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# Blood Cannabinoids. II. Models for the Prediction of Time of Marijuana Exposure from Plasma Concentrations of $\Delta^9$-Tetrahydrocannabinol (THC) and 11-nor-9-carboxy-$\Delta^9$-tetrahydrocannabinol (THCCOOH)

**Marilyn A. Huestis, Jack E. Henningfield,** and **Edward J. Cone***
*Addiction Research Center, NIDA, P.O. Box 5180, Baltimore, MD 21224*

## Abstract

**Two mathematical models are described for the prediction of time of marijuana use from the analysis of a single plasma sample for cannabinoids. The models were derived from cannabinoid data obtained from a controlled clinical study of acute marijuana smoking. Model I was based on plasma $\Delta^9$-tetrahydrocannabinol (THC) concentrations and Model II was based on the ratio of 11-nor-9-carboxy-$\Delta^9$-tetrahydrocannabinol (THCCOOH) to THC in plasma. The two models were validated with cannabinoid data from nine published and unpublished clinical studies. The data included plasma samples obtained from infrequent and frequent marijuana smokers and after oral marijuana administration. Cannabinoid plasma concentrations had been determined by a variety of analytical methods. The accuracy of model prediction was evaluated by comparison of the predicted time of prior drug use to the actual time of exposure. Predictions of time of exposure were generally accurate but tended to overestimate time immediately after smoking and tended to underestimate later times. A second assessment of the validity of the models was made by determining if actual time of use was within the 95% confidence interval. Model I correctly predicted the time of exposure within the 95% confidence interval for 235 of 261 samples (90.0%), and Model II was correct in 232 of 260 samples (89.2%). These prediction models may be beneficial to forensic scientists in the interpretation of cannabinoid plasma levels.**

## Introduction

Forensic scientists receive frequent requests to interpret the significance of cannabinoid concentrations in blood samples from individuals involved in accidents, criminal investigations, and traffic violations. Relevant facts, such as the amount of drug used, route of administration, and history of use generally are unknown. Accurate prediction of the time of marijuana exposure would provide valuable information in establishing the role of marijuana as a contributing factor to events under investigation. Individual drug levels and ratios of cannabinoid metabolite to parent drug concentration have been suggested as potentially useful indicators of recent drug use (1–3). There also have been attempts to identify analytes with short time courses of detection as markers of recent exposure (4,5). Generally, these attempts to predict the time of marijuana exposure have not been effective. Development of predictive models for the time of marijuana use is complicated by a number of complex factors. First, several cannabinoids are present in blood after marijuana exposure and their relative concentrations change over time. Second, the time course of appearance and disappearance of THC and metabolites change with the route of administration. Third, accumulation of THC and THCCOOH during frequent marijuana use can occur. Fourth, different analytical techniques have been employed for cannabinoid measurements, with each assay displaying a somewhat different pattern of sensitivity and specificity toward individual cannabinoid analytes.

During marijuana smoking, $\Delta^9$-tetrahydrocannabinol (THC), the major psychoactive component of marijuana, appears rapidly in blood with peak concentration noted near the end of smoking. THC has several distribution phases. There is an initial distribution phase to highly perfused tissues accompanied by a rapid decrease in plasma levels. A second distribution phase occurs that contributes to the accumulation of THC in poorly perfused tissues. The latter phase is characterized by a gradual decrease in plasma THC levels. The onset of metabolism of THC to the active metabolite, 11-hydroxy-$\Delta^9$-tetrahydrocannabinol (11-OH-THC), and inactive metabolite, 11-nor-9-carboxy-$\Delta^9$-tetrahydrocannabinol (THCCOOH), occurs within minutes of the initiation of marijuana smoking (6). As distribution and metabolism proceed, THC levels decline while THCCOOH levels increase. During the latter stages of elimination, THCCOOH may be substantially higher than THC levels. However, both analytes have long terminal elimination half-lives. In frequent smokers, residual levels of THC and THCCOOH have been measured for extended periods of time after cessation of drug use (7). Following oral marijuana administration, absorption is slower and the appearance of THC is delayed. In addition, lower concentrations of THC develop after oral administration compared to the smoking route (8).

The goal of this study was the development of a mathematical model for the prediction of the time of marijuana exposure based on plasma levels of THCCOOH and/or THC. Two models were derived from cannabinoid data obtained from a controlled clinical study of marijuana smoking (6). One model was based on plasma

*Author to whom correspondence should be addressed.

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THC concentrations and the second model utilized plasma THCCOOH/THC ratios. Corresponding confidence intervals were derived for future predictions at the 95% confidence level. The models were validated with cannabinoid data obtained from marijuana users in the nine clinical studies. Accuracies of the models in the prediction of the time of marijuana use were evaluated by comparison of the actual time of use to the predicted time of exposure and to the 95% confidence interval. Strengths and weaknesses of each model in the estimation of elapsed time of use after marijuana exposure in forensic plasma samples are described.

## Methods

### Development of mathematical models

Two equations were derived which described the relationships between THCCOOH and/or THC plasma concentrations of marijuana users and the time of drug exposure. Model I described the relationship between plasma THC concentrations and elapsed time after marijuana use. In a similar manner, Model II described the relationship between plasma THCCOOH/THC ratios and elapsed time. The cannabinoid data used in the analyses were obtained from a controlled clinical study of marijuana smoking (6). Plasma THC and THCCOOH concentrations were measured by negative chemical ionization GC/MS (3) following the smoking of a 1.75 or 3.55% THC cigarette. Briefly, six male subjects with a history of marijuana use smoked a single marijuana cigarette in a paced smoking protocol; frequent blood sampling occurred during and after smoking. Blood levels obtained during the 10-minute smoking period were not included in data analysis.

