed in the centre hexagon. The number of centre, inner and outer hexagons entered by the head and forepaws was counted for each minute from videotaped records. Each subject was tested twice in the open field at 77–80 days post-drug.

DRL-20 Tests. DRL tests were conducted in standard operant chambers (Stiglick and Kalant 1982b, for details of apparatus and procedures). Bar-pressing tests were carried out 92–120 days post-drug. After 1 day of 'magazine' training (day 1) and a continuous reinforcement (CRF) schedule (days 1–6), the subjects were run 7 days/week for 23 sessions on a DRL-20 schedule. Reinforcement was received only for the first bar press that followed a delay of at least 20 s after the previous response. A daily efficiency score [(number of pellets/number of responses) × 100] was calculated for each subject.

Shuttle-Box Avoidance Tests. The apparatus consisted of a Lehigh Valley Electronics (model 146-04) toggle-floor shuttle box (Fogelsville, PA, USA). Scrambled shock was delivered to either side of the chamber by a BRS Foringer (model SGS-001) shock generator-scrambler (Beltsville, MD, USA). A tone was generated from a point directly over the centre of the apparatus, either by a Mallory Sonalert (standard on the Lehigh Valley shuttle box), or by an Ashman Electronics (model 64-SP) tone generator (Greensville, Ontario, Canada), adjusted to an equivalent sound intensity at 2,000 cps. A cue light of 7.5 W was mounted on each end wall of the chamber.

Avoidance training was carried out 132–143 days post-drug. The subjects were tested 5 days a week until 10 days of data were collected. Each of the ten avoidance sessions consisted of 20 trials with an intertrial interval of 30 s. The conditioned stimulus (CS) was a compound of a light and tone presented together. The light stimulus was the onset of the cue light on the side of the chamber occupied by the subject at the beginning of each trial. The unconditioned stimulus (UCS) was a 0.6 mA shock, and the CS-UCS interval was 7.0 s. Both the CS and UCS stayed on until the animal avoided or escaped shock by going to the other ('safe') side of the apparatus, and then terminated simultaneously. An 'escape response' occurred whenever the subject received foot shock. An 'avoidance response' occurred whenever the subject moved to the safe side of the chamber during the CS-UCS interval, i.e. before the shock was delivered.

On test days 5–10 a metal barrier was put into the shuttle box to separate the two compartments. The barrier had an 8.0 cm diameter circle cut out to allow the subjects to move from one compartment to another. This barrier was introduced in an attempt to increase the disparity between the two groups of animals. Preliminary work with rats had shown that the barrier exaggerated the difference between slow and fast learners of this task. The barrier was also used because, without it, many animals were changing the test into a one-way active avoidance task, i.e. the rats were receiving the CS on only one side of the apparatus by moving back into the same compartment during the 30-s intertrial interval. Preliminary studies had shown that the barrier eliminated this problem.

On every avoidance session a PDP-11 computer (Digital Equipment Corporation, Ottawa, Canada) recorded the number of avoidance responses (out of a possible 20) and intertrial interval responses, and the mean latencies to avoid or escape for each subject.

Results

General Effects of THC. The initial effects of THC resembled those seen with cannabis extract in our earlier experiments and included squealing and urination on being handled, backward circling when placed on a flat surface and hunched posture with bulging eyes and piloerection. These effects appeared to wear off 3–4 h after THC intubation, versus 6–8 h after cannabis extract. After 2 weeks of daily treatment, these effects were markedly decreased: ataxia and sedation were not observed, and the THC animals were usually more active than controls.

The effect of THC on body weight was similar to the effect of cannabis extract reported previously (Stiglick and Kalant 1982a). Control rats gained weight more rapidly than THC-treated animals for the first 4–5 weeks of intubation, during which both groups had food continuously available (regression analysis $F = 226.63$, df 1,528, $P < 0.001$). Control subjects reached the criterion weight for food restriction by week 5, while THC subjects did so by week 8. Since food was restricted in both groups, for the duration of the experiment there was no difference in body weights between the two groups.

