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Fitness to drive and cannabis: validation of two blood THCCOOH thresholds to distinguish occasional users from heavy smokers

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Highlights

- In Switzerland, a medical assessment and follow-up of the long term fitness to drive is mandatory when a drug addiction or dependence is suspected. Regarding cannabis, a problem of addiction can be strongly suspected in case of heavy use.
- In a previous controlled cannabis smoking study with placebo, we suggested the use of 2 thresholds based on free 11-nor-9-carboxy-∆9-tetrahydrocannabinol (THCCOOH) concentration in whole blood to distinguish occasional cannabis users (≤ 1 joint/week) from heavy regular smokers (≥ 10 joints/month).
- These thresholds were ≤ 3 µg THCCOOH/L for occasional cannabis smokers and ≥ 40 µg THCCOOH/L for heavy users.
- These thresholds were validated in the present study with 146 traffic offenders' real cases in which the whole blood cannabinoid concentrations and the self-rated frequencies of cannabis use were known.

• We propose the following procedure based on the self-reported frequency of cannabis use and the THCCOOH blood concentration to rank the priority level of a medical assessment of the long-term fitness to drive (AFD): \geq 40 µg THCCOOH/L -> high priority; 39.1-3.1 µg/L -> low priority; \leq 3 µg/L and > 1 joint/week -> low priority; \leq 3 µg/L and \leq 1 joint/week -> AFD not recommended.

Abstract

Many studies based on either an experimental or an epidemiological approach, have shown that the ability to drive is impaired when the driver is under the influence of cannabis. Baseline performances of heavy users remain impaired even after several weeks of abstinence. Symptoms of cannabis abuse and dependence are generally considered incompatible with safe driving. Recently, it has been shown that traffic safety can be increased by reporting the long-term unfit drivers to the driver licensing authorities and referring the cases for further medical assessment. Evaluation of the frequency of cannabis use is a prerequisite for a reliable medical assessment of the fitness to drive. In a previous paper we advocated the use of two thresholds based on 11-nor-9-carboxy-Δ9tetrahydrocannabinol (THCCOOH) concentration in whole blood to help to distinguish occasional cannabis users ($\leq 3 \mu g/L$) from heavy regular smokers (\geq 40 µg/L). These criteria were established on the basis of results obtained in a controlled cannabis smoking study with placebo, carried out with two groups of young male volunteers; the first group was characterized by a heavy use (≥ 10 joints/month) while the second group was made up of occasional users smoking at most 1 joint/week. However, to date, these cutoffs have not been adequately assessed under real conditions. Their

validity can now be evaluated and confirmed with 146 traffic offenders' real cases in which the whole blood cannabinoid concentrations and the frequency of cannabis use are known. The two thresholds were not challenged by the presence of ethanol (40% of cases) and of other therapeutic and illegal drugs (24%). Thus, we propose the following procedure that can be very useful in the Swiss context but also in other countries with similar traffic policies: If the whole blood THCCOOH concentration is higher than 40 μ g/L, traffic offenders must be directed first and foremost toward medical assessment of their fitness to drive. This evaluation is not recommended if the THCCOOH concentration is lower than 3 μ g/L and if the self-rated frequency of cannabis use is less than 1 time/week. A THCCOOH level between these two thresholds can't be reliably interpreted. In such a case, further medical assessment and follow-up of the fitness to drive are also suggested, but with lower priority.

Keywords: THCCOOH; cannabis; whole blood; heavy use; occasional use

Introduction

Road safety remains a major problem across countries in terms of economic, medical and social costs (1). In this context, several epidemiological studies have shown that driving under the influence of cannabis is widespread in Switzerland (2, 3) as well as in many other occidental countries (4). Concern over cannabis use in conjunction with driving is justified because it approximately doubles both the odds of being severely injured and the risk of being responsible for a fatal traffic accident (5-7). Several experimental studies based on the use of psychomotor tests and computerized driving simulation have confirmed the impairment effects

