Estimating the Time of Last Cannabis Use from Plasma Δ^9-Tetrahydrocannabinol and 11-nor-9-Carboxy-Δ^9-Tetrahydrocannabinol Concentrations

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Background: Knowing the time cannabis was last used is important for determining impairment in accident investigations and clinical evaluations. Two models for predicting time of last cannabis use from single plasma cannabinoid concentrations—model I, using Δ^9-tetrahydrocannabinol (THC), and model II, using the concentration ratio of 11-nor-9-carboxy-THC (THCCOOH) to THC—were developed and validated from controlled drug administration studies. Objectives of the current study were to extend the validation by use of a large number of plasma samples collected after administration of single and multiple doses of THC and to examine the effectiveness of the models at low plasma cannabinoid concentrations.

Methods: Thirty-eight cannabis users each smoked a 2.64% THC cigarette in the morning, and 30 also smoked a second cigarette in the afternoon. Blood samples (n = 717) were collected at intervals after smoking, and plasma THC and THCCOOH concentrations measured by gas chromatography–mass spectrometry. Predicted times of cannabis smoking, based on each model, were compared with actual smoking times.

Results: The most accurate approach applied a combination of models I and II. For all 717 plasma samples, 99% of predicted times of last use were within the 95% confidence interval, 0.9% were overestimated, and none were underestimated. For 289 plasma samples collected after multiple doses, 97% were correct with no underestimates. All time estimates were correct for 76 plasma samples with THC concentrations between 0.5 and 2 μg/L, a concentration range not previously examined.

Conclusions: This study extends the validation of the predictive models of time of last cannabis use to include multiple exposures and low THC concentrations. The models provide an objective and validated method for assessing the contribution of cannabis to accidents or clinical symptoms.

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Cannabis is one of the most widely abused drugs in the world, second only to alcohol (1). As one might expect with a high prevalence of use in the general population, cannabis is often involved in accidents and other mishaps of operations that require skill. For example, Soderstrom et al. (2) reported in 1988 that 34.7% of 1023 patients admitted to a large city trauma center as a result of vehicular and nonvehicular accidents had cannabinoids present in their blood. In a 1992 national safety study, Crouch et al. (3) found that 13% of truck drivers killed in traffic accidents in the United States had Δ^9-tetrahydrocannabinol (THC),[3] the primary active component in cannabis, or its metabolite 11-nor-9-carboxy-THC (THC-COOH) in their blood or urine at autopsy. These and similar studies have demonstrated a connection between accidents and cannabis use, but have not established causation by cannabis, despite the knowledge that individuals who use cannabis have impaired performance in driving simulator and on-the-road tests (4–8). In the driving studies, the strongest decrements were in the drivers' abilities to concentrate and maintain attention, estimate time and distance, and demonstrate coordination on divided attention tasks, all important requirements for driving (9, 10). Drummer et al. (11) did determine causality in a study of 3398 fatally injured drivers in Australia,

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[3] Nonstandard abbreviations: THC, Δ^9-tetrahydrocannabinol; THCCOOH, 11-nor-9-carboxy-THC; CI, 95% confidence interval; and LOQ, limit of quantification.

using culpability analysis, and reported that drivers with blood THC concentrations of 5 μg/L or greater were 6.6 times more likely than drug-free drivers to have a fatal accident. Medical and forensic investigators tasked with establishing causality and impairment use information from these and similar studies. Knowing the elapsed time from last drug use is necessary for applying these data to an individual case.

Scientists currently evaluate impairment in individual cases by estimating the time of drug use and relating these parameters to those found in pharmacodynamic studies (12). Unlike cases involving use of alcohol, impairment of performance from cannabis use is not easily correlated to blood or plasma concentrations of THC or its metabolites. Maximum drug effects may occur later than peak blood concentrations of THC or its active metabolites. Effects on the brain continue as blood concentrations of active drug decrease, a process termed hysteresis (13).