Model I was derived by plotting the log of THC plasma concentrations versus the log of the time elapsed after marijuana use (Eq. 1). Linear regression analysis provided estimates of the slope and intercept.

$$\text{Log } T = m * \log [\text{THC}] + b \qquad \text{Eq. 1}$$

where $T$ = predicted elapsed time (hours) after marijuana use, $m$ = slope, [THC] = THC plasma concentrations (ng/mL), and $b$ = intercept. The 95% confidence interval (9) for the log of the predicted time of use for Model I was determined as follows:

$$CI = \text{Log } T \pm t\sqrt{\text{MS}(1 + 1/N + x_i^2 / \sum_{i=1}^{N} x^2)} \qquad \text{Eq. 2}$$

where $CI$ = 95% confidence interval, $T$ = predicted elapsed time (hours) after marijuana use, $t$ = Student's $t$-distribution, MS = mean square error, $N$ = number of data points included in Model I, and $x$ = log [THC] - mean log [THC].

Model II was developed in a similar manner, by plotting the log of the THCCOOH/THC ratio of plasma concentrations versus the log of the time elapsed after marijuana exposure (Eq. 3).

$$\text{Log } T = m * \log [\text{THCCOOH}]/[\text{THC}] + b \qquad \text{Eq. 3}$$

where $T$ = predicted elapsed time (hours) after marijuana use, $m$ = slope, [THCCOOH]/[THC] = THCCOOH/THC plasma ratio, and $b$ = intercept. The 95% confidence interval for the log of the predicted time of use for Model II was determined as follows:

$$CI = \text{Log } T \pm t\sqrt{\text{MS}(1 + 1/N + x_i^2 / \sum_{i=1}^{N} x^2)} \qquad \text{Eq. 4}$$

where $CI$ = 95% confidence interval, $T$ = predicted elapsed time (hours) after marijuana use, $t$ = Student's $t$-distribution, MS = mean square error, $N$ = number of data points included in Model II, and $x$ = log [THCCOOH/THC] – mean log [THCCOOH/THC].

### Evaluation of model accuracy

Accuracy of the mathematical models was evaluated by two different methods. The first approach determined the absolute time error by subtracting the actual elapsed time after marijuana exposure from the predicted elapsed time. The absolute time error of the prediction was calculated as follows:

$$\text{TE} = | T - T_a | \qquad \text{Eq. 5}$$

where TE = absolute time error, $T$ = predicted elapsed time (hours) after marijuana use, and $T_a$ = actual elapsed time (hours) after marijuana use. Mean absolute time errors were determined for the following time intervals after marijuana use: 0 – 0.50, 0.51 – 1.0, 1.1 – 2.0, 2.1 – 4.0, and 4.1 – 8.0 hours.

The second method utilized for evaluation of the accuracy of Models I and II compared the actual time of exposure to the 95% confidence interval of the predicted time of use. Predictions were considered to be accurate if the actual times of marijuana exposure were within the estimated confidence intervals. Equations 1 and 3 were used to predict the time of marijuana use from the corresponding plasma data. Equations 2 and 4 were used to calculate the 95% confidence intervals associated with the predicted times of use.

The accuracies of Models I and II were assessed with cannabinoid data collected in nine marijuana studies (Table I). These studies represented a variety of marijuana exposure conditions and included smoking and oral routes of administration. The assays encompassed a range of analytical methods, including radioimmunoassays (RIA) of varying specificities (2, 10–14, 17), high performance liquid chromatography separations combined with RIA (5), gas chromatography/mass spectrometry (GC/MS) with internal standardization (15,16), and GC/MS without internal standardization (4).

Only plasma levels greater than or equal to 2.0 ng/mL THC were included in the evaluations of model accuracy. Several factors influenced the decision to limit model application to THC concentrations greater than 2.0 ng/mL, including the presence of low THC concentrations found during the absorption phase after marijuana ingestion, residual THC concentrations noted after frequent marijuana use, and decreased assay precision at THC concentrations less than 2.0 ng/mL.

## Results

### Derivation of Model I

Analysis of cannabinoid plasma data obtained from a controlled clinical study of marijuana smoking (6) demonstrated that THC concentrations were highly correlated ($r$ = 0.949) with time of exposure (Figure 1a). This analysis included plasma samples collected over a period of 0–12 h after marijuana smoking. Linear regression analysis of this data provided the following numerical equation for Model I:

$$\text{Log } T = -0.698 \log [\text{THC}] + 0.687 \qquad \text{Eq. 6}$$

The corresponding 95% confidence interval ($CI$) determined for Model I was as follows:

$$CI = \text{Log } T \pm 1.975\sqrt{0.030(1.006 + \{(\log [\text{THC}] - 0.996)^2 / 89.937\})}$$