of cannabis on driving skills (8-10). These detrimental effects on driving performances and cognitive functions can be either temporary or long lasting, followed by a slow or rapid, partial or complete recovery (11, 12). Consequently, the expert must carry out a careful distinction between short-term inability and long-term impaired fitness to drive (13-15). As such, it was shown recently that the risk of accidents can be significantly decreased by reporting the unfit driver to the driver licensing authorities and referring the case for further medical assessment and toxicological investigations (16). For safety reasons, the driver's licenses of these unfit drivers are generally confiscated by administrative authorities. Unlicensed drivers can get back their licenses when they are able to prove they have become abstinent. In making these investigations, the expert must take into account that the intensity and duration of the expected and adverse effects of cannabis are influenced by the quantity, the frequency, the time of onset and the time span of cannabis consumption (17). In this regard, several studies have shown that chronic use of cannabis negatively impacts longterm psychomotor and cognitive performances of drivers and that these performances improve over 3 weeks of abstinence, but do not recover to equivalent control group performance (12). If tolerance develops to some of the impairing neurocognitive and psychomotor effects of cannabis (18, 19), these detrimental effects are not completely compensated, e.g. by physiological or learned compensatory behavior (13). For instance, impairment of motor impulse control (a driving-related skill that may be linked to risky behavior) remains almost unchanged after regular cannabis exposure (10, 17, 20). In this context, Richer and Bergeron have found that self-reported driving under the influence of cannabis is related to selfreported risky driving, negative emotional driving, and dangerous driving (21). Furthermore, tolerance effects to the detrimental effects of dronabinol (synthetic THC) are not detected in all heavy users since a large subset of subjects (\approx 1/4) remains almost insensitive (22). Crash risk studies (23) also suggest that habitual users of marijuana have about 10 times the risk of car crash injury or death compared to infrequent or non-users, after adjustment for other crash-related variables included an objective measure of blood alcohol level. However, the mechanism by which habitual marijuana use increases the risk of car crash was not identified. In a recent paper (24), we provide evidence that regular cannabis use is associated with gray matter volume reduction in regions rich in cannabinoid CB1 receptors in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex. These regions are functionally linked to motivational, emotional and affective processing. Diminution of brain gray matter in these regions may be linked to alteration of impulsive behavior and to long term impairment of the fitness to drive.

In Switzerland, marijuana smoking is generally detected by police officers who suspect drug use (e.g. because of erratic driving in conjunction with a negative alcohol breath test, or because of a positive rapid roadside saliva test for cannabis). Then, the medical staff is asked to collect urine and blood samples for subsequent formal identification and assay of toxicologically relevant substances. The medical expert completes a questionnaire describing the condition of the driver while the police officer prepares a report on the circumstances of his intervention. The police officer and the medical expert generally ask the driver about his drugs habits. The state prosecutor then appoints an officially acknowledged forensic Swiss laboratory for toxicological investigations to demonstrate unequivocally the presence of cannabinoids at a concentration exceeding the legally predefined analytical cutoff (3, 14). Since in Switzerland a zerotolerance policy is applied toward driving and marijuana smoking, the demonstration of delta-9-tetrahydrocannabinol in blood above the Swiss analytical cut-off (1.5 µg/L plus a confidence interval of 30%) is enough to substantiate an inability to drive at the time of event (25). Even if the THC level is below the cutoff, the authorities may still request an expert to evaluate the ability to drive, especially if the time lapse between the relevant event and the blood sampling is long or if other psychoactive substances that may impair driving performance are detected. The authorities will also require the expert to assess the extent of cannabis use and the long-term fitness to drive. In Switzerland, the legal regulations of the Swiss road traffic act (741.51 RTA) and the guidelines listed in the road traffic ordinances as well as the directives of the Federal roads office (FEDRO) make compulsory the medical assessment and follow-up of the long term fitness to drive when a drug addiction or dependence is suspected. The administrative authority of the Canton is obliged to prohibit persons to operate motor vehicles if the fitness to drive is impaired as a result of disease or of physical or mental disability, due to alcoholism or other forms of addiction. A revocation of the driving license is made until the unfit driver proves him or herself sober or drug(s) abstinent. Regarding cannabis, a problem of addiction can be strongly suspected in case of heavy use. Obviously, compared to occasional users, addicted drivers are more likely to be detected behind the wheel during an acute episode of cannabis smoking or during the post-acute withdrawal stage that may last until the next smoking episode. In this respect, unfit drivers undergo longterm and costly administrative and toxicological investigations that may include repeated urine screenings, hair analysis (26) and assessment of