Investigations dating back to those by Lemberger (14) have attempted to relate blood or plasma cannabinoid concentrations with the time after smoking or oral ingestion of cannabis (14–19). Using different methods of analysis, scientists produced expected time-vs-plasma concentration profiles but described large inter- and intraindividual variations in peak values, times to reach maximum concentrations, and areas under the curve. Most persons who were infrequent cannabis users had plasma THC concentrations <1 μg/L after 4 h (20). Peat (21) introduced results for frequent cannabis users showing mean (SE) plasma THC and THCCOOH concentrations of 0.86 (0.22) and 45.8 (13.1) μg/L, respectively, for persons who reported their last cannabis use more than 12 h before blood collection. In a well-controlled study of 6 cannabis users, Huestis et al. (19) collected blood samples from volunteers after they had smoked single cannabis cigarettes containing 0%, 1.75%, and 3.55% THC. Participants were housed in a secure medical unit with dosing delayed until urine concentrations of cannabinoids were <20 μg/L. Conditions that contribute to interindividual variation in plasma concentrations of THC and its metabolites were carefully controlled, e.g., cigarette potency, number of puffs, time between puffs, length of inhalation, and length of time that smoke was held in the lungs were standardized, but for safety reasons other variables, such as depth of inhalation, were not. First samples were collected at 1 min after smoking and at frequent intervals up to 168 h. From these data, the authors developed 2 models to predict time of last cannabis use within 95% confidence intervals (CIs). The first model computed the elapsed time between smoking cannabis and blood collection based on plasma THC concentration alone, whereas the second model used the plasma THCCOOH/THC concentration ratio. They applied the models to results from all published studies at the time that reported THC and/or THCCOOH concentrations measured by either RIA or gas chromatography–mass spectrometry with either internal or external standardization. They found that the models correctly predicted time of use within the CI for ~90% of samples. The models appeared to slightly overestimate time immediately after smoking and underestimate later times. The models were not challenged with samples having plasma THC concentrations <2 μg/L because of analytical limitations at the time. When applying the models to whole blood concentrations, it is important to remember that blood THC and THCCOOH concentrations are lower than in plasma because of restricted distribution of these analytes into erythrocytes. The blood-to-plasma ratio is estimated to be 0.5 for living humans, although supporting data are limited (22, 23).

Scientists in North America, Europe, Australia, and Canada have applied these predictive models in forensic and medical situations in which it was important to estimate the time of last cannabis use. Challenging the models with samples containing lower THC concentrations and with other samples collected after multiple cannabis doses extends the method validation and increases the usefulness of the models. The current study examines plasma THC and THCCOOH concentrations in 717 plasma samples collected from 38 males after each smoked a cannabis cigarette in the morning and from 30 of these same individuals after they had smoked a second cigarette 4 h later. The original models were evaluated for accuracy in predicting the time of last cannabis use, the magnitude of error of estimations, and instances when actual times were longer or shorter than predicted time intervals.

Materials and Methods

PARTICIPANTS AND STUDY DESIGN

Descriptions of the participants and study design were reported previously (24). Thirty-eight males with a history of cannabis use provided informed consent to this National Institute on Drug Abuse Intramural Research Program Institutional Review Board–approved protocol. The study participants were compensated for their time and effort. All resided on the secure clinical research unit for at least 1 day before dosing and 2 days afterward. No drugs were administered until the urine cannabinoid concentrations were <20 μg/L. For safety, participants were medically evaluated during and for 1 week after drug administration.

At 0900 on the day of testing, participants received a single oral dose of placebo (n = 10) or up to 90 mg of rimonabant. Two hours later, they smoked a cannabis cigarette containing 2.64% THC by weight, estimated to contain ~20 mg of THC. The number of puffs and time between puffs were standardized. Blood for THC and THCCOOH assays was drawn from an indwelling venous catheter in the arm 120 and 5 min before cannabis smoking and at 2, 5, 10, 15, 20, 25, 30, 50, 70, 90, 110, and 235 min after the start of smoking. Heparinized plasma was stored at −20 °C until analysis. Four hours after smoking the first cigarette, 30 of the men smoked a second

cigarette containing 2.64% THC. Blood samples were collected at the same time intervals as described for the first dose, except that the 235-min collection was omitted.

The previously published study designed to investigate the blockade of cannabis effects demonstrated that rimonabant had no effect on THC and THCCOOH pharmacokinetics *(24)*. The participants receiving rimonabant and placebo could therefore be grouped together for the current study and the results generalized to cannabis users.