Radial-Arm Maze. Although no shaping was used in this study, all of the rats in both groups learned to run down the arms to obtain food. THC-treated and control rats showed the same latency to first entry into any arm of the maze on the first test day. However, five animals in the THC group, but only two rats in the vehicle group, could not be scored on that

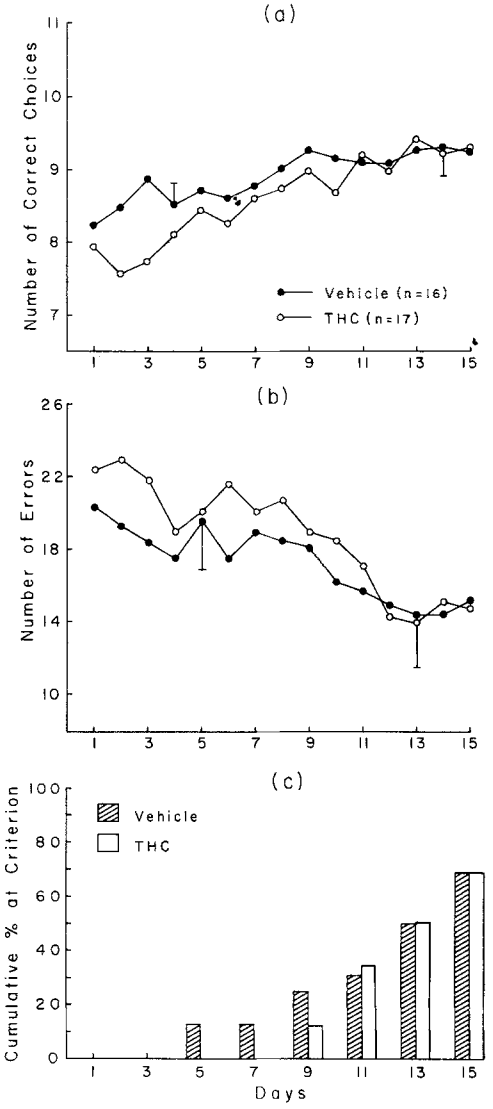

Fig. 1a–c. Acquisition of 12-arm radial maze performance by THC-treated and control rats. THC animals had received daily gavage during 3 months with a dose of 20 mg/kg in olive oil and controls received only olive oil. Tests began 34 days after the last gavage. **a** Correct performance scores on successive test days. The largest SEM for each group is shown. **b** Error scores (incorrect entries) on successive tests. **c** Cumulative percentage of each group attaining a criterion of one or more scores of 11/12 correct responses

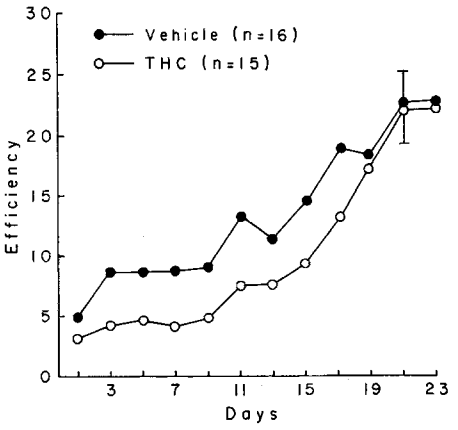

Fig. 2. Acquisition of DRL-20 performance by THC-treated and control rats following a 98-day drug-free period. Percent of responses reinforced (efficiency score) is calculated as [(number of pellets obtained/number of bar presses) × 100]

day since they failed to make at least 12 entries in the time allowed. Therefore data from day 1 were not included in the statistical analyses. After day 1, all animals in both groups consumed all pellets available in the maze sessions.

As shown in Fig. 1, prolonged THC administration slowed down the learning of the radial-arm maze. Analysis of variance revealed that subjects in the THC group initially made fewer correct entries (significant group- × -days interaction $F = 2.05$, df 13,403, $P < 0.02$), and more errors (significant group- × -days interaction $F = 1.82$, df 13,403, $P < 0.04$) than vehicle controls (Fig. 1a, b), but these differences disappeared by the last session. Tests of simple effects (Winer 1971) showed that the differences between the groups were confined to the first 11 days of testing (significant Student's t-test values 2.03 – 4.15, df 430 and 416 for correct and error scores respectively; $P < 0.05$ for all comparisons), after which there were no significant differences between the groups.