Eq. 7

### Derivation of Model II

THCCOOH/THC ratios from the cannabinoid plasma data also correlated ($r = 0.919$) with the elapsed time after drug use (Figure 1b). Linear regression analysis provided the following equation:

$$\text{Log } T = (0.576 * \log [\text{THCCOOH}]/[\text{THC}]) - 0.176$$

Eq. 8

The corresponding 95% confidence interval ($CI$) determined for Model II was as follows:

$$CI = \text{Log } T \pm 1.975 \times \sqrt{0.045(1.006 + \{(\log [\text{THCCOOH}]/[\text{THC}] - 0.283)^2 / 123.420\})}$$

Eq. 9

### Determination of confidence intervals at predicted times of marijuana usage

The 95% confidence intervals for Models I and II at selected times after marijuana use were determined by Equations 7 and 9, respectively, as shown in Table II. Intervals increased with elapsed time after exposure and were asymmetric about the predicted time of use. The increasing intervals and assymetry occurred as a result of the logarithmic relationship between elapsed time and analyte concentration (or ratio).

### Validation of Models I and II with clinical data

Models I and II were evaluated for accuracy in the prediction of time of marijuana usage with cannabinoid plasma data from nine clinical studies. Both models were assessed for accuracy with Eq. 5. The absolute time errors in the prediction of time of marijuana exposure are summarized by time intervals in Table III. The second method utilized for evaluation of the accuracy of Models I and II compared the actual time of exposure to the 95% confidence interval of the predicted time of use (Figure 2 and 3).

### Prediction accuracy in infrequent marijuana smokers

Cannabinoid plasma data was available for 29 infrequent marijuana smokers from four independent clinical studies [Studies #1 (11, 13,14), #2 (15,16), #4 (10), and #6 (17)]. Plasma levels were measured in these studies by different analytical techniques, including RIA and GC/MS, as described in Table I. Subjects in the four studies smoked a single marijuana cigarette containing THC in amounts ranging from 2 to 23 mg. Individual smoking patterns were not controlled. Samples were collected in some studies for up to 14 days after smoking marijuana; however, THC levels declined below 2 ng/mL within 6 h in all subjects.

*Model I.* The mean absolute time error in 238 samples from infrequent marijuana smokers for the 0–8.0 h period after smoking was 0.45 h (Table III). Mean error increased with time after drug exposure, and was largest in the 4.1–8.0 hour period. The time of exposure generally was overestimated during the first hour after smoking in this population (Figure 2a). Thereafter, Model I tended

**Table I. Clinical Marijuana Studies for Validation of Models I and II**

| Study (Ref.) | Population | Dose (THC) | Route | Method | Subjects | N | Sampling period |
|---|---|---|---|---|---|---|---|
| Study 1 (11,13,14) | infrequent users | 1 cigarette, 37.5 or 75 µg/kg | smoke | RIA | 12 | 178 | 0–2 h |
| Study 2* (15,16) | infrequent users | 1 cigarette, 18 mg | smoke | GC/MS | 5 | 9 | 0–14 days |
| Study 3* (15,16) | frequent users | 1 cigarette, 18 mg | smoke | GC/MS | 5 | 10 | 0–14 days |
| Study 4* (10) | infrequent users | 1 cigarette, 1.32, 1.97, or 2.54% | smoke | RIA | 6 | 33 | 0–6 h |
| Study 5 (1) | naive subjects | 20 mg | oral | HPLC/RIA | 4 | 13 | 0–72 h |
| Study 6 (17) | infrequent users | 1 cigarette, 2.54% | smoke | RIA | 6 | 18 | 0–5.25 h |
| Study 7 (4) | infrequent users | 2 cigarettes, 150 µg/kg | smoke | GC/MS | 10 | 84 | 0–5 h |
| Study 8*† (2) | frequent users | 1 cigarette, 19.8 mg | smoke | RIA | 45 | 4 | approx. 0–4 h |
| Study 9 (12) | infrequent, frequent users | 1 cigarette, 200 µg/kg | smoke | RIA | 4 | 4 | 0–3 h |

* Mean data only
† Ratios and actual times of use were estimated from reference 2.

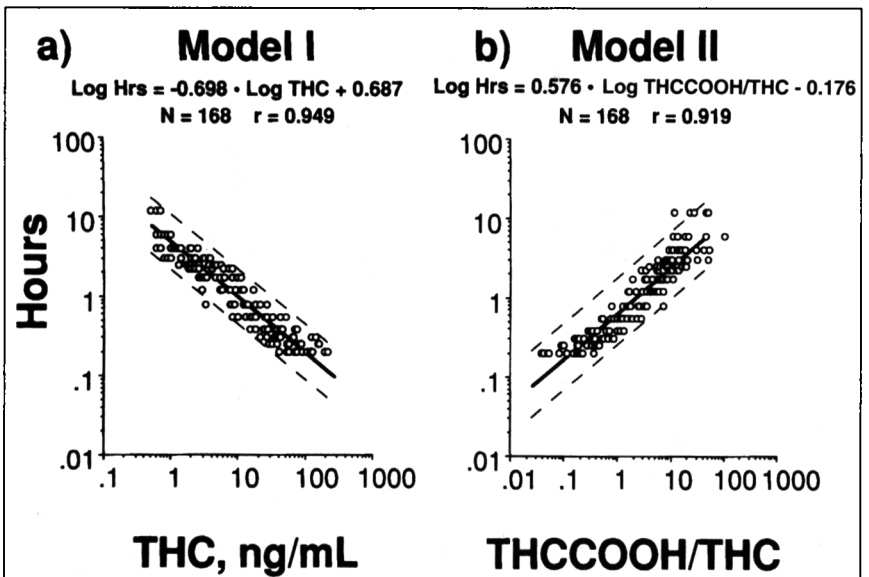


**Figure 1.** Mathematical models for the prediction of time of marijuana exposure based on cannabinoid plasma levels: (a) Model I was derived from linear regression analysis of plasma THC levels vs. elapsed time after marijuana smoking; (b) Model II was derived from linear regression analysis of plasma THCCOOH/THC ratios vs. elapsed time after marijuana smoking. Plasma data were obtained from a controlled clinical study of acute marijuana use and analyzed by GC/MS (6). Dotted lines represent 95% confidence intervals.