Plasma THC and THCCOOH concentrations were determined in plasma from blood collected from 38 participants in the morning smoking session and 30 who also smoked in the afternoon. Occasional samples had THCCOOH <2.5 μg/L, the limit of quantification (LOQ) for the method. In all, 717 plasma THC and 704 plasma THCCOOH concentrations were evaluated with the two predictive models.

ANALYTICAL METHOD

Plasma samples were analyzed for THC and THCCOOH by a previously published method *(25)*. Briefly, trideuterated THC and THCCOOH internal standards were added to plasma to improve identification and quantification. Proteins were precipitated with acetonitrile. The extraction method used CleanScreen solid-phase extraction columns (United Chemical Technologies), with THC eluted with hexane–ethyl acetate–ammonia hydroxide (93:5:2 by volume) and THCCOOH eluted with hexane–ethyl acetate (70:30 by volume). Trifluoroacetyl-THC and trifluoroacetyl-hexafluoroisopropyl-THCCOOH derivatives in the same reconstituted extract were injected into a Finnegan/MAT Model 4023 gas chromatograph–mass spectrometer operated in the negative-ion chemical ionization mode with methane as reagent gas, helium as carrier gas, and a DB 1 capillary column (J & W Scientific). Cannabinoid concentrations were determined by use of ion m/z 410 for THC and m/z 422 for THCCOOH. The LOQs were 0.5 μg/L for THC and 2.5 μg/L for THCCOOH, with CVs across the analytical range of 4.1%–11% and 4.9%–12%, respectively.

PREDICTIVE MODELS

Huestis et al. *(19)* previously published models for estimating time of last cannabis use. Model I determined time estimates from plasma THC concentrations and model II from the plasma THCCOOH/THC concentration ratios. The formulas are reproduced below, with t representing the elapsed time in hours between the beginning of cannabis smoking and blood collection, and CI representing the 95% confidence interval for the estimate of t. The subscripts 1 and 2 refer to models I and II, respectively, and brackets indicate the concentrations of THC or THCCOOH in μg/L:

$$\text{Model I: } \log t = -0.698 \log [\text{THC}] + 0.687$$

$$\log \text{CI}_1 = \log t \pm 1.975 \times$$

$$\sqrt{0.030 \left\{ 1.006 + \frac{(\log[\text{THC}] - 0.996)^2}{89.937} \right\}}$$

$$\text{Model II: } \log t = (0.576 \log [\text{THCCOOH}]/[\text{THC}]) - 0.176$$

$$\log \text{CI}_2 = \log t \pm 1.975 \times$$

$$\sqrt{0.045 \left\{ 1.006 + \frac{(\log[\text{THCCOOH}]/[\text{THC}] - 0.283)^2}{123.420} \right\}}$$

These equations were developed from cannabinoid concentrations in plasma samples collected for up to 168 h after controlled smoking of a 1.75% and a 3.55% THC cigarette by each of 6 cannabis users residing continuously in a secure clinical research unit *(19)*. Drug administration was not initiated until their urine cannabinoid concentrations were <20 μg/L. Table 1 is reproduced from that report *(19)* and displays the 95% CIs, in hours, for selected predicted times after smoking using models I and II. These results are presented to show that the models predict last use within an interval of time. The magnitude of the interval is smaller when the elapsed time between cannabis use and blood collection is shorter.

In the current study, model I was applied to each plasma sample with a valid THC measurement and model II to those with valid THC and THCCOOH concentrations. All analyte results at or above the LOQs of the method were selected. For each model, the CI for time of last use was determined. The actual times of smoking were examined to determine whether they were within (i.e., correct) or outside (i.e., incorrect) the CI. The following parameters were calculated for each model: (*a*) accuracy [(number of correct time estimates/total number of estimates) $\times$ 100%]; (*b*) the mean magnitude of error (mean of absolute values of $t_{\text{actual}} - t_{\text{calculated}}$ for all incorrect estimates); and (*c*) the number of samples with actual times greater than the upper limit of the CI (i.e., the model estimated a shorter t than actual, termed an underestimate) or below the lower limit (i.e., the model estimated a longer t than actual, termed an overestimate) for each situation examined.

Table 1. 95% CIs for models I and II at predicted times of cannabis use.[a]

Predicted elapsed time, h	95% CI, h	
	Model I	Model II
0.5	0.2–1.1	0.2–1.3
1	0.5–2.2	0.4–2.6
2	0.9–4.4	0.8–5.3
4	1.8–8.8	1.5–10.5
6	2.7–13.2	2.3–15.8
8	3.6–17.6	3.0–21.0

[a] Reproduced from Huestis et al. [*J Anal Toxicol* 1992;16:283–90 *(19)*] by permission of Preston Publications, A Division of Preston Industries, Inc.