The initial slowness of learning of THC-treated rats was confirmed by the cumulative percentage of rats in each group that achieved at least one score of 11/12 on any test day. Figure 1c shows that a higher proportion of control animals reached this criterion initially, but that subjects in the THC group quickly reached the same level as the vehicle controls. This is reflected by a significant difference in slopes between the two groups ($F = 23.57$, df 1,17, $P < 0.001$) by regression analysis.

The occurrence of perseverative responding was not appreciably different between THC-treated (8.42% of total errors) and vehicle-treated (8.92%) subjects in this experiment. In addition, the two groups did not differ significantly in rate of entry into the arms.

Open Field. The THC-treated rats tended to display less activity than controls at the start of the session and more activity near the end of the session during both open field tests. However, analysis of variance revealed that these trends were not significant: there were no appreciable differences in either the number or type (inner, outer, centre) of hexagons crossed by subjects in each group.

DRL-20. All animals readily learned to bar press under the CRF schedule and no significant difference was found between the THC and vehicle groups over the 6 days of CRF training. However, as shown in Fig. 2, under the DRL-20 schedule the initial learning of the THC-treated rats was slower than that of vehicle controls (significant groups- × -days interaction $F = 2.10$, df 22,638, $P < 0.002$), even though the actual numbers of bar presses made were not significantly different in the two groups. Tests of simple effects revealed that the slower learning of THC-treated animals was confined to the first 13 days of testing ($t = 2.13 - 5.37$, df 57, $P < 0.05$ for all comparisons), after which the THC group reached the level of vehicle controls.

Shuttle Box. As measured by the mean number of daily avoidances (Fig. 3a), there was no difference between THC- and vehicle-treated animals during the first 4 days of testing without a barrier, although rats in the THC group showed a

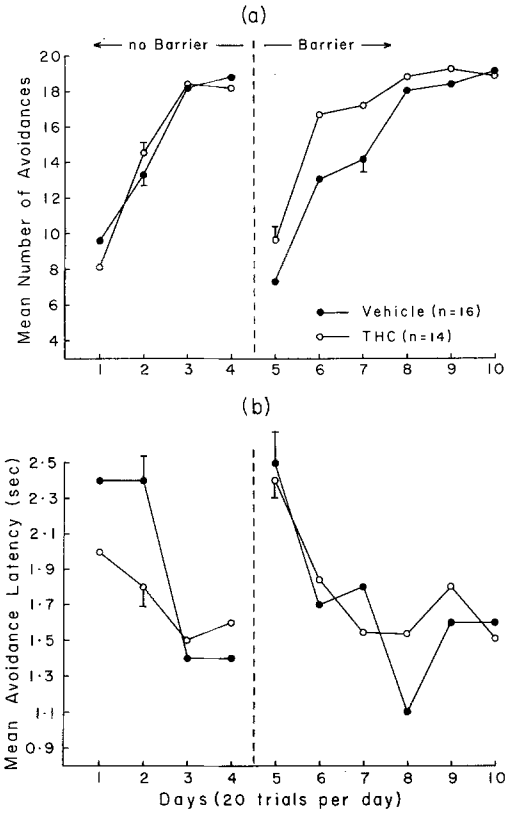

Fig. 3a, b. Learning of shuttle-box avoidance by THC-treated and control rats. Testing began 132 days after the last gavage. A barrier separated the two chambers of the box during days 5–10. **a** Mean number of avoidances on successive test days (20 trials per test day). **b** Mean latencies for successful avoidance responses on successive tests

shorter mean latency to avoid the shock (Fig. 3b) at the outset of testing (significant group × days interaction $F = 2.98$, df 3,81, $P < 0.04$). Tests of simple effects showed that this difference in avoidance latencies between the groups was significant on the first 2 days of testing (significant Student's t-test values 2.84 and 3.23, df 94, $P < 0.05$ for both comparisons).