their medical condition. These investigations are carried out at regular intervals until these regular cannabis users demonstrate abstinence. As for occasional users, as long as they do not drive under the acute influence of cannabis (up to several hours after smoking), they don't represent a significant traffic safety problem.

Previously, in a controlled cannabis joint smoking study with placebo (27), we showed that the 11-nor-9-carboxy- Δ 9-tetrahydrocannabinol (THCCOOH) whole blood concentration could help to distinguish occasional from high-risk heavy cannabis smokers. We proposed two thresholds: a 40 µg/L cutoff above which drivers have a very high likelihood of being heavy smokers, and a blood level below 3 µg/L, strongly suggestive of occasional use. A concentration of THCCOOH in the grey zone between these two thresholds prevents any accurate diagnostic regarding the frequency of marijuana smoking.

However, to date, these two thresholds have not yet been appropriately tested under real-life conditions. To this end, in the present study, we investigated their validity and usefulness on the basis of 146 consecutive and recent medico-legal road traffic cases. These thresholds will facilitate the triage of driver's offenders and assign a priority level regarding the necessity and urgency of a forensic assessment of their fitness to drive.

Materials and Methods

Blood specimens were collected during police controls or after traffic crashes. During police investigations, in case of suspicion of drug-based impairment, a salivary rapid roadside test was occasionally performed (28). Then, the administrative and judicial authorities determined, based on police and medical reports and on the toxicological investigations, whether

the driver was under the influence of cannabis at the time of the incident and whether his/her fitness to drive was long-term impaired. To demonstrate an alteration of the fitness to drive, a formal medical assessment was carried out by forensic experts to evaluate whether cannabis had been chronically and heavily used or not.

All consecutive cases (2009-2013) considered for this study (N=161) were those referred to the Unit of Psychology and Traffic Medicine (UMPT) of the University Center of Legal Medicine of the Canton of Vaud and Geneva for evaluation of the fitness to drive (long term impairment). The local populations of the cantons of Vaud and Geneva are about 730.000 and 470.000 inhabitants, respectively. Drivers who never came for medical assessment despite they were officially summoned were of course not included. The cases that did not match the criteria for inclusion (15 cases) in the occasional (\leq 1 time/week) or heavy smokers group (\geq 10 times/month) were not considered. During this time period, forensic experts were unaware of the cut-off levels we had recently suggested for assessing occasional vs. heavy cannabis use (in a paper available online only since the end of 2013 (27)).

In each case, the forensic expert mentioned in his report if an inconsistency existed in the declarations of the driver about the frequency and intensity of his/her cannabis use. The past history of cannabis use, the concurrent use of other psychoactive drugs (type and blood levels), and comments of the forensic expert were obtained from the police report and medical assessment. The medical examination is designed to assess a driver's overall fitness to drive, with a focus on any past or present alcohol and/or drugs abuse, misuse or dependency problems. Driver's offenders will be required to provide urine sample(s) and undergo a brief physical medical

