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Δ9-tetrahydrocannabinol (THC) is present in the body between smoking sessions in occasional non-daily cannabis users

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ABSTRACT

Background: THC can be measured in blood up to a month after last intake in heavy cannabis users. The cognitive deficits during abstinence have been hypothesized to be at least in part due to residual THC in brain. To which extent THC accumulation will occur after occasional cannabis use has gained limited attention. We aimed to predict THC-levels between smoking sessions in non-daily as well as daily cannabis users and to compare these predictions with published THC levels.
Methods: Predictions were based on pharmacokinetic principles on drug accumulation after repeated dosing, applied to different cannabis smoking patterns, using data from a three-compartment model for THC pharmacokinetics and results on the terminal elimination half-life of THC in humans. We searched the literature for THC measurements which could be compared with these predictions. We found no such results from controlled studies of long-term repeated cannabis consumption of known THC amounts. Thirteen published studies contained, however, enough information on cannabis use and results from THC-measurements to make tentative comparisons with the predictions.
Results: The predictions of THC-plasma levels present after different cannabis smoking patterns assuming terminal elimination half-lives of THC of 21.5 h or longer, had some support in published THC levels measured in individuals self-reporting their cannabis consumption. We found no consistent discrepancies between the predictions and reported THC plasma levels after non-daily or daily cannabis use. The predictions indicate that THC might be present in plasma between smoking sessions above usual analytical limits when smoking every third and second day, and at lower levels after once weekly smoking.
Conclusions: The study indicates that THC might be present continuously even in non-daily smokers at low levels, even if the smoking occasions are separated by a week. This is different from alcohol, where ethanol has disappeared after a day. From a toxicological point of view the persistance of THC in the brain, raises questions whether this should be given more attention as with other toxicological thinking where long-term presence of bioactive substances gives rise to concern. There are some uncertainties in this analysis, and controlled studies on THC-accumulation accompanying different use patterns seem warranted.

1. Background

With rapidly changing legislation across the world on recreational and medicinal use of cannabis, increased use can be expected [1]. There is also a public tendency to view cannabis as less dangerous than in the past [2] and such views might further lead to increased use [3]. Cannabis use can result in various degrees of acute intoxication with cognitive and psychomotor impairment. Chronic use might be related to long-term effects on cognition, brain structure, psychiatric disorders and cannabis use disorders [4,5]. The cognitive deficits during early abstinence in chronic daily users have been hypothesized to be at least in part due to residual THC in brain [6,7] as THC can be measured in blood for up to a month after last intake in such users [8,9]. This prolonged THC-elimination has been reported related to years of prior cannabis use [9], and has been suggested to represent gradual transfer into the blood stream from storage in adipose tissue [6,10].

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Most cannabis users are not daily smokers [11,12] and the question whether occasional recreational smoking can lead to THC accumulation between smoking sessions has only gained limited research attention. Mounting THC levels in blood have not been expected in occasional users as there are numerous observations of a rapid decline of blood THC concentrations after smoking, with the detection limit of usual analytical methods reached within 6–12 h [6,13]. Elimination half-lives ($T_{1/2}$) determined from blood THC concentration measurements during the hours following smoking have accordingly been below 2 h [14–19].

The pharmacokinetics of THC is, however, complex and different multiple compartment models have been suggested [19,20]. Recently, Heuberger and co-workers [21] developed a more complete population pharmacokinetic model of THC, representing a three compartment model, based on detailed analysis of several previous unpublished and published [22] experimental studies. Heuberger's paper suggests that THC regardless of route of intake and intake frequency has a fast initial and intermediate $T_{1/2}$, but an apparent terminal $T_{1/2}$ that is about 21.5 h. Other previous studies have also reported $T_{1/2}$ in the order of 18–36 h [15,23,24]. One study with blood sampling for an extended period of at least 10 days after THC administration even reported a mean terminal $T_{1/2}$ of 4.3 days in daily cannabis users [25].

Whether there is a short (few hours) or long (days) $T_{1/2}$ of THC would greatly influence the possibility of THC to being present in the body of recreational cannabis users between cannabis intake episodes.