When the barrier was introduced into the apparatus during the fifth session both groups decreased avoidance responding appreciably, but rats in the THC group showed a strong trend to recover more quickly than controls (Fig. 3a). This trend did not quite reach the 5% level of significance (main effect of group $F = 3.32$, df 1,28, $P < 0.08$). There was no significant difference in avoidance latencies between the groups after the barrier was introduced (Fig. 3b).

The THC animals tended to escape more quickly and freeze less than vehicle controls when foot shock was delivered, especially on the first test day, but the group differences were not significant. There was also no significant difference between the groups in the mean number of spontaneous crossings made during the 30-s intertrial interval over the 10-day test period.

Comparison with Cannabis Extract. Table 1 compares the residual effects of THC with those of cannabis extract as reported previously (Stiglick and Kalant 1982a, b). In the previous experiments the extract provided the same daily dose of THC (20 mg/kg) for 3 months, and behavioral testing was started after at least a 1-month drug-free period. Table 1

Table 1. Comparison of present THC results with representative cannabis extract data (Stiglick and Kalant 1982a, b). All data are compared with vehicle control rats

Type of test	Measure taken	THC (20 mg/kg)	Cannabis extract containing THC (20 mg/kg)
Open field	Percent increase in activity in drug-treated groups[a]	7%	158%
Radial-arm maze	Ratio of drug-treated learners[b]/vehicle learners	1/1	1/4
DRL-20	Percent reduction in efficiency[c]	2%	31%

[a] Data from last 2 min of second test
[b] Learners defined as rats that reached criterion used in each study
[c] On final DRL test of each study

shows that chronic cannabis treatment produced more residual hyperactivity in the open field, and greater learning impairment on the radial-arm maze and DRL-20 task. Furthermore, chronic cannabis treatment resulted in a very pronounced facilitation of shuttle-box avoidance learning (A. Stiglick, M. Llewellyn and H. Kalant, unpublished observations). In contrast, chronic THC treatment produced only a slight facilitation of shuttle-box avoidance in the present experiment.

Discussion

This experiment demonstrates that 3 months of chronic THC treatment, at a daily dose of 20 mg/kg, can produce a variety of behavioral changes that are demonstrable months after the last drug administration. Because the half-life of THC and its metabolites is approximately 21 h in the rat (Klausner and Dingell 1971), it is extremely unlikely that the behavioral effects were due to residual drug in THC-treated subjects more than 100 days after the last drug treatment.

The major effects of prolonged THC administration were on the learning of the radial-arm maze and DRL-20 task. In both cases THC-treated animals showed a significant impairment, although they did reach the level of control rats by the end of testing. It is likely that the initial impairment was due to a true learning deficit rather than to impaired motivation for food, since there was no difference between the groups in willingness to eat food in the maze nor in their bar-pressing behavior on the CRF schedule before DRL-20 tests began. Prolonged administration of THC also produced a slight facilitation of shuttle-box avoidance learning. On the open field, THC-treated rats showed a slight hypoactivity, followed by hyperactivity, but these effects were not significant.

The dose of THC used here (20 mg/kg orally) is not a toxicological dose in the rat. For comparisons between species differing greatly in size, better comparability of blood levels and of drug effects is obtained when doses are equated on the basis of body surface area than of body weight. On this basis, according to Rosenkrantz (1983), oral THC doses of 6–30 mg/kg/day in the rat are directly relevant to human consumption, and may be considered as 'moderate' when extrapolated to humans.