We applied the same evaluations to each sample, using the models in combination. With this application, estimates were considered correct if the true value of t fell within a range defined by the lower limit of the CI of either model and the upper limits of the CIs, whichever was highest.

Results

The results for predicted elapsed times between the beginning of cannabis smoking and blood collection obtained with model I, model II, and a combination of the models are summarized in Table 2. The conditions for the single cigarette study were similar to those in the study used to produce the models, except that cigarettes contained 2.64% THC instead of either 1.75% or 3.55% THC, and length of inhalation and the time smoke was held in the lungs were not controlled. For model I, Table 2 reflects that, for 392 of 427 samples collected from 38 individuals after they began smoking the first cigarette, the observed time fell within the predicted range of elapsed time. Another way to view this result is that the model was correct for 91.8% of cases. For those cases that were overestimated, the average error of actual elapsed times was 14 min lower than the lowest value in the CI. There were no underestimates when model I was applied to data obtained after the first cigarette.

As can also be seen in Table 2, the models provided similar results after volunteers (n = 30) smoked a second cannabis cigarette in the afternoon. A difference noted after multiple cigarettes was that 3 of 290 samples had actual elapsed times longer than predicted by model I, i.e., for these 3 samples the time of last use was underestimated.

Model II correctly estimated the time of last smoked dose for 94.0% of samples after a single cigarette. Unlike model I, most of the errors (21 of 415 samples) were underestimates. Estimates were more accurate after multiple doses.

We evaluated whether the CIs for models I and II could be combined to produce superior results. Shown in the lower portion of Table 2 are the accuracy, overestimates, and underestimates in predicted elapsed times when we used models I and II in combination. If the actual elapsed time after the beginning of smoking fell within a range with a lower limit equal to the lowest predicted confidence limit for either model and an upper limit equal to the highest predicted confidence limit for either model, then results were considered correct. Accuracies were near 99%, and there were no instances of underestimated predictions.

One of the limitations mentioned in the introduction was that the models had not been challenged for plasma THC concentrations <2 μg/L. This is an important limitation because concentrations in this range are expected in the first 4 h after cannabis smoking, the timeframe in which many individuals are impaired and attempt to perform skilled operations (20). In this study, 77 plasma samples from 26 individuals had THC concentrations in the range of 0.5–2 μg/L. The results of application of the models to these samples are shown in Table 3. All valid predictions were accurate with the combination of models I and II. Independently, the models were not as accurate for these concentrations as they were for samples with concentrations >2 μg/L: 80.5% compared with 91.2% for model I, and 77.6% compared with 95.5% for model II.

Discussion

For most forensic and medical applications, the ultimate goal of determining the time of last cannabis use is to relate this time to effects of the drug on the body. Effects vary among individuals, but most people experience the physiologic effects of increased heart rate and conjuncti-

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Table 2. Predicted elapsed time between cannabis smoking and blood collection with plasma THC ≥0.5 μg/L and THCCOOH ≥2.5 μg/L.

	n	Accuracy (samples within 95% CI), %	Elapsed time overestimated		Elapsed time underestimated	
			n	Mean (range) time, min	n	Mean (range) time, min
Model I						
Single dose	427	91.8	35	14 (<1 to 41)	0	
Multiple doses	290	90.3	25	18 (<1 to 50)	3	5 (2–11)
All cases	717	91.2	60	16 (<1 to 50)	3	5 (2–11)
Model II						
Single dose	415	94.0	4	3 (<1 to 6)	21	38 (2–94)
Multiple doses	289	97.6	7	2 (<1 to 4)	0	
All cases	704	95.5	11	2 (<1 to 6)	21	38 (2–94)
Combination of models I and II[a]						
Single dose	415	99.5	2	1 (<1 to 1)	0	
Multiple doses	289	98.6	4	2 (<1 to 4)	0	
All cases	704	99.1	6	2 (<1 to 4)	0	

[a] Time interval defined by the lowest and highest 95% confidence limits of both models.