In the present study, we first wanted to develop a model that could predict THC-levels in plasma present between intakes with certain patterns of repeated recreational cannabis use. Knowledge of drug half-life and dosing frequency gives the possibility to calculate extent of drug accumulation [26] after repeated dosing. Recreational non-daily use of cannabis does not occur with great regularity but estimates of the THC-levels present in blood between intakes were performed for individuals with smoking patterns of e.g. once a week, every third and every second day.

The second purpose of the present study was to compare the predictions from the pharmacokinetic model with published data from users with long-term repeated smoking of cannabis, to the extent that such data could be retrieved from the existing literature.

2. Methods

2.1. Prediction of plasma THC levels after different repeated cannabis use patterns

If a drug is eliminated according to first-order kinetics, the amount of drug in the body will increase until a steady state (a plateau level) is reached after a period corresponding to approximately 5 times $T_{1/2}$. At this plateau, the amount of drug dosed per interval is equal to the amount of drug eliminated during that interval. For any drug with multiple dosing, the accumulated amount of the drug in the body at plateau conditions can be calculated according to the expression [26]:

$$AI = \frac{1}{1 - e^{-k\tau}}$$

K is the elimination constant of the drug in question ($k = \frac{0.693}{T1/2}$), and τ is the dosing interval.

AI is the accumulation index, i.e. the ratio between the amount of drug in the body at plateau any given time after the last dose and the amount of drug in the body at the same time after a single dose. After distribution equilibrium is attained, the AI would also be valid for circulating drug concentrations.

To apply this general pharmacokinetic principle of drug accumulation to THC after cannabis use, a certain regularity of smoking a given dose was postulated. We did this for the prediction of THC concentrations after cannabis used once a week, 2–3 times per week (every third day), every second day, once every day, and twice every day. Daily smoking (once or twice) was included among the predictions for the purpose of possible comparison with more published data (see below). The pharmacokinetic model of Heuberger and co-workers [21] indicates that the distribution of THC is finalized at 12 h after smoking and the terminal phase is reached at this time. We thus calculated the expected THC concentrations in plasma 12 h after smoking until the next intake. We decided to use smoking of a dose of 54 mg THC the standard dose in our calculations. This allowed us to use some of the predictions calculated by Heuberger's group [21]. This dose is probably higher than often used by occasional users, about 25 mg THC and closer to that accepted by experienced users, 35–54 mg [15,21,27]. Thus, we obtained a representation of near maximal accumulation obtainable by different smoking patterns. Based on previous studies [24,28] we assumed that there was no difference in terminal THC half-life between light and heavy cannabis users. In the present predictions we used both the THC terminal half-life of 21.5 h [21] and the mean value of 4.3 days as found by Johansson and co-workers [25]. These half-lives cover roughly the range of published elimination half-lives of THC from studies with sampling periods longer than 12–24 h. The results of the predictions are shown in Table 1.

2.2. Published data on THC levels in cannabis users with long-term repeated intake

To collect studies with data that could be compared with the calculated predicted THC levels, we searched Ovid Medline and PubMed for relevant studies. We used the search terms "cannabis or cannabinoid or marijuana or THC" and "accumulation or excretion or disposition or half-life or pharmacokinetics or

Table 1
The effect of different dosing intervals on accumulation index (AI) and calculations of typical predicted THC plasma concentrations (95 % prediction interval) [21], 12 h after smoking 54 mg THC, and at next intake, assuming terminal $T_{1/2}$ of 21.5 h or 4.3 days, respectively.

Pattern of use	$T_{1/2}$ = 21.5 h			$T_{1/2}$ = 4.3 days		
	Accumulation Index (AI)	THC plasma concentrations (ng/ml)		Accumulation Index (AI)	THC plasma concentrations (ng/ml)	
		12 h after smoking	At next intake		12 h after smoking	At next intake
Infrequent	1.00	1.2 (0.6–3.0)		1.00	1.2 (0.6–3.0)	
Once a week	1.01	1.2 (0.6–3.0)	0.01 (0.0-0.02)	1.48	1.8 (0.9–4.4)	0.7 (0.3–1.6)
Every third day	1.11	1.3 (0.7–3.3)	0.2 (0.1-0.5)	2.61	3.1 (1.6–7.8)	2.1 (1.1–5.2)
Every second day	1.27	1.4 (0.7–3.6)	0.4 (0.2–1.1)	3.64	4.4 (2.2–10.9)	3.5 (1.7–8.6)
Once daily	1.87	2.2 (1.1–5.6)	1.5 (0.7–3.8)	6.71	8.1 (4.0–20.1)	7.5 (3.7–18.6)
Twice daily	3.13	3.8 (1.9–9.4)	3.8 (1.9–9.4)	12.83	15.4 (7.7–38.5)	15.4 (7.7–38.5)

concentration in blood/plasma/serum", restricting the search to human studies in the English language. From the retrieved papers, we selected those, which had some information on the frequencies of use of cannabis in the subjects and some measure of THC-levels in whole blood (B), serum (S) or plasma (P). We also searched the publications' reference lists for additional publications. The search led to 13 scientific publications with this kind of information.