to underestimate time of exposure. Accuracy also was assessed by comparison of actual elapsed time after marijuana administration with the 95% confidence interval (Eq. 7). The actual times of exposure for 221 (92.8%) cannabinoid plasma samples were within the corresponding confidence interval of Model I (Figure 2a). Exposure times of 17 samples were outside the estimated confidence interval.

*Model II.* The mean absolute time error in 233 samples from infrequent marijuana smokers for the 0–8.0 h period after smoking was 0.51 h (Table III). Mean error increased with time after drug exposure and was largest in the 4.1–8.0 h period. The time of exposure generally was overestimated during the first hour after smoking in this population. Thereafter, Model II tended to underestimate time of exposure. The actual times of exposure for 209 (89.7%) cannabinoid plasma samples were within the confidence interval of Model II (Figure 3a). Exposure times of 24 samples were outside the confidence interval.

**Table II. Confidence Intervals (95%) for Models I and II at Predicted Times of Marijuana Use**

| Predicted elapsed time (h) | CI | |
|---|---|---|
| | Model I (h) | Model II (h) |
| 0.5 | 0.2–1.1 | 0.2–1.3 |
| 1.0 | 0.5–2.2 | 0.4–2.6 |
| 2.0 | 0.9–4.4 | 0.8–5.3 |
| 4.0 | 1.8–8.8 | 1.5–10.5 |
| 6.0 | 2.7–13.2 | 2.3–15.8 |
| 8.0 | 3.6–17.6 | 3.0–21.0 |

**Table III. Mean Absolute Time Error (h) in the Prediction of Time of Marijuana Use with Models I and II***

| Time Interval (h) | Infrequent smokers (Studies #1, 2, 4, & 6) | | Frequent smokers (Studies #3 & 8) | | Oral users (Study #5) | | Infrequent smokers (Study #7) | | Mean error† (h) |
|---|---|---|---|---|---|---|---|---|---|
| | *N* | Error | *N* | Error | *N* | Error | *N* | Error | |
| **Model I** | | | | | | | | | |
| 0–0.50 | 82 | 0.12 | 4 | 0.07 | – | – | – | – | 0.12 |
| 0.51–1.0 | 40 | 0.16 | 2 | 0.16 | 1 | 2.0 | 36 | 0.45 | 0.32 |
| 1.1–2.0 | 75 | 0.47 | 2 | 0.11 | 3 | 0.38 | 20 | 0.82 | 0.53 |
| 2.1–4.0 | 35 | 1.07 | 2 | 0.46 | 4 | 2.61 | 17 | 1.58 | 1.30 |
| 4.1–8.0 | 6 | 3.02 | – | – | 5 | 4.43 | 11 | 2.61 | 3.14 |
| **Mean error†** | | | | | | | | | |
| 0–8.0 | 238 | 0.45 | 10 | 0.17 | 13 | 2.75 | 84 | 1.05 | 0.68 |
| **Model II** | | | | | | | | | |
| 0–0.50 | 82 | 0.24 | 4 | 0.61 | – | – | – | – | 0.26 |
| 0.51–1.0 | 39 | 0.23 | 2 | 1.26 | 1 | 1.2 | 36 | 0.48 | 0.38 |
| 1.1–2.0 | 74 | 0.46 | 3 | 0.93 | 3 | 1.1 | 20 | 0.78 | 0.56 |
| 2.1–4.0 | 34 | 1.14 | 4 | 1.28 | 4 | 0.86 | 17 | 1.99 | 1.38 |
| 4.1–8.0 | 4 | 4.22 | 1 | 2.48 | 5 | 1.55 | 11 | 3.90 | 3.33 |
| **Mean error†** | | | | | | | | | |
| 0–8.0 | 233 | 0.51 | 14 | 1.10 | 13 | 1.21 | 84 | 1.31 | 0.75 |

* *N* represents the number of cannabinoid blood samples.
† Mean error represents average absolute time error (h) across all observations.

**Prediction accuracy in infrequent marijuana smokers in study #7**

An additional clinical marijuana study was evaluated, but the findings were not comparable with those of the other studies. Therefore, these data were examined independently. Models I and II were tested with cannabinoid plasma data from 10 infrequent marijuana smokers [Study #7 (4)] who smoked two marijuana cigarettes containing 150 µg/kg THC over a period of 30 min. Individual smoking patterns were not controlled. For prediction of time of marijuana exposure, the time of drug use was defined as the beginning of the smoking period. Plasma samples were collected for up to five hours after smoking and were analyzed by GC/MS with external standardization.