examination depending on the severity of the case. The expert doctor will also perform a medical interview which includes a complete substance abuse and alcohol history. Some questions asked during the interview are based on the revised CUDIT (29) or CAST (30, 31) evaluations. Determination of cannabinoid concentrations had been performed in different officially recognized laboratories. Major cannabinoids (THC, 11-OH-THC and free THCCOOH) were analysed by validated GC or LC-MS/(MS) methods in forensic laboratories (usual limit of quantification: 1 µg THCCOOH/L and 0.5 µg THC/L) (32, 33). All laboratories complied with legal requirements of periodic quality control tests, met high quality standards and were officially acknowledged by the FEDRO. All laboratories must demonstrate equivalent accuracy in the reporting of results yielding comparable data. The performances of each laboratory were therefore regularly evaluated with blind blood tests containing varying concentrations of THC and THCCOOH. Therefore, results obtained in one or another laboratory should be considered as equivalent. The criteria of evaluation and formal recognition of the different laboratories and of their methods have been already described elsewhere (25). The documentation regarding the official requirements to become an officially acknowledged laboratory are described in a Swiss directive of the FEDRO (34). In cases involving a traffic accident or a positive alcohol breath test, ethanol concentration was determined in whole blood by chromatographic methods. Furthermore, a screening for a wide range of recreational drugs, narcotics and therapeutic drugs was carried out by combining different analytical methods (3).

Data, receiver operating characteristics (ROC) curve, and scatter graphs were processed and plotted using Excel 2007 and GraphPad Prism 6.02 software. True positives (TP) were correctly identified smokers, i.e., heavy

smokers with THCCOOH concentrations higher than the threshold. False positives (FP) were incorrectly identified heavy smokers, i.e., occasional smokers with THCCOOH concentrations higher than the threshold. True negatives (TN) were correctly rejected consumers, i.e., occasional smokers with THCCOOH concentrations lower than the threshold. False negatives (FN) were incorrectly rejected users, i.e. heavy smokers with THCCOOH levels lower than the threshold. Sensitivity was the proportion of true positives in heavy smokers who presented sample values exceeding the threshold; sensitivity was calculated as TP / TP + FN. Specificity was estimated by the ratio: TN / TN + FP. The positive likelihood ratio (LR+) was calculated as follows: sensitivity divided by 1 - specificity. The Receiver Operating Characteristic (ROC) is a graphical plot of true positive rate (sensitivity) versus false positive rate (1-specificity) for each THCCOOH threshold (27). The maximum specificity cut-off to rule in the heavy users was set close to the lower left corner of the ROC curve while the maximum sensitivity cut-off to rule out the heavy smokers was set close to the upper right corner.

This study was conducted in accord with good clinical practices. Approval was obtained from the ethics committee for human research of the Canton de Vaud, Lausanne, Switzerland.

Results

All official reports of traffic offenders mentioned both the estimated frequency of cannabis use, as reported by the driver, and the whole blood levels of cannabinoids, which include that of THCCOOH. Indications regarding the sex and age, the concurrent use of alcohol and of other recreational and therapeutic drugs or narcotics, and the medical condition

of the driver were also reported. The relevant data for this study are listed in the synoptic table I: Traffic offenders were mostly young men. Ethanol was detected (> 0.1 g/kg) in 40% of all cases while other psychoactive drugs were found in 35 out of 146 cases (24%). The great majority were recreational drugs or narcotics, with cocaine (26 cases) being the predominant one. Using the information provided by the traffic drivers and our classification (based on frequency of use) of cannabis smokers into two groups, 27% of cases could be identified as belonging to the "occasional smokers' group" while about 73% were classified as "heavy users". The median blood levels of THCCOOH for cannabis occasional and heavy users were 9.4 and 33 µg/L, respectively. The ranges for the same groups were 1.0-74 µg/L and 1.0-312 µg/L (left boxplot in Fig. 1). If we consider the two thresholds defined in the previous study (3 and 40 µg/L (27)), we observe that for occasional users, 8 were below 3 µg/L, 29 between 3 and 40 µg/L, and 3 above 40 µg/L. For heavy smokers, 44 cases were higher than 40 µg/L, 60 were between 40 and 3 µg/L, and 2 below 3 µg/L. The ranges of THC levels for occasional and regular users significantly overlap with many values below the LOQ (0.5 μ g/L) (right boxplot in Fig. 1). THC values of occasional and regular cannabis users ranged from < LOQ to 14 μ g/L and from < LOQ to 38 μ g/L, respectively. Their respective mean and median values were 2.1 and 2.7 µg/L, and 5.2 and 6.6 µg/L. A two tailed Mann Whithney test revealed significant differences between both groups of cannabis users (p < 0.0001). Significant differences were also found when comparing the distribution of THCCOOH blood levels across the 2 groups of cannabis users (p < 0.0001). A ROC curve was then established with all THCCOOH values, irrespective of inclusion in the heavy users group. The results are displayed in figure 2 that reports the % sensitivity (to

