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Driving under the influence of cannabis: A 5-year retrospective Italian study

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ABSTRACT

Introduction: Cannabis consumption is associated with driving impairment and increased crash risk, endangering road safety. Toxicological analyses play a fundamental role in detecting a recent consumption of psychoactive substances. The aim of this study was to examine the concentration of cannabinoids in blood samples of driving-under-the-influence (DUI) offenders in order to investigate whether delayed sample collection affects the toxicological assessment of the offenders.

Materials and Methods: An observational retrospective study was performed using anonymized toxicological data referring to cannabis-related DUI offenders involved in road traffic accidents (RTA) or apprehended by the police from 1 January 2017–31 December 2021 archived at Legal Medicine and Toxicology Department of the University Hospital of Padova, Italy.

Results: In a total sample of 318 drivers, 143 blood samples tested positive for tetrahydrocannabinol (THC) and metabolites 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-THC) and 11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), and 173 blood samples were positive for THC-COOH with THC negative. In the first group, the mean concentrations of THC and THC-COOH were 4.05 ng/mL and 28.29 ng/mL, respectively. In THC-negative cases, the mean THC-COOH concentration was 7.3 ng/mL. The time elapsed between the event and sample collection varied from 15 min to 7 h (mean 2 h 29 min). The average estimated time elapsed after consumption of cannabinoids was 3 h 7 min (Model I) and 2 h 36 min (Model II).

Conclusions: The present research discussed the main difficulties in the toxicological evaluation of drivers under the influence of Cannabis. Issues related to the time between RTA and sample collection, the laws and legal limits in force in various Countries were presented

1. Introduction

Cannabis is the most widely used illicit drug in the world. In 2019, it was estimated that 7.8% of the European population aged 15–64 had consumed cannabis at least once in their lifetime.[1] Δ9-Tetrahydrocannabinol (THC) is the main psychoactive constituent of cannabis.[2] THC is mainly absorbed in the lungs after pyrolysis and then rapidly distributed to fat tissue, liver, brain, lung, and spleen. Metabolism of THC occurs mainly in the liver through microsomal hydroxylation and oxidation catalysed by enzymes of the cytochrome P450 complex, producing the active metabolite 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-THC) and the inactive compound 11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH).[3–5] THC can be rapidly detected in plasma after inhalation: plasmatic concentrations reach their peak during or immediately after smoking and begin to drop due to rapid distribution into tissues and metabolism. 11-OH-THC concentration reaches its peak in less than 1 h: the initial [11-OH-THC]/[THC] plasma ratio is low, and then increases due to a more gradual reduction in 11-OH-THC concentration. The detection window of THC-COOH vary depending on the frequency of consumption; THC can be measured in the blood up to 12–24 h after smoking moderate doses.[6–9] THC consumption leads to acute effects, such as increased reaction time, impaired coordination, divided attention and reduced motor performance. [10] It also causes sedation, lethargy, and euphoria/dysphoria.[11] These effects are dose-related and vary with THC concentration and frequency of consumption, although tolerance occurs after frequent consumption [12]. Recent smoking and blood THC concentrations of 1–5 ng/mL are commonly associated with driving impairment, especially in occasional smokers. Driving under the influence

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of cannabis is associated with increased crash risk, mainly due to short-term impairment producing increased deviation of lateral position (an index of lane weaving, swerving -*i.e.* a sudden change of direction-, and overcorrecting).[13] In the case of road traffic accident (RTA), toxicological analysis for psychoactive drugs is essential to assess the influence of these substances on the driver, thus defining the culpability of the event. In Italy, Article 187 of the "Nuovo Codice della Strada" (Highway Code) prohibits driving under the influence of a psychoactive drug (D.L. 285, 30 April 1992) [14]. Although a maximum blood concentration of 0.5 g/L alcohol is tolerated for expert drivers, for drugs of abuse, a zero-tolerance system has been imposed, based on toxicological analyses combined with evaluation of the impaired neuro-psychic state, to ensure greater road safety and to drastically reduce the number of accidents and road deaths.