*Model I.* The mean absolute time error in 84 samples for the 0–8.0 h period after smoking was 1.05 h (Table III). The mean error increased throughout the 0–8.0 h time period but reflected a consistent underestimation of the time of drug usage with Model 1 (Figure 2d). This systematic bias of the data appeared to have been due to the lack of internal standardization and/or the uncertainly in actual time of smoking. The actual times of exposure of only 33 (39.3%) cannabinoid plasma samples were within the 95% confidence interval of Model I (Figure 2d). Exposure times of 51 samples were outside the estimated confidence interval. All of the predicted times of usage were underestimated when compared to the actual times of drug exposure.

*Model II.* The mean absolute time error in 84 samples for the 0–8.0 h period after smoking was 1.31 h. A bias similar to that observed with Model I was apparent for Model II. The mean error increased throughout the 0–8.0 h time period, with a systematic bias in the data of 50 to 70% (Figure 3d). The actual times of exposure of only 30 (35.7%) cannabinoid plasma samples were within the 95% confidence interval of Model II (Figure 3d). Exposure times of 54 samples were outside the estimated confidence interval. Almost all of the predicted times of usage were underestimated, when compared to the actual times of drug exposure.

**Prediction accuracy in frequent marijuana smokers**

Mean cannabinoid plasma data were available for 50 frequent marijuana smokers from two independent clinical studies [Studies #3 (15,16) and 8 (2)]. Plasma levels were measured in these studies by RIA and GC/MS, as described in Table I. Subjects in these studies smoked a single marijuana cigarette containing 18–19.8 mg THC. Individual smoking patterns were not controlled. Samples were collected up to 14 days after smoking marijuana in Study #3; however, THC levels declined below 2 ng/mL within 4 h. Plasma samples were collected up to 4 h after smoking in Study #8. However, only THCCOOH–THC ratios were reported; consequently, Model I could not be evaluated with data from Study #8.

*Model I.* The mean absolute time error in 10 samples from frequent smokers (Study #3) for the 0–8.0 h period after smoking was 0.17 h (Table III). The largest mean error (0.46 h) occurred in the 2.1–4.0 h interval. Model I was highly accurate for all samples in the prediction of time of marijuana exposure (Figure

2b). The actual times of exposure for 10 (100%) cannabinoid plasma samples were within the 95% confidence interval of Model I (Figure 2b).

*Model II.* The mean absolute time error in 14 samples from frequent smokers (Studies #3 and #8) for the 0–8.0 h period after smoking was 1.1 h (Table III). The largest mean error was observed in the 4.1–8.0 h time interval. Model II generally overestimated the time of marijuana exposure with samples from frequent smokers in Study #3 and underestimated the time of use with samples from Study #8 (Figure 3b). The actual times of exposure for 10 (71.4%) cannabinoid plasma samples were within the 95% confidence interval of Model II (Figure 3b). In the four cases that were outside the 95% confidence interval, the actual times of use were within 10 min of the lower confidence limit.

#### Prediction accuracy in an oral marijuana study

Cannabinoid plasma data were evaluated for four marijuana-naive subjects who ingested 20 mg of THC [Study #5 (1)]. Plasma samples were collected for 72 h after ingestion and were analyzed by HPLC/RIA. THC concentrations declined below 2 ng/mL within 24 h in all subjects.

*Model I.* The mean absolute time error in 13 samples for the 0–8.0 h period after smoking was 2.75 h (Table III). Mean error was variable and ranged from 0.38–4.43 h. Generally, the predicted time of marijuana use was underestimated with Model I (Figure 2c). The actual times of exposure of only five (38.5%) cannabinoid plasma samples were within the 95% confidence interval of Model I (Figure 2c). Exposure times of eight samples were outside the estimated confidence interval.

*Model II.* The mean absolute time error in 13 samples for the 0–8.0 h period after smoking was 1.21 h (Table III). The mean error ranged from 0.86–1.55 h during the 0–8.0 h time period. Actual times of use were evenly distributed above and below the predicted times of exposure (Figure 3c). The actual times of exposure of 13 (100.0%) cannabinoid plasma samples in the oral marijuana study were within the 95% confidence interval of Model II (Figure 3c). There were no exposure times outside the estimated confidence interval.

#### Prediction accuracy in infrequent and frequent marijuana smokers Models I and II

Cannabinoid plasma data were evaluated for four infrequent and frequent marijuana smokers [Study #9 (12)] who smoked a single marijuana cigarette containing 200 μg/kg THC. Samples were collected within 3 h of drug administration, but actual sampling times were not specified. Samples were analyzed by RIA. Model I and Model II accurately predicted that the time of drug use occurred within 3 h. Absolute time error could not be determined and comparison of actual time of use with the 95% confidence interval could not be performed.