We found no controlled studies of THC-levels obtained after long-term repeated smoking of cannabis with known amounts of THC. We used data from some studies, where THC concentrations in blood or plasma were measured in people who had self-reported their consumption of cannabis in the preceding period. Other studies where THC was administered for pharmacodynamics/kinetic purposes to people with different prior cannabis consumption, the baseline levels related to previous self-reported cannabis intake, were also used for comparison with the prediction model. The results are presented in Table 2.

3. Results

3.1. Prediction of plasma THC levels after different repeated cannabis use patterns

Table 1 shows the calculated accumulation indices (AIs) and the predicted THC-plasma levels between intakes after certain non-daily cannabis use patterns. For comparison, Table 1 also shows data for infrequent smoking and two patterns of daily smoking.

The AIs increased with increasing frequency of use. The difference between use once a week and every third or every second day was about 10 % or 25 %, respectively when $T_{1/2}$ was set to 21.5 h. Corresponding differences were around 70 % or 145 %, respectively when a $T_{1/2}$ of 4.3 days was applied (column 1 and 4, Table 1). These differences were reflected in THC levels present between intakes for the three different smoking patterns (once a week, every third or second day).

Based on a $T_{1/2}$ of 21.5 h the THC plasma concentration was below 1 ng/ml 24 h after the last smoking for all three non-daily smoking patterns (not shown in Table 1) and decreased to plasma levels below 0,5 ng/ml at next intake (column 3, Table 1). As most routine analytical methods for plasma THC have LOQs of 0.5 or 1 ng/ml, no finding of THC in the period between intakes would often occur. But even for the least frequent pattern (once a week), some THC was present in plasma.

Based on a $T_{1/2}$ of 4.3 days the THC plasma levels were substantially higher and would in most cases except for smoking once a week, be above the analytical LOQs during the whole period between intakes (column 6, Table 1).

3.2. Comparison of predicted and published data on THC levels in cannabis users with long-term repeated intake

Table 2 summarizes data from 13 studies with data on both long-term repeated cannabis consumption and measurements of THC-levels in whole blood (B), serum (S) or plasma (P) after distribution equilibrium of the last dose was reached. The studies are listed according to intake of cannabis: once a week, every third day, every second day, once a day or several times per day.

Table 2
Data from 13 studies measuring THC levels in blood/plasma/serum after preceding long-term repeated cannabis use. Abbreviations about time: w: weeks, d: days, h: hours. Abbreviations on statistics: me: mean, md: median, r: range, SE: standard error, SD: standard deviation, 95 CI: 95 % confidence interval. Abbreviations about sample matrix: S: serum, P: plasma, B: whole blood.