rule out heavy users) on the y-axis versus 100-Specificity on the x-axis. The specificity allows us to rule in the heavy users. Figure 2 shows that blood samples with a THCCOOH concentration below 3 μ g/L (upper right corner) belong almost exclusively to occasional smokers. Conversely, specimens with a whole blood level higher than 75 μ g/L belong only to heavy users (Fig. 1). Consequently, 100% of occasional cannabis smokers are below this value. The sensitivity at 40 μ g/L was improved from 19 to 41% while the specificity was slightly diminished, reaching 93%. The area under the ROC curve was 0.81, indicating that occasional and heavy smokers were well distinguished.

Discussion

A controlled administration study of cannabis smoking with placebo carried out with 48 volunteers divided into two groups characterized by the frequency of consumption had previously made it possible for us to propose 2 thresholds to discriminate occasional smokers from heavy users (27). Our goal was to provide the forensic expert with a diagnostic tool that would facilitate the triage of driver's offenders, i.e. a tool able to rank their smoking habits by frequency of use and above all to make easier their stratification according to the level of priority required for further assessment of their long-term fitness to drive. The reliability of these two thresholds was then questioned in this study with 146 real cases of driving under the influence of cannabis for which a medical assessment of the long-term fitness to drive had been requested. The contexts of these two studies are very different since the first one deals with a placebo-controlled clinical trial performed without particular challenge or issue for the participants except that of scientific curiosity and a modest financial compensation. Regarding this present second study, the main purpose of which is to validate the first one, the stakes for the offender drivers were obviously much higher. Among these stakes is the confiscation of the driving license for an unspecified but definitely long time period due to chronic cannabis use. Another issue at stake is the possibility of an obligation to participate in a series of lengthy, costly and restrictive toxicological investigations until abstinence is demonstrated. In both studies, two parameters were confronted: one is objective, the blood concentration of THCCOOH, and the other is subjective, the self-reported frequency of consumption. Since in the second study, the interviews of the drivers were carried out in a medico-legal context with the possibility of a long-term withdrawal of the offender's driving license, the drivers may have been reluctant to report their true drug habits. Therefore, an underreporting of the extent and frequency of use is expected. In this respect, three subjects among 40 claimed to be occasional smokers and showed a THCCOOH blood level exceeding the threshold of 40 µg/L (Fig. 1). Two of them were reported by the forensic expert as being unreliable because of an inconsistency of their declarations during the interviews. Interestingly, both showed relatively high THC blood concentrations (8.3 and 9.1 μ g/L). The third who claimed only 1 cannabis use per year admitted smoking while driving, the blood THC level was 14 μ g/L and the urine THCCOOH level was 1400 µg/L. These observations argue for recent and repeated smoking rather than for a single use. The application of model I developed by Huestis et al. (35) to predict the time of cannabis exposure also suggests recent use (< 1 hour). Then, these cannabinoid concentrations can be compared to those determined in drivers suspected of driving under the influence of narcotics, alcohol and/or therapeutic drugs in Switzerland