Several studies in our laboratory (Stiglick and Kalant 1982a, b; A. Stiglick, M. Llewellyn and H. Kalant, unpublished observations) have examined the residual effects of 3 months of treatment with cannabis extract, adjusted to provide the same daily dose of THC (20 mg/kg). The residual effects of the extract on learning of the radial-arm maze, DRL-20 and shuttle-box tasks were similar to the present effects of THC, but they were more dramatic with the extract. It is unlikely that the differences between the extract and THC were due to unusual time or order effects in the present experiment, since the testing schedule used was very similar to the schedule employed in previous extract experiments. Instead, it is likely that the efficacy of THC was not as great as that of cannabis extract, thus permitting the THC-treated rats to recover to control levels on the radial-arm maze and DRL-20 tests. Similarly, the lower efficacy of chronic THC treatment produced only a slight facilitation of shuttle-box avoidance learning, permitting vehicle controls to reach the level of the drug-treated rats very quickly.

The fact that there were no significant residual effects of THC on open-field activity is more difficult to reconcile with the residual hyperactivity produced by chronic cannabis treatment (Stiglick and Kalant 1982b). It is possible, however, that the lower efficacy of chronic THC treatment resulted in a transient residual hyperactivity that disappeared by the time the open field tests were conducted. This has been observed after certain nondrug manipulations. For example, lesions of the entorhinal cortex, an area intimately associated with the hippocampus, often result in transient hyperactivity (Steward et al. 1977), despite more persistent changes on performance of mazes and other tasks (Kimble 1978).

Whatever interpretation is advanced to explain the differential effects of chronic THC treatment on various tests, it seems clear that most of the effects resemble those produced by cannabis extract, but are less marked (Table 1). Similar observations have been obtained previously in other studies: for example, Karniol and Carlini (1972) and Carlini et al. (1974) compared the two preparations in tests of spontaneous motor activity and catatonia in mice, rope-climbing performance in rats and a variety of physiological and subjective effects in humans. They found that the effects of various cannabis samples were two-to five-times greater than should be expected from their THC content. Similar results in relation to various acute effects have been presented by other authors (Fairbairn and Pickens 1981; Galanter et al. 1973; Kubena and Barry 1972; Pickens 1981).

There are at least two possible explanations for the apparently lesser residual effects of pure THC than of an equivalent dose of cannabis extract. First, it is possible that other cannabinoids have psychoactive effects that add to those of THC. On the basis of acute studies, however, this 'additive' hypothesis seems unlikely. For example, acute administration of other cannabinoids such as CBD and CBN does not produce psychoactive effects (Mechoulam 1970; Bird et al. 1980). Nevertheless, it is still possible that the combination of non-THC constituents may have some residual effects on behavior when administered chronically.

A second possibility is that other constituents in cannabis potentiate the actions of THC itself and cause more substantial residual effects when administered chronically. Inactive doses of CBD or CBN were shown to potentiate many depressant effects of THC in animals (Anderson et al. 1974; Fernandes et al. 1974; Takahashi and Karniol 1975) and in humans (Karniol et al. 1975; Musty et al. 1976). This potentiation was purportedly due to inhibition of THC metabolism by other cannabinoids (Jones and Pertwee 1972; Fernandes et al. 1973). It is not clear, however, whether the greater potency of the extract can still be ascribed to CBD or CBN. There are recent claims that CBD and CBN do not potentiate THC effects in humans (Bird et al. 1980), and may even antagonize them in animals (Brady and Balster 1980). The fact that CBD or CBN appeared to potentiate the effects of THC in early studies may have been due to contamination by other cannabinoids, such as cannabigerol and cannabichromene (Fernandes et al. 1974). Since the extract used in the previous studies contained a variety of cannabinoids, one or more of these may have potentiated the effects of THC. It seems clear that future studies are necessary to determine which cannabinoids are responsible for this apparent enhancement of residual effects.

The extract that was used in our previous experiments was prepared so that most, or all of the cannabinoid acids were converted to their neutral active forms (Fehr et al. 1976; Fehr 1977; Stiglick and Kalant 1982a), as they are found in cannabis smoke (Mechoulam et al. 1976). This means that both the extract and smoke contain other cannabinoids that may add to, or potentiate the effects of THC. Moreover, cannabis smoke contains particulate matter, carbon monoxide, and other substances not found in the extract (Mechoulam et al. 1976; Rosenkrantz 1983 for reviews), which may contribute further to the behavioral toxicity of cannabis smoke.

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