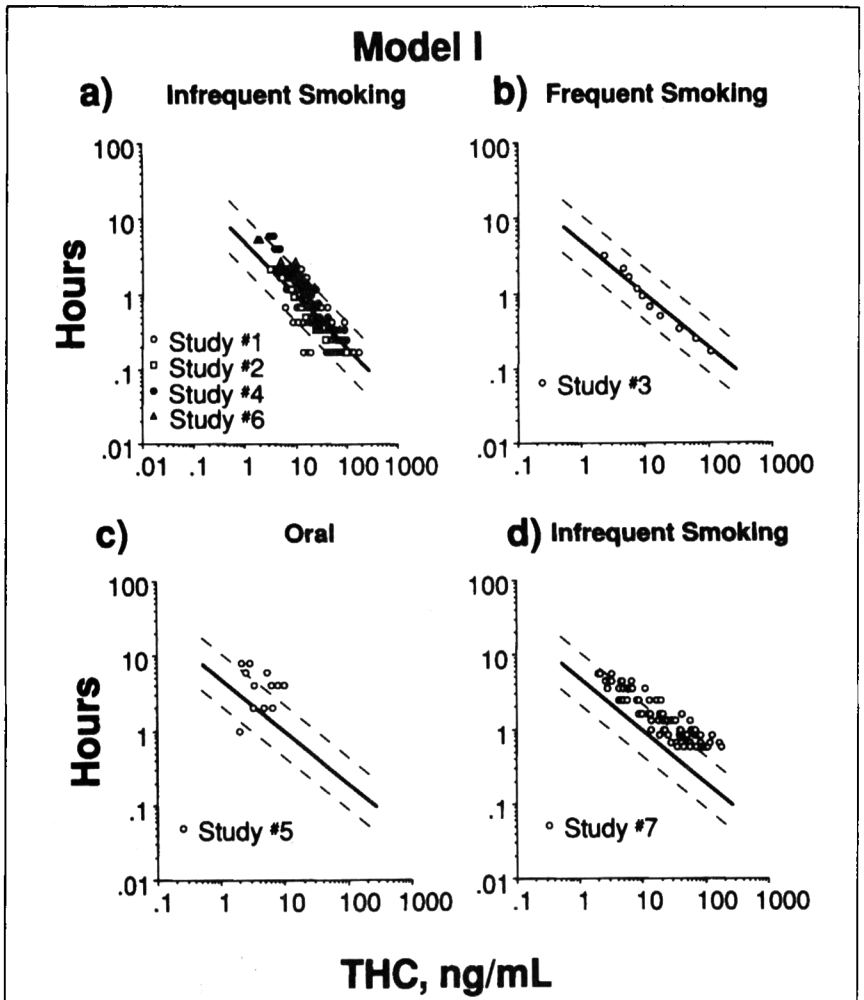


**Figure 2.** Accuracy evaluation of Model I. Actual times of marijuana exposure were compared to the 95% confidence interval of the predicted time of drug usage for plasma THC levels obtained from seven controlled clinical studies. Studies included (a) infrequent marijuana smoking, (b) frequent marijuana smoking, (c) oral marijuana use, and (d) infrequent marijuana smoking (Study 7). Dotted lines represent 95% confidence intervals for future predictions.

#### Overall prediction accuracy of Models I and II

The mean absolute time error for all clinical studies (Studies #1–8) was 0.68 h ($N$ = 345) for Model I. The actual times of exposure of 269 of 345 (78.0%) cannabinoid plasma samples were within the 95% confidence interval of Model I. The majority of the samples (51 of 76) that were not predicted accurately originated from Study #7. If Study #7 samples were excluded, the actual times of marijuana exposure of 235 of 261 (90.0% cannabinoid samples were within the 95% confidence interval.

The mean absolute time error for all clinical studies (Studies #1–8) was 0.75 h ($N$ = 344) for Model II. The actual times of exposure of 262 of 344 (76.2%) cannabinoid plasma samples were within the 95% confidence interval of Model II. Again, the majority of samples that were not predicted accurately originated from Study #7. If these samples were excluded, the actual times of marijuana exposure of 232 of 260 (89.2%) cannabinoid samples were within the 95% confidence interval.

## Discussion

Marijuana has been implicated as a potential causative factor in a number of epidemiolog-

ical studies of motor vehicle accidents. A study of drugs found in 600 operators killed in single-vehicle accidents in North Carolina reported 47 cases (7.8%) with blood THC greater than 3.0 ng/mL (18). Considerably higher percentages of marijuana usage have been found in other studies. Twenty-eight percent of all motor vehicle drivers tested positive for cannabinoids in a study of fatalities in Texas (19), and in a recent study in Maryland, 31.8% of automobile drivers involved in vehicular accidents were found to have cannabinoids in their blood (20).

Interpretation of marijuana's role as a causative agent has been difficult due to a lack of information relating cannabinoid levels to time of drug exposure. Development of an accurate mathematical model to aid in the prediction of time of prior exposure would be useful in establishing marijuana's role in accidents, but such a model must be applicable to many situations. The pattern of marijuana use and the route of administration can vary substantially. The method of cannabinoid analysis also can vary. A useful model must be capable of prediction of time of exposure for both frequent and infrequent users, for different routes of marijuana administration, and for different analytical techniques.

Plasma THC levels or THCCOOH/THC ratios have been proposed as indicators of recent marijuana usage. Recent exposure and possible impairment have been linked to THC concentrations in excess of 2–3 ng/mL (4,21). Other investigators have recommended that THC levels greater than 10 ng/mL could be used as indicators of recent use (22). Hanson et al. (2) were the first to propose the use of metabolite-to-parent ratios. Others suggested that a ratio < 20 of total metabolites to THC could be indicative of recent use, although individuals with regular cannabis consumption could be expected to have ratios of > 30 following multiple dosing (1). None of these approaches have been rigorously evaluated with data from clinical studies of frequent and infrequent marijuana smokers and with data from different routes of marijuana administration.