This project reviewed blood (and urine) concentrations of cannabinoids (THC, THC-COOH, 11-OH-THC) in 318 DUI offenders, also considering their blood alcohol concentration (BAC) and the presence of other psychoactive substances. Second, the time lapse between the event (accident, road control) and collecting the samples was considered to assess whether delayed sample collection affected the toxicological assessment of the offenders. All parameters have been evaluated in relation to varying legal limits and laws in force in various Countries and to similar studies published by other authors.

2. Materials and methods

The project was structured as an observational retrospective study. Data were collected from anonymous archived records of the Legal Medicine and Toxicology Department of the University Hospital of Padova. The project was conducted by evaluating the results of the toxicological analyses performed on blood and urine samples collected from drivers involved in RTAs or stopped by police in casual road controls, and consequently admitted to one of the hospitals of the Province of Padova. The samples were collected between 1 January 2017 and 31 December 2021 and analysed for the presence of alcohol and drugs of abuse or exclusively for alcohol, according to the authority's request.

Of all records collected, only data from drivers who tested positive for cannabinoids (THC, THC-COOH, 11-OH-THC) in blood and/or urine samples were selected for inclusion in the present study.

All toxicological analyses had been previously performed at the Laboratory of Legal Medicine and Toxicology, with a routine, in-house validated method. Briefly, the deuterated internal standards (30 μL of methanol solution of THC-D3 and THC-COOH-D3 at 1 μg/mL) were added to 2 mL of blood and urine. Blood samples were hydrolysed: hydrolysis was carried out with 0.1 M KOH at 60 °C for 20 min; the pH was adjusted between 4 and 5 with acetic acid and phosphoric acid. Extraction was then carried out with 5 mL of 90:10 hexane/ethyl acetate containing 0.4% v/v glacial acetic acid. The extract was dried under nitrogen, and the residue was treated with 50 μL N-trimethylsilyl-N-methyl trifluoroacetamide, 1% trimethylchlorosilane, for 30 min at 75 °C. Two μL of derivatized extracts were injected into an Agilent 5973 GC-MS instrument equipped with an Agilent HP5-MS column, 30 m lenght × 0.25 mm internal diameter × 25 μm film thickness; the carrier gas was helium at 0.8 mL/min; a temperature gradient was programmed from 50 °C to 300 °C; and acquisition was in single ion monitoring under electron ionization conditions.A multi-point calibration curve was set up in parallel by adding standards of THC, 11-OH-THC, and THC-COOH in a known quantity to negative blood samples in the range 0.5–50 ng/mL. Seven calibration points (0.5, 1, 2, 5, 10, 20, 50) were used. Samples exceeding 50 ng/mL were diluted (occasionally for THC-COOH in blood, frequently for THC-COOH in urine), depending on the immunoassay screening value.

The panel of other substances analysed included: opiates (heroin, 6-monoacetylmorphine, morphine, codeine), cocaine and metabolites (benzoylecgonine, ecgonine methylester, coca-ethylene), amphetamines and amphetamine-like drugs, opioids (oxycodone, hydrocodone, oxymorphone, hydromorphone), buprenorphine, methadone, tramadol, ketamine, benzodiazepines, barbiturates, and Z-hypnotic drugs, analysed by LC-MS/MS in a triple quadrupole. Alcohol was analysed in blood and urine by headspace gas chromatography with flame ionization detection (HS-GC-FID).

The toxicological data taken into account were the following: blood concentrations of cannabinoids (THC, THC-COOH, 11-OH-THC), urinary concentrations of THC-COOH, concentrations of alcohol, and presence/absence of other drugs of abuse. Mean, median, and range of values were assessed for all the parameters.

Hospital and police data concerning the RTA or the casual control were recorded, focusing in particular on the timing of the event, and the time elapsed between the event and the biological sample collection was calculated. To estimate the time elapsed following consumption of cannabinoids, Model I and II proposed by Huestis et al. [15,16] were applied to subjects whose records contained police data specifying the time of the event.

3. Results

A total of 318 records were analysed. Among all drivers, the gender distribution was 32 females and 284 males. (For privacy reasons, age and gender were not specified for 2 drivers.) All records were complete with toxicological tests. Police data relative to police control or RTA times were available in 103 cases.

Table 1 and Fig. 1 show data of the 143 drivers found with detectable blood levels of THC. Of these, 135 (94.4%) were male, and 7 (4.9%) were female. Women were significantly younger than men (25.3 and 30.0 yrs.); the maximum age of a woman involved was 33 years, while the oldest man was 61 years old. In 1 case of this group, age and gender of the driver were not specified for privacy reasons.