Table 3. Predicted elapsed time between cannabis smoking and blood collection with plasma THC between 0.5 and 2.0 μg/L and THCCOOH $\geq$2.5 μg/L.

	n	Accuracy (cases within 95% CI), %	Elapsed time overestimated		Elapsed time underestimated	
			n	Mean (range) time, min	n	Mean (range) time, min
Model I	77	80.5	15	31 (3–50)	0	
Model II	76	77.6	0		17	37 (5–87)
Models I and II[a]	76	100.0	0		0	

[a] Time interval defined by the lowest and highest 95% confidence limits of both models.

val injection, or bloodshot eyes (26, 27). These effects begin during smoking and may last up to several hours. Effects on the brain include euphoria and decrements in memory, the ability to maintain attention, estimating time, and coordination on divided attention tasks (23). The length of time that acute effects on the brain continue has been debated among scientists. Some investigators have reported subjective and impaired behavioral effects for up to 3 h after the end of smoking but could not find significant effects the following day (7, 28–30). Others have reported decrements in cognitive function and complex performance tasks for more than 24 h (31–33). A consensus panel of experts that met to determine the current state of knowledge for effects of cannabis on driving performance reported that "most behavioral and physiological effects return to baseline levels within 3–5 h after drug use, although some investigators have demonstrated residual effects in specific behaviors such as complex divided attention tasks for up to 24 h" (23). Using the models and an individual's plasma THC and THCCOOH concentrations, one may estimate the time the individual last used cannabis and from this time predict cognitive or performance decrements.

The results of this study demonstrate that model I accurately predicts the time of last cannabis use for >90% of cases and that incorrect predictions are overestimates after single doses. After multiple doses of cannabis, accuracy remains high, but 3 of 290 results were underestimated. Although that number is small, we pay special attention to these underestimates because in general they have a greater impact on actual cases than do overestimates. For example, if a judicial investigator or physician wants to know whether a person with THC in his or her blood was impaired at the time of an accident, it is important to know how long before the accident that person smoked cannabis. Underestimating this time increases the potential for falsely accusing an individual of being impaired at the time of the accident. For our 3 cases, the underestimates were not serious problems, however, because the magnitudes were small, ranging from 2 to 11 min. If we used the estimated times in these cases to predict the effects of cannabis on the individuals, the errors in time are small compared with the variability in specific effects and will not impact our decision.

Determining accuracy after a second cigarette is an important finding because previous studies did not ad-

dress applying the models to multiple THC administrations. Bogusz, in a letter to the editor in the *Journal of Analytical Toxicology (34)*, questioned the applicability of the predictive models when individuals ingested multiple doses of cannabis. Huestis and Cone addressed many, but not all, of his concerns in a response and suggested that the models be examined in a multiple-dose study (34). We now demonstrate that model I gives accurate predictions for >90% of plasma samples collected after multiple cannabis doses.

After single doses, model II was 94.0% accurate, but most errors (21 of 415 samples) were underestimates. However, all 21 were from samples collected >3 h after smoking. Huestis et al. (19) noted in the publication of the models that predictions at longer elapsed times were occasionally underestimated. For those times that were underestimated, the magnitude ranged from 2 to 94 min with a mean of 38 min.

The combined models gave time estimates that were 99.1% accurate with no underestimates. In addition, when overestimates occurred, they were less than 4 min. For the subset of samples with THC concentrations between 0.5 and 2.0 μg/L and THCCOOH concentrations $\geq$2.5 μg/L, the combined-model approach was correct in all instances. This method of analysis yields a longer estimated time interval, but greater certainty in prediction. One important outcome of greater certainty is that underestimates of time of use were eliminated. For forensic cases in which finders of fact wish to avoid underestimating time of use, the combined CI model offers greater accuracy and is the method of choice.

The cannabis cigarettes used in our study contained 2.64% THC. Individuals smoked 1 puff/min but chose their own depth of inhalation. This rate is greater than self-paced smoking. All had increases in heart rate and subjective drug effects. According to ElSohly et al. (35), in 1997 the mean THC concentration in seized cannabis was 4.2%. Of course, cannabis can have a higher THC content. The models were developed from plasma data collected after persons smoked a 1.75% and a 3.55% cigarette, the latter having more THC than used in the current study (19). Although peak concentrations were higher for the 3.55% cigarettes, the times of use fell within a range similar to that for the lower-dose cigarette. Other studies also have shown that cannabis users tend to titrate their dose of drug to maintain the level of intoxication they

prefer (20). One might expect users who are free to choose their own smoking pattern to keep the dose of THC within a range that produces this effect even if the cigarette THC content is high. Their plasma THC and THCCOOH concentration profiles would be similar to those after smoking of a less potent cigarette. In addition, the models have been shown to be accurate in many legal proceedings in multiple countries over the last 13 years when the times of cannabis use were known.