Reference	Group size, amount and frequency of cannabis use	Time between last smoking and blood sampling	Measured THC conc. ng/ml	THC conc.[g] in plasma ng/ml
Smoking once a week				
Skopp & Pötsch, 2008 [41]	N=6, up to 1 joint/w	36 (24–48) h me (r)	S: 0 (0–1.4) md (r)	0 (0–1.4) md (r)
Ramaekers et al. 2016 [39]	N=5[a], 10-15 occasions/3 months, i.e. 0.8-1.2 occasions/w	Not specified	S: 0 (0–1) md (r)[a]	0 (0–1) md (r)
Smoking every third day				
Hartman et al. 2015[c] [42]	N=32, up to 2–3 occasions/w	2 (0.3–4) d md (r)	P: 0.9 md[b]	0.9 md
Hartman et al. 2016[c] [43]	N=19, up to 2–3 occasions/w	2 (0.3–4) d md (r)	B: (0–6.3) (r)	0-9.7 r
Smoking every second day				
Skopp & Pötsch, 2008 [41]	N=15, up to one joint /d, i.e. 3–4 joints/w(?)	36 (24–48) h me (r)	S: 0.3 (0–2.6) md (r)	0.3 (0–2.6) md (r)
Hjorthøy et al. 2012 [29]	N=88, on average 40.4 (3.24 SE) joints on 13.8 (0.76 SE) d/month	1 d md	P: 4.1 (0.76) me (SE)	4.1 (0.76) me (SE)
Smoking once daily				
Skopp & Pötsch, 2008 [41]	N=16, more than 1 joint/d	36 (24–48) h me (r)	S: 1.3 (0–6.4) md (r)	1.3 (0–6.4) md (r)
Toeness et al. 2008[c] [15]; Ramaekers et al. 2009[c] [44]	N=12, using 340 (86) times me (SD) per year, 2 joints on 7 (4–25) md (r) occasions last week	One night (8 h?) + 4h after smoking placebo	S: 2.8 (3.4) me (SD)	2.8 (3.4) me (SD)
Smith et al. 2018 [30]	N=16, using 0.30 (0.22) g me (SD) cannabis per occasion, on 1.3 (0.8) me (SD) daily occasions	At least 12 h	B: 1.2 (1.5) me (SD)	1.8 (2.3) me (SD)
Smoking multiple times daily				
Odell et a. 2016 [40]	N=21, daily using 4–6 joints, or 20 (5–50) bongs, or 2 (0.5–4) g heads, md (r)	25.5 (12–31) h[d] md (r)	B: 2 (1–13) md (r)	3.1 (1.5–20) md (r)
Desrosiers et al. 2014 [27]	N= 14, using 4.5 (1.5–21) joints/d, md (r) for the last 14 (11–14) d, md (r)	22 (19–41) h md (r)	P: 4.8 (3.3–6.3) me (95% CI)[e]	4.8 (3.3–6.3) me (95CI)
Schwope et al. 2011 [45]	N=10, using 5 (1–12) joints/d, md (r); for the last 11 (8–14) d, md (r)	65 (39–116) h md (r)	P: 1.6 (0–7.3) md (r)	1.6 (0–7.3) md (r)
Bergamashi et al. 2013[c] [8]; Karschner et al.2016[c] [9]	N=28, using 9 (1–30) joints/d, md (r); for the last 14 (11–14) d, md (r)	At least 24 h	P: 2.7 (0–8.7)[f] md (r)	2.7 (0–8.7) md (r)
Smith et al. 2018 [30]	N=10, using 0,62 (0.36) g me (SD) cannabis per occasion on 2.7(0.93) me (SD) daily occasions	At least 12 h	B: 2.3 (2.9) me (SD)	3.5 (4.5) me (SD)

[a] Approximate numbers from fig. 1 and 4 [39].
[b] Calculated from data after placebo smoking, their supplementary table 5 [42].
[c] The two papers present different aspects of the same study.
[d] Time to first blood sample after 12 h since smoking [40].
[e] Data from supplementary data table 1e [27].
[f] Data from day 1, the day after admission day [8,9].
[g] Conversion factor from blood to plasma: x 1.54 [45,46]; serum to plasma ratio equals 1.0.

Two studies in Table 2 reported THC levels from smoking once a week, representing 11 individuals. For 5 of these the time between smoking and blood sampling was unknown, for the other 6 it was between 24 and 48 h. The highest value was 1.4 ng/ml, but in most cases, the THC concentration was below the LOQ of 1 ng/ml. These results were compatible with the predictions in Table 1.

Two studies presented THC-levels from 32 people smoking every third day or less often (Table 2). The time between last smoking and blood sampling was 2 days (median, with a range of 0.3–4 days). The measured THC plasma levels ranged from 0 to 9.7 ng/ml. The highest value was somewhat higher than the highest predicted THC-level.

Two studies measured THC levels from 103 individuals smoking every second day (Table 2). The median time since last smoking was 24 h or more. The study with the most detailed description of cannabis consumption and most participants [29] reported a mean THC plasma concentration of 4.1 ng/ml for the period between smoking occasions compatible with the predictions in Table 1, column 5 and 6, i.e. those based on a terminal THC $T_{1/2}$ of 4.3 days.