between the years 2005 to 2007 (36). The median blood levels for THCCOOH and THC were respectively of 35 (N=6375) and 3.7 µg/L (N=5451). Regarding the urine total concentration of THCCOOH, the median level was 363 µg/L (N=973). No data about the frequency of cannabis use was provided. For all the three aforementioned alleged cannabis occasional smokers, their cannabinoid concentrations are above these median levels. Despite possible under-estimation, the evaluation of the frequency of consumption that relies on self-reported use is considered to be the best strategy available today, and is widely approved and of common practice. In this respect, the same procedure was used to validate carbohydrate-deficient transferring (CDT) as a suitable alcohol abuse marker (37). In our study, the information about the frequency of use was obtained from the police report and also from the medical examination of the driver. While we remain aware of a potential bias, the results of this second real-case study offer compelling support of the findings reported in the first paper (27): except for five cases, all measurements from subjects referred for forensic medical assessment were consistent with the suggested thresholds ($\leq 3 \mu g/L$ is indicative of occasional use; $\geq 40 \mu g/L$ reveals a heavy use). This finding was not called into question by the concurrent use of alcohol (40% of cases) and/or the intake of other therapeutic, recreational drugs or narcotics (24% of cases). Considering the relatively large proportion of multiple drug use cases included in our study, one might suspect many alcohol and drug interactions, genetic polymorphisms (e.g. of CYP2C9) (38) affecting the metabolism, and rates of elimination of cannabinoids. In spite of these various conditions, the two threshold values proved resilient with no significant inconsistencies.

A recent controlled administration study carried out with 19 heavy cannabis smokers published by Toennes et al. (39) supports our findings. The investigation of 3 different alcohol dosing conditions preceding the smoking of a marijuana cigarette did not disclose any blood specimen taken from heavy smokers with a THCCOOH serum concentration that disagrees with our two suggested thresholds. For accurate interpretation, the thresholds determined for whole blood must be recalculated for serum by multiplying by 1.7, i.e. the serum to whole blood THCCOOH concentration ratio (40, 41). The corresponding cutoff values become respectively 5 and 70 μ g/L. None of the THCCOOH levels reported in the study of Toennes et al. for serum sampled during the enrollment day and prior the three study days (74 serum samples) showed a value below 5 µg/L (indicative of occasional use). Conversely, 29 out of these 74 serum specimens (39%) were characterized by a THCCOOH level higher than 70 µg/L. This proportion was slightly higher if we consider all measured values determined before and after smoking a cannabis joint, and whether they had been drinking alcohol or not. In this respect, the sensitivity at which regular consumers could be detected was 45%. The sensitivity of the test may seem low to some clinicians, but it is comparable to the blood CDT commonly used for detecting patients at risk of excessive alcohol consumption. The performances of the CDT tests are indeed quite low with sensitivities of 34 and 57% for alcohol abusers and alcohol dependent patients, respectively (42). Furthermore, in forensic practice, a high specificity is always required to avoid a false accusation of substance abuse. As mentioned previously (27), the time interval between the forensic relevant event and blood sampling was relatively short (median: 1.5 hours, range: 0.08-7.4 hours). Assuming that the event occurred at least after the absorption and distribution phase of THC and taking into account the very long elimination half life of THCCOOH (about 1 day) (43-46), a retrospective calculation for estimating the THCCOOH level at the time of the vehicle traffic event was of little interest. Fig 1 shows that about 41% of heavy users can be formally attributed to this group of smokers using the threshold of 40 µg/L. These drivers deserve further investigation with a medical assessment of the fitness to drive and should be directed to a medical follow-up intended to lead to cannabis abstinence. Conversely, drivers with THCCOOH level below 3 µg/L (20% of declared occasional smokers) and a self-rated frequency of cannabis use not exceeding 1 time/week are almost certainly occasional users who don't require long and costly administrative and forensic investigations, provided they are notified not to drive several hours after acute consumption. Cases lying between these two limits are difficult to characterize and require further investigation. It is interesting to notice that two alleged heavy smokers were characterized by a very low THCCOOH level (1 µg/L). In our opinion, these two cases may result from an incorrect self-estimation of the frequency of consumption. The overestimation could be deliberate if the driver is also a drug dealer trying to justify the police discovery in his/her belongings of a large amount of attributing the possession to his/her high personal cannabis bv consumption. In other similar cases, the driver reported a heavy cannabis use that he considered to be less legally consequential, in order to conceal the intake of other narcotics for which he thought he would be more likely to be prosecuted. Another explanation could be put forward: the alleged heavy smoker can be also a so-called "crapoteur", who puffs on a joint without inhaling, e.g. to fulfill his craving for social approval influenced by peers and models (47). Finally, a fair estimate of the mean frequency of use is hardly possible if the driver is a very irregular consumer (e.g. a "binge" or "weekend cannabis smoking" enthusiast). Interestingly, no THC could be detected in their blood. The THCCOOH levels measured in urine reached similar concentrations: 88 and 86 µg/L (to be compared to the median level of 363 µg/L found in 973 Swiss DUID cases). The first reported to be a "binge cannabis smoker" while the other indicated a regular use of 3 joints per week. Taking this into account, we suggest that these driving offenders should be also assessed for their fitness to drive, but with less priority than those with THCCOOH levels reaching or exceeding 40 µg/L. A decision tree based on the self-rated frequency of cannabis use and the free THCCOOH concentration in whole blood illustrates the usefulness of our model and of its selected thresholds (table II). This three-level priority ranking model is useful to list offending drivers by order of assessment priority (high, low, not recommended) of their fitness to drive. Of course, in complex cases involving the use of several psychotropic drugs (e.g. alcohol, cannabis and cocaine), a medical assessment of the fitness to drive is always recommended. In agreement with Fabritius et al. (27), the proposed threshold of 40 µg/L is in the same range as that recently suggested by the French Society of Analytical Toxicology (50 µg/L) (48). This value corresponds more or less to the cutoff proposed in this study plus a usual safety margin of about 20%.