The average concentration of THC in the blood was 4.05 ng/mL (range 0.5–30 ng/mL). Similar values were found in male subjects (mean 4.02; range 0.5–30). In the few cases involving women, the mean concentration was 3.54 ng/mL and the range was 1–13 ng/mL. The mean concentration of THC-COOH was 28.29 ng/mL, without significant differences between the sexes. In this group of drivers.

(positive for THC in blood) toxicological analyses performed on urine revealed high concentrations of THC-COOH, often higher than 400 ng/mL.

Data related to psychoactive substances other than cannabinoids are shown in Table 2. Of 143 cases examined, 39 subjects tested positive for ethanol. Of these, 35 drivers had alcohol concentrations greater than or equal to 0.5 g/L. The mean concentration of alcohol in the blood was 1.25 g/L. Thirty-six drivers tested positive for other psychoactive substances. Cocaine and its metabolites were detected in the blood of 18 drivers, while opioids, benzodiazepines, amphetamines, or ketamine were observed in the remaining cases.

In 173 drivers (54.4% of the total), blood THC was negative,

Table 1
Blood cannabinoids concentrations (THC-positive subjects).

	Total*	Men	Women
n (%)	143 (100%)	135 (94.4%)	7 (4.9%)
Age [Years]	Mean 29.8 (18–61) Median 26	Mean 30.0 (18–61) Median 26	Mean 25.3 (18–33) Median 25
Blood THC [ng/mL]	Mean 4.05 (0.5–30) Median 2.6	Mean 4.02 (0.5–30) Median 2.6	Mean 3.54 (1–13) Median 2.2
Blood THC-COOH [ng/mL]	28.29 (0.7–96) Median 24.0	Mean 28.12 (0.7–96) Median 24.5	Mean 30.17 (1–76) Median 20.8
Blood 11-OH-THC [ng/mL]	Mean 2.12 (0.5–15) Median 1.4	Mean 1.96 (0.5–23) Median 1.4	Mean 4.8 (0.8–23) Median 1.4