Ten different studies on smokers with intakes once or multiple times daily with times between last smoking and blood sampling from 12 to 116 h were collected (Table 2). The median or mean THC plasma levels were ranging from 1.3–4.8 ng/ml, with individual values ranging from 0 to 20 ng/ml. The highest individual values recorded were compatible with the predictions presented in column 5 and 6 in Table 1.

4. Discussion

The present predictions of THC-plasma levels present after different cannabis smoking patterns assuming terminal elimination half-lives of THC of 21.5 h or longer, had some support in published THC levels measured in individuals self-reporting their cannabis consumption. We found no consistent discrepancies between the predictions and reported THC plasma levels after non-daily or daily cannabis use, supporting the reliability of the predictions. It is therefore reason to assume that THC will be present in plasma and organs in equilibrium with blood as e.g. the brain, between smoking sessions in non-daily users.

Inaccurate reporting of smoking frequency in the published studies cannot be excluded. Deliberate over- or underreporting may, however, be less of a problem than expected, as several studies comparing self-report and THC-biometrics have concluded that self-report can be quite reliable [30,31]

It could be argued that some of the higher values measured fitted with predictions due to the inclusion of THC results from samples taken before a distribution period of 8−12 h after last smoking had passed. This seems however very unlikely given the information in the different papers. On the other hand, for all consumption patterns we observed some deviations as several published individual THC-levels were lower than those predicted. In some instances, the broad range of smoking frequencies included in the group thus containing less frequent smoking than the pattern used to define the group, could explain this.

Another factor that would give rise to lower measured levels than those predicted was intake of lower doses than the dose (54 mg) THC used in the predictions, although this dose was considered to represent a medium-strong marihuana cigarette [21]. None of the studies in Table 2 reported the amount of THC consumed per dose, occasion or day. In general, the knowledge about doses of THC smoked by different individuals is quite limited. A recent Spanish study estimated a “median joint” to consist of 260 mg marihuana and to contain 7 mg THC [12]. The median number of joints smoked per occasion were 3 giving an intake of 21 mg per occasion. Other studies have estimated an average marihuana joint weighing 320 mg [11] or to be within the 3−500 mg range [32]. A meta-analysis found increasing mean THC content in herbal cannabis over the years, reaching about 10 % in 2010 [33]. Thus, a joint of 320 mg would contain about 32 mg THC. However all these studies showed large variations in joint size and THC content, in addition smokers often titrate the absorbed dose by adjusting the way they smoke according to the influence they experience during smoking [6], and considerable individual variation in the amount absorbed might be expected [13,14,27].

As it is possible that the dose used in the predictions was in the upper end of the usual dose range, the predicted THC plasma levels might probably be somewhat higher than those usually experienced by non-daily smoking. The most likely levels predicted for those smoking once a week (Table 1) did generally not exceed 2 ng/ml during the period until next smoking. THC concentrations in plasma below 2 ng/ml probably do not inflict psychomotor or neurocognitive impairment, but concentrations from 2−5 ng/ml might [34]. The relations between pharmacodynamic and pharmacokinetic parameters are, however, limited [28]. Some studies have shown a rough concentration effect relationship for THC levels in plasma [34–37], while others have not [13].Tolerance to certain effects of THC as a possible consequence of chronic use have been suggested in some studies [38], but is not found by others [39]. It might therefore be difficult to relate certain cognitive or psychomotor effects to the levels of THC being present between smoking sessions for once a week smokers. The chances of persistent cognitive impairment would probably be higher for those smoking every third or second day, with higher accumulated THC levels. On the other hand, development of tolerance might obscure such effects.

However, if we assume that THC will be present continuously in non-daily smokers, even if the smoking occasions are separated by a week, we face a situation quite different from that present among those drinking alcohol once a week and where ethanol has left the body after a day. From a toxicological point of view the persistent presence of a psychoactive substance (THC) in the brain, raises questions whether this should be given more attention as is the case elsewhere in toxicological thinking.