In the present study, two mathematical models were developed from cannabinoid data obtained in a controlled clinical study of the effects of smoked marijuana (6). Model I was based on plasma levels of THC and Model II was based on plasma ratios of THCCOOH to THC. Both models were tested with cannabinoid plasma data from nine clinical studies for their accuracy in establishing the time of marijuana exposure.

Model I accurately predicted the elapsed time after marijuana use with plasma samples from infrequent and frequent smokers. The mean absolute time error (difference between actual time of use and predicted time of use) was 0.45 h for 238 samples from infrequent smokers and 0.17 h for samples from 10 frequent smokers (Table IV). Model I was also accurate in the comparison of time of marijuana use within a 95% confidence interval in 92.9% of samples from infrequent smokers, and 100.0% of samples from frequent smokers. The accuracy of Model I was substantially less accurate (39.3%) with samples from infrequent smokers of Study #7. As noted earlier, it appeared likely that the data in Study #7 was biased from the lack of internal standardization. In addition, the actual time of drug exposure was uncertain due to the long smoking period (30 min) employed in the study.

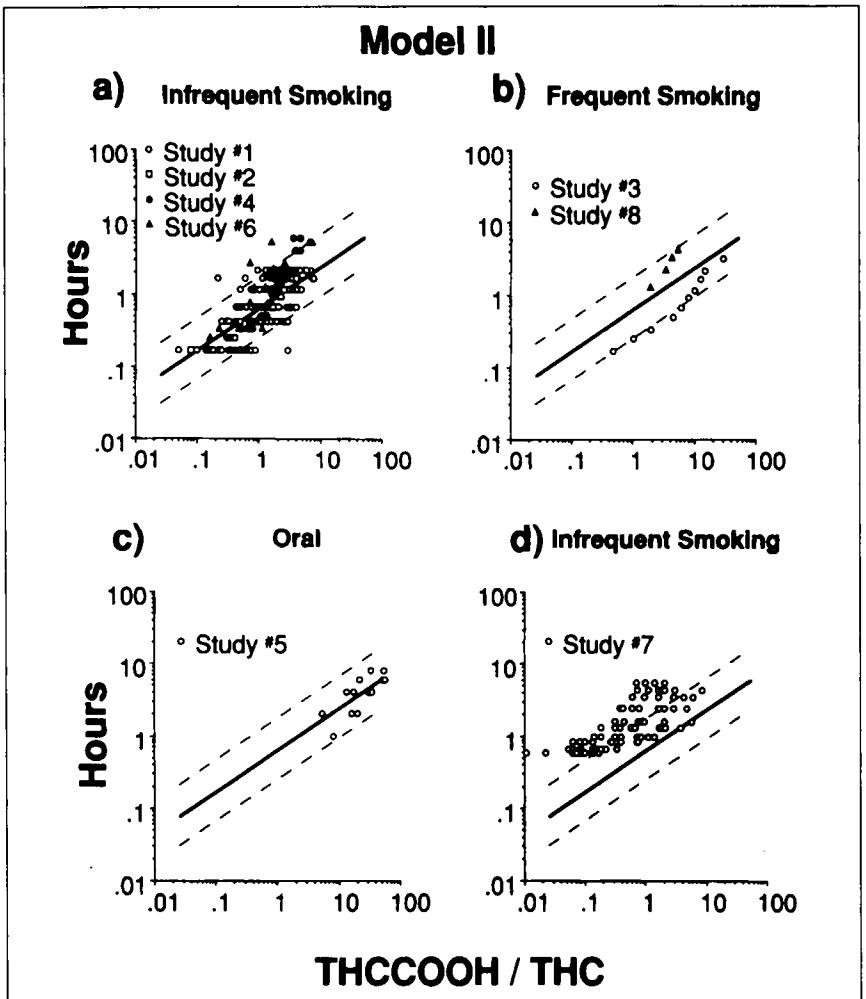


**Figure 3.** Accuracy evaluation of Model II. Actual times of marijuana exposure were compared to the 95% confidence interval of the predicted time of drug usage for plasma THCCOOH/THC ratios obtained from eight controlled clinical studies. Studies included (a) infrequent marijuana smoking, (b) frequent marijuana smoking, (c) oral marijuana use, and (d) infrequent marijuana smoking (Study 7). Dotted lines represent 95% confidence intervals for future predictions.

Model I was less accurate (absolute time error = 2.75 h) in the prediction of time of use after oral marijuana administration. In addition, only 5 of 13 samples were within the 95% confidence interval. Generally, Model I underestimated the elapsed time after marijuana ingestion. Administration of marijuana by the oral route initially produced low THC levels, and higher THC concentrations thereafter. These low THC concentrations during the absorption phase led to overestimation of the predicted time of use with Model I, as noted in one observation in Figure 2c. However, most of the early plasma samples had less than 2.0 ng/mL of THC and were excluded from evaluation. Increased THC concentrations at later times led to an underestimation of the predicted time of use with Model I (Figure 2c).

Residual THC levels following frequent marijuana use also could limit the usefulness of Models I and II. Peat (15) reported an average THC concentration of 0.9 ng/mL in frequent users 12 h after smoking. In the same study, THC levels of greater than 1 ng/mL were reported for up to two days after smoking. Because of the problems of residual

THC concentrations in frequent users, THC levels below 2.0 ng/mL were excluded from use in both Model I and Model II. With samples from frequent marijuana smokers, Model I reliably predicted the time of drug exposure in the limited sample set available for evaluation.