As far as cannabis consumption assessment is concerned, an often neglected difficulty deals with the definition of occasional and heavy smokers based on the frequency of cannabis use. An investigation of the available academic literature shows that today no broad consensus exists (Fig. 3). For instance, Huestis and Cone in 1998 (49) reported frequencies of use ranging between 0.4 and 7.9 times per week for the occasional use

while they restricted this range to up to 2 times/week in several recent papers published in 2013 (50, 51). The French Observatory for Drugs and Drug Addiction (OFDT) established different criteria for the classification of cannabis smokers. They distinguish 6 categories of users: ever used or abstinent, experimenter, occasional, repeated, regular and daily users (52, 53). We present both repeated and occasional users together in Fig. 3a, because both of those types of users fall under the category we and Huestis et al. consider "occasional" smokers. More recently, the same organization revised the definition of the different categories of use based on calendar classification (yearly, monthly, regular and daily use). In agreement with most recent studies, we favored the use of two broad categories of users that we separated with a small interval (1.0 time/week up to 10 times/month). Forensic experts report that when asked about their frequency of use, traffic offenders very often tend to under-report their consumption. In our opinion, the use of a broad definition for heavy smokers has the advantage of keeping them in the same group even if they under-evaluate their level of consumption.

Our experience shows that the evaluation of cannabis smokers with respect to the extent and frequency of use is difficult, especially with regard to occasional users. The reasons are numerous: the joints are not always self-made; they are shared or partially consumed. Their properties may vary considerably depending on their size, THC content, and proportion of tobacco used to cut the cannabis. In spite of this challenge, this study based on real cases confirms our previous proposal that occasional and heavy smokers can be successfully distinguished on the basis of the whole blood THCCOOH level.

Consequently, this work has several strengths but also some limitations: This study allows to test in tough real-life conditions a model that has been developed under controlled experimental conditions. We are convinced that we provide the forensic expert with a valuable tool able to stratify the drivers according to the level of priority that is required for further assessment of their fitness to drive. This tool should be used for conducting investigations, not for applying immediate negative sanctions. If the definition of the consumer groups is changed, for example by selecting two adjacent rather than two distinct groups of users (the choice of this work), or by introducing a new group with different frequencies of use, the THCCOOH threshold values should be checked, and if appropriate redefined and validated again. The extent of individual cannabis consumption, a necessary prerequisite to calculate diagnostic sensitivity and specificity, is merely based on personal reports of the subjects or on structured questionnaires. This approach may lead to a downward bias in the estimation of the frequencies of cannabis use. The selection of two distinct groups of cannabis smokers could mitigate this negative bias. If a majority of officially recognized forensic laboratories decide to measure separately the concentrations of free THCCOOH and of its glucuronide metabolite, it will be appropriate to define new thresholds that take into account the blood levels of THCCOOH-glucuronide. The finding of a better marker of frequency of cannabis use would be a major improvement (39), especially if it could be combined with the diagnostic THCCOOH thresholds. To date, as far as we know, only hair analysis could fill this gap, but with serious limitations (smoke contamination, poor sensitivity and correlation between THCCOOH concentrations and self-reported pattern of cannabis use) (54).