Presently, it is probably somewhat speculative to conclude that THC has a terminal half-life of days in all users, which could result in accumulation of THC and possible chronic impairing effects in regular users who use cannabis only once or a couple of days per week. There are, however, as discussed above, several indications that this could be the case. Also rough estimates of $T_{1/2}$ of THC from data presented by Odell and co-workers [40] and Bergamaschi and co-workers [8] indicate values of more than 4 days and around 6 days, respectively. Our current understanding of the pharmacokinetics of THC may be less than comprehensive. There is a great need for controlled studies clarifying the accumulation of THC after repeated cannabis smoking. Smoking frequency, in particular, should be addressed in such studies, as this is a critical variable for accumulation. This was recently indicated in a study where the frequency rather than amount of cannabis used in the last month correlated better with subsequent blood THC measurements [30]. Because cannabis potency and use in many parts of the world is increasing, it is fundamental to evaluate the risk of possible neurocognitive impairment of periods lasting substantially longer than the hours of acute inebriation.

Declaration of Competing Interest

JM has received remuneration from the Norwegian Department of Transportation, from Norwegian courts and police for reports on THC pharmacokinetics and effects related to driving behaviour. JGB does not have any conflicts of interests to declare.

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References

[1] J.G. Ramaekers, Driving under the influence of Cannabis: an increasing public health concern, JAMA 319 (14) (2018) 1433–1434.
[2] L.R. Pacek, P.M. Mauro, S.S. Martins, Perceived risk of regular cannabis use in the United States from 2002 to 2012: differences by sex, age, and race/ethnicity, Drug Alcohol Depend. 149 (2015) 232–244.
[3] Y. Shi, M. Lenzi, R. An, Cannabis liberalization and adolescent Cannabis use: a cross-national study in 38 countries, PLoS One 10 (11) (2015)e0143562.
[4] N.D. Volkow, J.M. Swanson, A.E. Evins, L.E. DeLisi, M.H. Meier, R. Gonzalez, et al., Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review, JAMA Psychiatry 73 (3) (2016) 292–297.
[5] Y.M. Terry-McElrath, P.M. O'Malley, L.D. Johnston, B.C. Bray, M.E. Patrick, J.E. Schulenberg, Longitudinal patterns of marijuana use across ages 18-50 in a US national sample: a descriptive examination of predictors and health correlates of repeated measures latent class membership, Drug Alcohol Depend. 171 (2017) 70–83.
[6] M.A. Huestis, Human cannabinoid pharmacokinetics, Chem. Biodivers. 4 (8) (2007) 1770–1804.
[7] W.M. Bosker, E.L. Karschner, D. Lee, R.S. Goodwin, J. Hirvonen, R.B. Innis, et al., Psychomotor function in chronic daily Cannabis smokers during sustained abstinence, PLoS One 8 (1) (2013)e53127.
[8] M.M. Bergamaschi, E.L. Karschner, R.S. Goodwin, K.B. Scheidweiler, J. Hirvonen, R.H. Queiroz, et al., Impact of prolonged cannabinoid excretion in chronic daily cannabis smokers' blood on per se drugged driving laws, Clin. Chem. 59 (3) (2013) 519–526.
[9] E.L. Karschner, M.J. Swortwood, J. Hirvonen, R.S. Goodwin, W.M. Bosker, J.G. Ramaekers, et al., Extended plasma cannabinoid excretion in chronic frequent cannabis smokers during sustained abstinence and correlation with psychomotor performance, Drug Test. Anal. 8 (7) (2016) 682–689.
[10] E. Johansson, K. Noren, J. Sjovall, M.M. Halldin, Determination of delta 1-tetrahydrocannabinol in human fat biopsies from marihuana users by gas chromatography-mass spectrometry, Biomed. Chromatogr. 3 (1) (1989) 35–38.
[11] G. Ridgeway, B. Kilmer, Bayesian inference for the distribution of grams of marijuana in a joint, Drug Alcohol Depend. 165 (2016) 175–180.