Model II accurately predicted the time of marijuana use in samples from infrequent smokers and after marijuana ingestion but was somewhat less accurate than Model I with samples from frequent smokers (Table IV). The overall mean absolute time error in the predicted time of use for up to 8 h after marijuana exposure in samples from infrequent smokers was 0.51 h, 1.21 h in samples from oral users and 1.10 h in samples from frequent smokers. Correct results were also obtained for 89.7% of samples from infrequent smokers, 100.0% of samples from oral marijuana users, and 71.4% of samples from frequent smokers in the comparison of the actual times of use to the 95% confidence intervals.

Overall, Models I and II accurately predicted elapsed time after drug use but tended to underestimate the actual time of use at later times. Generally, Model II appeared to offer some advantages over Model I. Model II was considerably more accurate than Model I in prediction of time of exposure with samples from oral users. In addition, Model II tended to overestimate the time of use with samples from frequent users, which was preferable to underestimation in forensic cases. Furthermore, although 4 of 13 samples from frequent smokers were not within the 95% confidence interval of Model II, the actual times of use were only 10 min less than the lower limit of the confidence interval. Although additional data is needed for further validation of Models I and II, analysis of existing data indicate that these models can be used for the prediction of time of marijuana use from cannabinoid plasma concentrations within defined confidence limits.

**Table IV. Overall Accuracy of Models I and II in the Prediction of Time of Marijuana Use**

| Population* | Model I | Model II | Comments† |
|---|---|---|---|
| **Infrequent smokers** | | | |
| Mean absolute time error | 0.45 h | 0.51 h | Large blood database available: (Studies 1, 2, 4, & 6) |
| Accuracy by CI analysis | 92.9% | 89.7% | Model I ($N$ = 238)<br>Model II ($N$ = 233) |
| | | | Later timepoints were underestimated by both models |
| | | | RIA and GC/MS analyses |
| **Frequent smokers** | | | |
| Mean absolute time error | 0.17 h | 1.10 h | Limited data available: (Studies #3 & 4) |
| Accuracy by CI analysis | 100.0% | 71.4% | Model I ($N$ = 10)<br>Model II ($N$ = 14) |
| | | | RIA and GC/MS analyses |
| **Oral users** | | | |
| Mean absolute time error | 2.75 h | 1.21 h | Limited data available: (Study #5) |
| Accuracy by CI analysis | 38.5% | 100.0% | Model I ($N$ = 13)<br>Model II ($N$ = 13) |
| | | | HPLC/RIA analysis |

* CI = Confidence interval (95%)
† $N$ = Number of cannabinoid blood samples

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## Appendix 1

An example of calculations for the prediction of time of prior marijuana use with Models I and II.

Data: Plasma THC = 8.3 ng/mL; THCCOOH = 21.3 ng/mL
Actual elapsed time after smoking was 1.17 h.

**Model I**

Calculation of the predicted time of use:

$$\text{Log } T\text{ (h)} = -0.698 * \log [\text{THC}] + 0.687$$
$$= -0.698 * \log 8.3 + 0.687$$
$$= 0.045$$
$$T\text{ (h)} = 1.11 \text{ h}$$

Calculation of the 95% confidence interval of log $T$:

$$CI = \text{Log } T \pm 1.975\sqrt{0.030(1.006 + \{(\log [\text{THC}] - 0.996)^2 / 89.937\})}$$
$$= 0.045 \pm 1.975\sqrt{0.030(1.006 + \{(\log 8.3 - 0.996)^2 / 89.937\})}$$
$$= 0.045 \pm 0.343$$

Lower 95% confidence limit of $T$ = antilog (0.045 – 0.343)
= 0.50 h

Upper 95% confidence limit of $T$ = antilog (0.045 + 0.343)
= 2.44 h

Actual time of sample collection was 1.17 h after marijuana smoking. Model I predicted time of marijuana use as 1.11 h prior to sample collection with a 95% confidence interval from 0.50 to 2.44 h.

**Model II**

Calculation of the predicted time of use:

$$\text{Log } T\text{ (h)} = (0.576 * \log [\text{THCCOOH}]/[\text{THC}]) - 0.176$$
$$= (0.576 * \log 21.3/8.3) - 0.176$$
$$= 0.060$$
$$T\text{ (h)} = 1.15 \text{ h}$$

Calculation of the 95% confidence interval of log $T$:

$$CI = \text{Log } T \pm 1.975\sqrt{0.045(1.006 + \{(\log [\text{THCCOOH}]/[\text{THC}] - 0.283)^2 / 123.420\})}$$
$$= 0.060 \pm 1.975\sqrt{0.045(1.006 + \{(\log 21.3/8.3 - 0.283)^2 / 123.420\})}$$
$$= 0.060 \pm 0.420$$

Lower 95% confidence limit of $T$ = antilog (0.060 – 0.420)
= 0.44 h

Upper 95% confidence limit of $T$ = antilog (0.060 + 0.420)
= 3.02 h

Actual time of sample collection was 1.17 h after marijuana smoking. Model II predicted time of marijuana use as 1.15 h prior to sample collection with a 95% confidence interval from 0.44 to 3.02 h.

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