* Age and gender of the driver were not specified for one driver

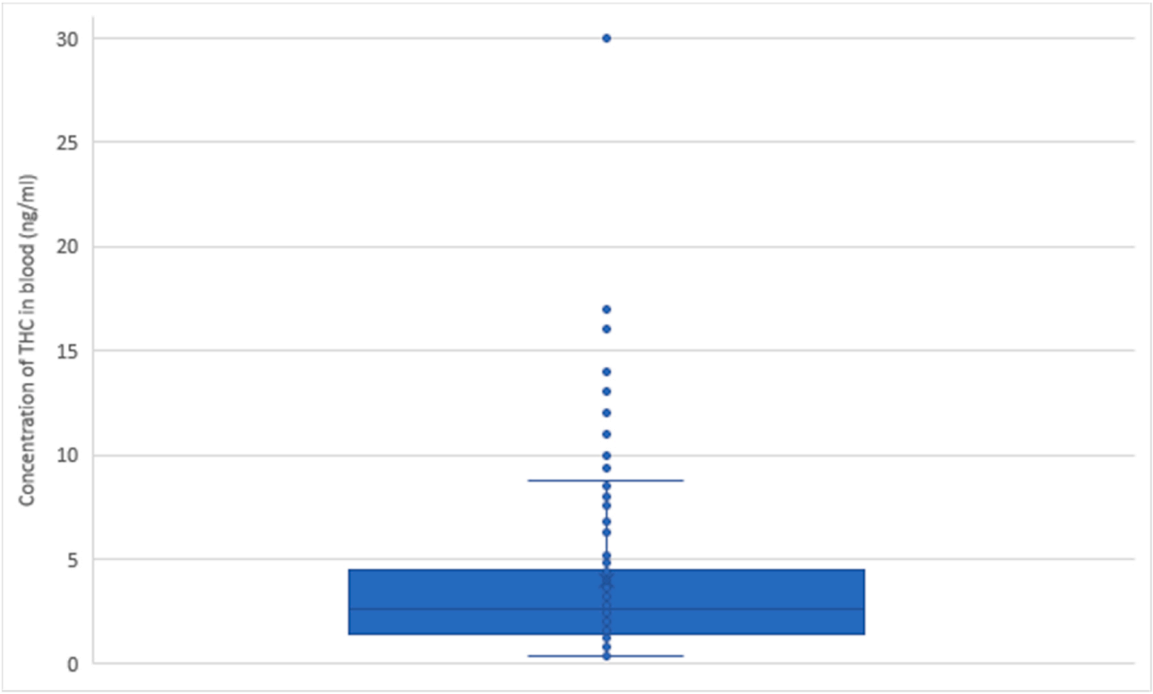

Fig. 1. Distribution of THC concentrations in blood (ng/mL).

Table 2
Number of blood samples positive for psychoactive substances other than cannabinoids (THC-positive subjects).

	Total	Men	Women
THC + alcohol	39*	35	3
THC + alcohol (> 0,5 g/L)	35*	31	3
BAC (g/L)	Mean 1.25 (0.13–2.77) Median 1.15	Mean 1.25 (0.13–2.77) Median 1.15	Mean 1.14 (0.68–1.96) Median 0.82
THC + other drugs of abuse	36	32	4
All cases (THC + alcohol and/or drugs of abuse)	57*	52	4

* Age and gender of the driver were not specified for one driver

although its metabolite THC-COOH was detected (Table 3). Gender distribution showed a higher percentage of women than that observed in the group shown in Table 1 (14.5% vs. 4.9%). No age differences were noted between the two groups. Mean urinary and blood concentrations of THC-COOH were significantly lower in subjects with no THC in the blood ($p < 0.001$) (Fig. 2).

Of the population shown in Table 3, 48 (41 males and 7 females) tested positive for blood ethanol, with an average value of 1.35 g/L.

Table 3
THC-COOH concentrations in blood and urine (THC-negative subjects).

	Total**	Men	Women
N (%)	173 (100%)	147 (84.9%)	25 (14.5%)
Age [Years]	Mean 29.4 (17–69) Median 26	Mean 29.3 (17–69) Median 26	Mean 31 (17–57) Median 29
Blood THC-COOH [ng/mL]	Mean 7.3 (0.5–35) Median 5.3	Mean 7.5 (0.5–35) Median 5.5	Mean 6.4 (0.7–20) Median 4.4
Urine THC-COOH [ng/mL]	Mean 75.5 (4.8–400) Median 50	Mean 77.6 (4.8–400) Median 50	Mean 67 (10–165) Median 56

** Age and gender of the driver were not specified for one driver

Statistical comparison between alcohol concentrations showed no significant differences between the groups examined ($p > 0.05$). In the group of subjects with blood samples positive for THC-COOH only, 59 drivers' blood tested positive for psychoactive substances other than cannabinoids (Table 4).

In 2 cases, blood samples were negative for cannabinoids, whilst THC-COOH was detected only in the urine at concentrations of 33 ng/mL and 86 ng/mL, respectively.

The time elapsed between the RTA/police control and blood collection ranged from 15 min to 7 h, with an average of 2 h 29 min. In 33 cases, time intervals varied between 1 and 2 h; in 34 cases, between 2 and 3 h; and in another 21 cases, the lapse stretched from 3 to 4 h. Considering only drivers testing positive for THC, an average time interval of 2 h 32 min was observed, with a median of 2 h 20 min. These values were similar to those calculated in the other group (mean 2:24 h; median 2:20 h).

4. Discussion

Data that emerged from the study of Augsburger et al. [17] were similar to the findings of the present research; in the cited study, of a total of 234 THC-positive drivers, the average blood concentration was 5 ng/mL (range 1–35 ng/mL). In contrast, a study conducted in Sweden by Jones et al. [18], analysing blood concentrations of cannabinoids in DUI subjects over 10 years, detected an average THC concentration of 2.1 ng/mL, lower than the value observed herein. Similar concentrations were also observed in a project by Khiabani et al. [19] exploring apprehended cannabinoid-impaired drivers (2.2 ng/mL). The reason for differences between studies could probably be explained by the time elapsed between cannabis intake and blood sample collection (not detailed in the studies) and/or the different quantities of the substance consumed by the drivers.