[12] C. Casajuana Kogel, M.M. Balcells-Olivero, H. Lopez-Pelayo, L. Miquel, L. Teixido, J. Colom, et al., The standard joint unit, Drug Alcohol Depend. 176 (2017) 109–116.
[13] S. Hartley, N. Simon, A. Larabi, I. Vaugier, F. Barbot, M.A. Quera-Salva, et al., Effect of smoked Cannabis on vigilance and accident risk using simulated driving in occasional and chronic users and the pharmacokinetic-pharmacodynamic relationship, Clin. Chem. 65 (5) (2019) 684–693.
[14] G.F. Kauert, J.G. Ramaekers, E. Schneider, M.R. Moeller, S.W. Toennes, Pharmacokinetic properties of delta9-tetrahydrocannabinol in serum and oral fluid, J. Anal. Toxicol. 31 (5) (2007) 288–293.
[15] S.W. Toennes, J.G. Ramaekers, E.L. Theunissen, M.R. Moeller, G.F. Kauert, Comparison of cannabinoid pharmacokinetic properties in occasional and heavy users smoking a marijuana or placebo joint, J. Anal. Toxicol. 32 (7) (2008) 470–477.
[16] P. Kelly, R.T. Jones, Metabolism of tetrahydrocannabinol in frequent and infrequent marijuana users, J. Anal. Toxicol. 16 (4) (1992) 228–235.
[17] C.C. Hunault, J.C. van Eijkeren, T.T. Mensinga, I. de Vries, M.E. Leenders, J. Meulenbelt, Disposition of smoked cannabis with high Delta(9)-tetrahydrocannabinol content: a kinetic model, Toxicol. Appl. Pharmacol. 246 (3) (2010) 148–153.
[18] A. Strougo, L. Zuurman, C. Roy, J.L. Pinquier, J.M. van Gerven, A.F. Cohen, et al., Modelling of the concentration–effect relationship of THC on central nervous system parameters and heart rate – insight into its mechanisms of action and a tool for clinical research and development of cannabinoids, J. Psychopharmacol. (Oxford, England) 22 (7) (2008) 717–726.
[19] A. Marsot, C. Audebert, L. Attolini, B. Lacarelle, J. Micallef, O. Blin, Population pharmacokinetics model of THC used by pulmonary route in occasional cannabis smokers, J. Pharmacol. Toxicol. Methods 85 (2017) 49–54.
[20] F. Grotenhermen, Pharmacokinetics and pharmacodynamics of cannabinoids, Clin. Pharmacokinet. 42 (4) (2003) 327–360.
[21] J.A. Heuberger, Z. Guan, O.O. Oyetayo, L. Klumpers, P.D. Morrison, T.L. Beumer, et al., Population pharmacokinetic model of THC integrates oral, intravenous, and pulmonary dosing and characterizes short- and long-term pharmacokinetics, Clin. Pharmacokinet. 54 (2) (2015) 209–219.
[22] A. Ohlsson, J.E. Lindgren, A. Wahlen, S. Agurell, L.E. Hollister, H.K. Gillespie, Single dose kinetics of deuterium labelled delta 1-tetrahydrocannabinol in heavy and light cannabis users, Biomed. Mass Spectrom. 9 (1) (1982) 6–10.
[23] M.E. Wall, B.M. Sadler, D. Brine, H. Taylor, M. Perez-Reyes, Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women, Clin. Pharmacol. Ther. 34 (3) (1983) 352–363.
[24] C.A. Hunt, R.T. Jones, Tolerance and disposition of tetrahydrocannabinol in man, J. Pharmacol. Exp. Ther. 215 (1) (1980) 35–44.
[25] E. Johansson, M.M. Halldin, S. Agurell, L.E. Hollister, H.K. Gillespie, Terminal elimination plasma half-life of delta 1-tetrahydrocannabinol (delta 1-THC) in heavy users of marijuana, Eur. J. Clin. Pharmacol. 37 (3) (1989) 273–277.
[26] M. Rowland, Clinical Pharmacokinetics and Pharmacodynamics, Williams & Wilkins, Philadelphia, 2010.
[27] N.A. Desrosiers, S.K. Himes, K.B. Scheidweiler, M. Concheiro-Guisan, D.A. Gorelick, M.A. Huestis, Phase I and II cannabinoid disposition in blood and plasma of occasional and frequent smokers following controlled smoked cannabis, Clin. Chem. 60 (4) (2014) 631–643.
[28] S. Agurell, M. Halldin, J.E. Lindgren, A. Ohlsson, M. Widman, H. Gillespie, et al., Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man, Pharmacol. Rev. 38 (1) (1986) 21–43.