In conclusion, two THCCOOH thresholds had been established from pairs of data collated during a controlled cannabis smoking study in order to distinguish heavy cannabis consumers from occasional users. The validity and robustness of these two tresholds have been evaluated and confirmed in our present study with 146 traffic offenders' real cases for which the THCCOOH concentration and frequency of cannabis use were known. Thus, we propose the following procedure, to be used in Switzerland and other countries with similar traffic policies: If the whole blood THCCOOH concentration is higher than 40 µg/L, traffic offenders must be directed first and foremost toward medical assessment of their fitness to drive. This evaluation is not recommended if the THCCOOH concentration is lower than 3 µg/L and if the self-reported frequency of cannabis consumption is lower than 1 time par week. Between 39.9 and 3.1 µg/L, an assessment of the fitness to drive is nevertheless recommended, but with less priority. When taking into consideration all the cases in the database, an offender driver with a THCCOOH whole blood concentration higher than 40 µg/L can be identified with a specificity of 93% as a heavy user. This specificity even reaches 97% if we omit the very few cases for which the substance use history was considered unreliable. We hope that forensic scientists called upon to assess the long-term fitness to drive will consider this threshold model as beneficial in the interpretation of THCCOOH blood levels.

Competing interests

The authors have declared that no competing interests exist.

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Figure Caption

Fig. 1 Scatter plot (median and interquartile) comparing the distribution of THCCOOH and THC concentrations in whole blood of 146 alleged occasional (40) and heavy (106) cannabis users. Mann Whitney tests (two tailed) comparing occasional and heavy cannabis smokers for THCCOOH or THC blood levels were significantly different (Pvalue < 0.0001).

Fig. 2 ROC curve of THCCOOH concentrations in whole blood from 146 traffic offenders. Circle at 3.0 μ g/L: cut-off to rule out heavy smokers. Circle at 40 μ g/L: cut-off to rule in heavy smokers. Circle at 75 μ g/L: maximum specificity to rule in heavy smokers.

Fig. 3 (a) Frequency of cannabis consumption for occasional users as reported by several references, (b) Frequency of cannabis consumption for heavy users as reported by several references.

Table 1 Sociodemographic characteristics, self-rated patterns of cannabis use, THCCOOH whole blood (WB) level, alcohol concentration and presence of psychoactive drugs in 146 traffic offender's cases.

	Ago	Sov	Frequency	THCCOOH WB concentration (µg/L)	Alcohol (g/kg)	Other psychoactive substances in WB
Ag (yea	(years)	(m/f)	of use (times/week)			
Heavy (n=106)		103/3			n = 37	n = 25
Min	15		2.5	1.0	0.10	
Max	58		70	312	2.44	
Median	25		7	33	1.07	
Mean	27		12	51	1.19	
Occasional (n=40)		39/1			n = 21	n = 10
Min	16		0	1.0	0.10	
Max	48		1	74	2.47	
Median	28		0.55	9.4	1.29	
Mean	29		0.61	16	1.23	

Table 2 Decision tree for determining whether an evaluation of the fitness to drive (long term impairment) is highly, moderately or not recommended.

Free THCCOOH	Self-reported frequency	Decision regarding the
concentration	of cannabis use	requirement of a medical
(µg/L)	(times/week)	the fitness to drive
≥ 40	any	Imperative and highly recommended
39.9-3.1	any	Recommended but with less priority
≤ 3	> 1	Recommended but with less priority
≤ 3	≤ 1	Not recommended



Figure 1