A common problem in applying the models to actual situations is that many accident victims die and THC and THCCOOH concentrations are available only for post-mortem blood. As mentioned in the introduction, the average antemortem blood-to-plasma ratio is ~0.5. One can estimate a plasma concentration from a blood concentration by dividing by 0.5 and inserting the plasma concentration into the formulas to estimate time of last cannabis use. However, in fatal accident cases, the important variables are the concentrations of drugs and metabolites in antemortem plasma; estimating these from postmortem blood has not been well documented. Giroud et al. (36) studied the concentrations of THC and THC-COOH in blood and plasma from live patients and found mean ratios similar to that reported above, specifically 0.67 and 0.59, respectively. These authors also measured postmortem blood and postmortem "serum" (obtained from centrifuging postmortem whole blood) cannabinoid concentrations and found variable ratios with mean blood-to-serum ratios of 0.45 for THC and 0.37 for THC-COOH. The causes of this variability can be many, including changes in serum after death and postmortem redistribution. The study did have an unavoidable limitation of being unable to relate postmortem blood and antemortem plasma analyte concentrations. Errors in converting postmortem blood to antemortem plasma concentrations may have an impact on predictions using model I but would have less effect on predictions using model II because model II estimates are based on the ratio of THCCOOH to THC. These 2 cannabinoid molecules are similarly partitioned between plasma and blood cells, making the ratio less sensitive to partition variability.

In conclusion, in this study we extended the validation of 2 previously described models for predicting the time of last cannabis use from plasma THC and THCCOOH concentrations to samples collected after multiple cannabis exposures and also those with low THC concentrations. The predictive models provide an objective and validated method for assessing the contribution of cannabis to accidents or clinical symptoms based on cannabinoid concentrations in a single plasma sample.

References

1. World Health Organization. Management of substance abuse: facts and figures. http://www.who.int/substance_abuse/facts (accessed March 2005).
2. Soderstrom CA, Trifillis AL, Shankar BS, Clark WE, Cowley RA. Marijuana and alcohol use among 1023 trauma patients. Arch Surg 1988;123:733–7.
3. Crouch DJ, Birky M, Gust SW, Rollins DE, Walsh JM, Moulden JV, et al. The prevalence of drugs and alcohol in fatally injured truck drivers. J Forensic Sci 1993;38:1342–53.
4. Smiley A. Marijuana: on-road and driving simulator studies. Alcohol Drugs Driving 1986;2:121–34.
5. Ramaekers JG, Robbe HWJ, O'Hanlon JF. Marijuana, alcohol and actual driving performance. Hum Psychopharmacol 2000;15:551–8.
6. Moskowitz H. Marijuana and driving. Accid Anal Prev 1985;17:323–45.
7. Kurzthaler I, Hummer M, Miller C, Sperner-Unterweger B, Gunther V, Wechdorn H, et al. Effect of cannabis use on cognitive functions and driving ability. J Clin Psychiatry 1999;60:395–9.
8. Walsh GW, Mann RE. On the high road: driving under the influence of cannabis in Ontario. Can J Public Health 1999;90:260–3.
9. Ogden EJD, Moskowitz H. Effects of alcohol and other drugs on driver performance. Traffic Inj Prev 2004;5:185–98.
10. Papafotiou K, Carter JD, Stough C. The relationship between performance on the standardised field sobriety tests, driving performance and the level of delta-9-tetrahydrocannabinol (THC) in blood. Forensic Sci Int 2005. http://www.sciencedirect.com (accessed June 2005).
11. Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid Anal Prev 2004;36:239–48.
12. Huestis MA, Smith ML. Human cannabinoid pharmacokinetics and interpretation of cannabinoid concentrations in biological fluids and tissues. In: Elsohly M, ed. Marijuana and the cannabinoids. New York: Humana Press, 2005;in press.
13. Cone EJ, Huestis MA. Relating blood concentrations of tetrahydrocannabinol and metabolites to pharmacologic effects and time of marijuana usage. Ther Drug Monit 1993;15:527–32.
14. Lemberger L. The metabolism of the tetrahydrocannabinols. Adv Pharmacol Chemother 1972;10:221–55.
15. Hunt CA, Jones RT. Tolerance and disposition of tetrahydrocannabinol in man. J Pharmacol Exp Ther 1980;215:35–44.
16. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma levels of delta-9-tetrahydrocannabinol after intravenous, oral and smoke administration. NIDA Res Monogr 1981;34:250–6.
17. McBurney LJ, Bobbie BA, Sepp LA. GC/MS and Emit analyses for delta-9-tetrahydrocannabinol metabolites in plasma and urine of human subjects. J Anal Toxicol 1986;10:56–64.
18. Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther 1983;34:352–63.
19. Huestis MA, Henningfield JE, Cone EJ. 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). J Anal Toxicol 1992;16:283–90.
20. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH

during and after smoking marijuana. J Anal Toxicol 1992;16:276–82.

21. Peat MA. Distribution of delta-9-tetrahydrocannabinol and its metabolites. In: Baselt RC, ed. Advances in analytical toxicology II. Chicago: Year Book Medical Publishers, 1989:186–217.

22. Mason AP, McBay AJ. Cannabis: pharmacology and interpretation of effects. J Forensic Sci 1985;30:615–31.

23. Couper F, Logan B, Corbett MJ, Farrell L, Huestis M, Jeffrey W, et al. Drugs and human performance fact sheets. Washington, DC: National Highway Traffic Safety Administration, 2004:1–100.

24. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Arch Gen Psychiatry 2001;58:322–30.

25. Huang W, Moody DE, Andrenyak DM, Smith EK, Foltz RL, Huestis MA, et al. Simultaneous determination of delta-9-tetrahydrocannabinol and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol in human plasma by solid phase extraction and gas chromatography-negative ion chemical ionization-mass spectrometry. J Anal Toxicol 2001;25:531–7.

26. Huestis MA. Cannabis (marijuana)—effects on human behavior and performance. In: Farrell LJ, Logan BK, Dubowski KM, eds. The effects of drugs on human performance and behavior, 1st ed. Taipei: Central Police University Press, 2002:15–60.

27. Huestis MA, Sampson AH, Holicky BJ, Henningfield JE, Cone EJ. Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther 1992;52:31–41.

28. Chait LD, Perry JL. Acute and residual effects of alcohol and marijuana, alone and in combination, on mood and performance. Psychopharmacology (Berl) 1994;115:340–9.

29. Liguori A, Gatto CP, Robinson JH. Effects of marijuana on equilibrium, psychomotor performance, and simulated driving. Behav Pharmacol 1998;9:599–609.

30. Harder S, Rietbrock S. Concentration-effect relationship of delta-9-tetrahydrocannabiol and prediction of psychotropic effects after smoking marijuana. Int J Clin Pharmacol Ther 1997;35:155–9.

31. Heishman SJ, Huestis MA, Henningfield JE, Cone EJ. Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. Pharmacol Biochem Behav 1990;37:561–5.

32. Leirer VO, Yesavage JA, Morrow DG. Marijuana carryover effects on aircraft pilot performance. Aviat Space Environ Med 1991;62:221–7.

33. O'Kane CJ, Tutt DC, Bauer LA. Cannabis and driving: a new perspective. Emerg Med 2002;14:296–303.

34. Bogusz M. Concerning blood cannabinoids and the effect of residual THCCOOH on calculated exposure time. J Anal Toxicol 1993;17:313–6.

35. ElSohly MA, Ross SA, Mehmedic Z, Arafat R, Banahan BFl. Potency trends of delta-9-THC and other cannabinoids in confiscated marijuana from 1980–1997. J Forensic Sci 2000;45:24–30.

36. Giroud C, Menetrey A, Augsburger M, Buclin T, Sanchez-Mazas P, Mangin P. Delta9-THC, 11-OH-delta9-THC and delta9-THCCOOH plasma or serum to whole blood concentrations distribution ratios in blood samples taken from living and dead people. Forensic Sci Int 2001;123:159–64.