[29] C.R. Hjorthoj, A. Fohlmann, A.M. Larsen, M. Arendt, M. Nordentoft, Correlations and agreement between delta-9-tetrahydrocannabinol (THC) in blood plasma and timeline follow-back (TLFB)-assisted self-reported use of cannabis of patients with cannabis use disorder and psychotic illness attending the CapOpus randomized clinical trial, Addiction (Abingdon, England) 107 (6) (2012) 1123–1131.
[30] M.J. Smith, E.C. Alden, A.A. Herrold, A. Roberts, D. Stern, J. Jones, et al., Recent self-reported Cannabis use is associated with the biometrics of Delta-9-Tetrahydrocannabinol, J. Stud. Alcohol Drugs 79 (3) (2018) 441–446.
[31] C.R. Hjorthoj, A.R. Hjorthoj, M. Nordentoft, Validity of Timeline Follow-Back for self-reported use of cannabis and other illicit substances–systematic review and meta-analysis, Addict. Behav. 37 (3) (2012) 225–233.
[32] B. Kilmer, R. Pacula, Estimating the size of the global drug market – a demand-side approach, in: P. Reuter, F. Trautmann (Eds.), A Report on Global Illicit Drug Markets 1998–2007, European Commission, Bruxelles, 2009.
[33] F. Cascini, C. Aiello, G. Di Tanna, Increasing delta-9-tetrahydrocannabinol (Delta-9-THC) content in herbal cannabis over time: systematic review and meta-analysis, Curr. Drug Abuse Rev. 5 (1) (2012) 32–40.
[34] J.G. Ramaekers, M.R. Moeller, P. van Ruitenbeek, E.L. Theunissen, E. Schneider, G. Kauert, Cognition and motor control as a function of Delta9-THC concentration in serum and oral fluid: limits of impairment, Drug Alcohol Depend. 85 (2) (2006) 114–122.
[35] C.C. Hunault, T.T. Mensinga, I. de Vries, H.H. Kelholt-Dijkman, J. Hoek, M. Kruidenier, et al., Delta-9-tetrahydrocannabinol (THC) serum concentrations and pharmacological effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg THC, Psychopharmacology 201 (2) (2008) 171–181.
[36] F. Grotenhermen, G. Leson, G. Berghaus, O.H. Drummer, H.P. Kruger, M. Longo, et al., Developing limits for driving under cannabis, Addiction 102 (12) (2007) 1910–1917.
[37] H.Z. Khiabani, J.G. Bramness, A. Bjorneboe, J. Morland, Relationship between THC concentration in blood and impairment in apprehended drivers, Traffic Inj. Prev. 7 (2) (2006) 111–116.
[38] M. Colizzi, S. Bhattacharyya, Cannabis use and the development of tolerance: a systematic review of human evidence, Neurosci. Biobehav. Rev. 93 (2018) 1–25.
[39] J.G. Ramaekers, J.H. van Wel, D.B. Spronk, S.W. Toennes, K.P. Kuypers, E.L. Theunissen, et al., Cannabis and tolerance: acute drug impairment as a function of cannabis use history, Sci. Rep. 6 (2016) 26843.
[40] M.S. Odell, M.Y. Frei, D. Gerostamoulos, M. Chu, D.I. Lubman, Residual cannabis levels in blood, urine and oral fluid following heavy cannabis use, Forensic Sci. Int. 249 (2015) 173–180.
[41] G. Skopp, L. Potsch, Cannabinoid concentrations in spot serum samples 24-48 hours after discontinuation of cannabis smoking, J. Anal. Toxicol. 32 (2) (2008) 160–164.
[42] R.L. Hartman, T.L. Brown, G. Milavetz, A. Spurgin, D.A. Gorelick, G. Gaffney, et al., Controlled Cannabis vaporizer administration: blood and plasma cannabinoids with and without alcohol, Clin. Chem. 61 (6) (2015) 850–869.
[43] R.L. Hartman, T.L. Brown, G. Milavetz, A. Spurgin, D.A. Gorelick, G.R. Gaffney, et al., Effect of blood collection time on measured Delta9-Tetrahydrocannabinol concentrations: implications for driving interpretation and drug policy, Clin. Chem. 62 (2) (2016) 367–377.
[44] J.G. Ramaekers, G. Kauert, E.L. Theunissen, S.W. Toennes, M.R. Moeller, Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users, J. Psychopharmacol. 23 (3) (2009) 266–277.
[45] D.M. Schwope, E.L. Karschner, D.A. Gorelick, M.A. Huestis, Identification of recent cannabis use: whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration, Clin. Chem. 57 (10) (2011) 1406–1414.
[46] R.L. Hartman, M.A. Huestis, Cannabis effects on driving skills, Clin. Chem. 59 (3) (2013) 478–492.