In this regard, we observed that the average time between events and sampling was about 2.5 h. Nonetheless, in a few cases, an average time greater than 5 h was recorded, as evidence of the non-homogeneity of the timing of this process. Unfortunately, it was not possible to identify the variables leading to time delays in collecting toxicological samples. In addition to the time required logistically to take the driver to the

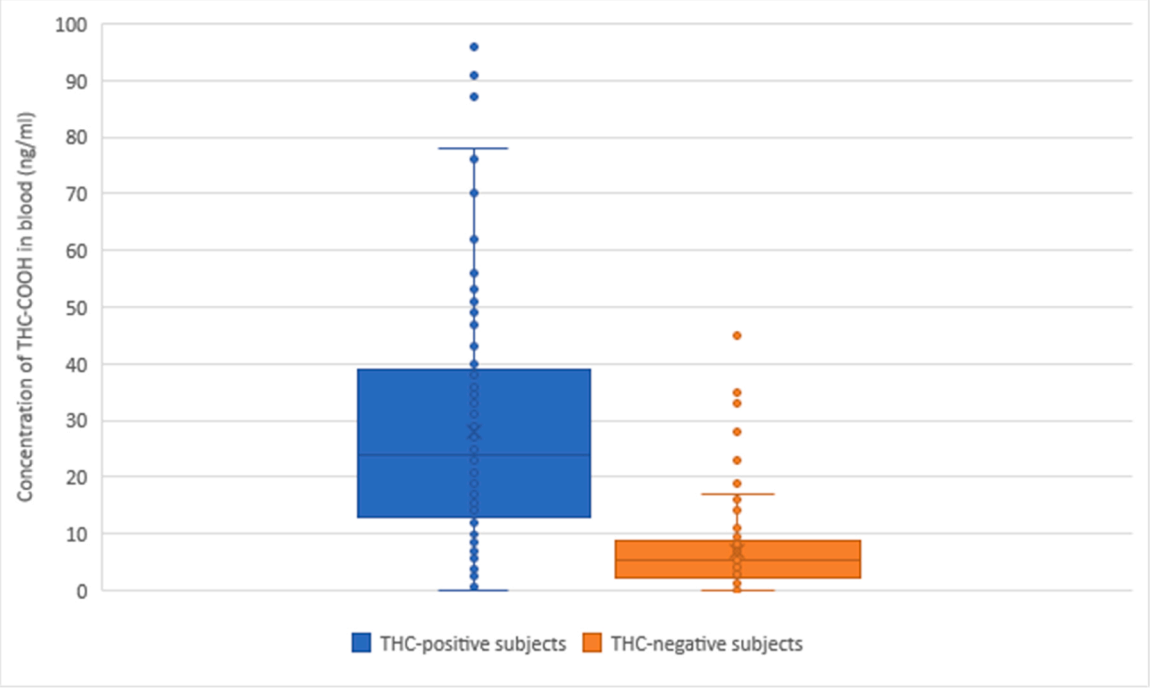

Fig. 2. Distribution of THC-COOH concentrations in blood (ng/mL).

Table 4
Number of blood samples positive for psychoactive substances other than cannabinoids (THC-negative subjects).

	Total	Men	Women
THC-COOH + alcohol	48	41	7
THC-COOH + alcohol (> 0,5 g/L)	41	34	7
BAC (g/L)	Mean 1.35 (0.08–2.89) Median 1.38	Mean 1.29 (0.08–2.89) Median 1.36	Mean 1.74 (1–2.66) Median 1.60
THC-COOH + other drugs of abuse	59	52	7
All cases (THC-COOH + alcohol and/or drugs of abuse)	84	70	14

hospital, we believe that other factors may also affect and extend the timeframes. For instance, in emergency conditions, patient stabilization takes priority over toxicological investigations. Moreover, samples are initially collected for the exclusive purpose of clinical analyses, while samples for toxicological assessment must be collected after a later request from the authority, even in stable patients. Technical time is also required for both police and physicians to compile and forward a request for toxicological analysis. Deferred execution of blood collection may result in the detection of values that are not describing the condition of the driver at the time of the RTA/police control, and thus may lead to consequences and sanctions inconsistent with the real psychophysical condition of the driver [20].

In the present research, analysis of the group who tested positive for THC and the group with only THC-COOH in blood did not identify significant differences regarding the time interval between the event and blood collection. This result is probably a consequence of different quantities of drugs consumed by drivers, or different times between consuming Cannabis and driving, which may be the most important variables in determining higher or lower hematic concentrations.

To take into account the time elapsed between cannabinoid intake and blood sampling, jointly consideration of model I and model II proposed by Huestis et al. [15,16,21] was applied to estimate time of use. While model I determines time estimated from plasma THC concentrations, model II uses plasma THC-COOH/THC concentration ratios. [16] Since both models are based on plasma concentrations of THC and THC-COOH, whole blood concentrations determined in the case samples were converted in plasma equivalent using the blood-to-plasma ratio proposed by Desrosiers et al. [22].

Model I: Log T (h) = – 0·698 * log [THC] + 0·687

Model II: Log T (h) = (0·576 * log [THC-COOH]/[THC]) – 0·176

Model II calculated the average estimated time since marijuana use at 3 h 7 min (range 30 min - 9 h 1 min), whilst the application of Model I calculated an average time of 2 h 36 min (range 37 min – 7 h 2 min). It must be noted that interpreting this result should consider, in particular, the confidence interval and the absolute mean time error, as suggested by the authors. In this regard, Huestis et al. [15] specified that, in the case of an estimated time lapse of 2 h, the confidence interval is equal to 0.8–5.3, and intervals increase with greater elapsed times after exposure. However, it can be seen that estimated time between the consumption of cannabinoids and the incident occurred with close timing, possibly meaning that many people drive without a real awareness of how rapidly cannabis use impairs their driving.

Further, different national laws in force that regulate the maximum accepted concentration of cannabinoids in the blood while driving were considered. In several Countries, a threshold concentration of blood THC has been established identifying the level beyond which it is forbidden to drive due to the onset of psychophysical alterations [23,24]. In some US states (such as Colorado), the legal THC limit has been set at 5.0 ng/mL [25]. Using that criterion, 114 of the 145 drivers in our study would not have been judged as"driving under the influence of drugs". As the ability to drive can be impaired with a plasma THC concentration greater than 1 ng/mL [7,15] we believe that a high threshold as 5 ng/mL does not guarantee adequate safety on the road. Other US states and some European countries have opted for lower legal limits. For instance, in Belgium, driving is allowed with blood THC levels below 1 ng/mL, while in Portugal the threshold is 3 ng/mL. In Countries such as Sweden, where a zero-tolerance system has been adopted and no "legal limits" have been set, the criterion of finding the active drug

(THC) in the blood at the lower limit of quantification of the confirmation method can be applied. In Italy, as stated above, the zero-tolerance system comes into effect with evaluation of an impaired neuro-psychic state, as the law generically prohibits driving under the influence of drugs. Each of the described legal systems has its own advantages and disadvantages. A system based on legal limits allows people to drive under the influence of cannabinoids as long as the concentration of the substance is low. Individuals with low tolerance to cannabis may be disabled from driving even with very low THC concentrations; however, law allows them to drive in those conditions, thus endangering road safety. On the other hand, a zero-tolerance system is more restrictive: the law punishes even non-disabling blood traces of cannabinoids, resulting from a consumption occurred several hours earlier.

According to the Legal Medicine and Toxicology of Padova, an interpretive threshold of 1 ng/mL of THC in the blood is applied as evidence of recent consumption of cannabis derivatives and the effective impairment of the driver. This limit is not much different from the *per se* limits proposed in Europe. Since THC can be found in the blood of frequent users for several days following frequent use of cannabis[26] the last intake of cannabinoids could have occurred a relatively long time before driving, for example the day before. Nonetheless, while THC persists in the blood for a longer period in chronic users[27], effects on vigilance and driving performance are more marked and last longer in occasional consumers.

The aim of a zero-tolerance approach is to reduce cannabis use in those who plan to drive in the hours following consumption. THC can indeed harm driving, as it impairs coordination, visual function, and attention; these alterations can persist for several hours after consumption.[28] On the other hand, a threshold policy that tolerates minimal blood residues of cannabinoids suggests that there can be a legal limit for an illegal substance.

Another point to consider is the medical use of cannabis: patients who regularly take cannabis-derived medicinal products, containing THC and/or cannabidiol (CBD), often have high blood concentrations of cannabinoids which might exceed the legal limit. Hence, these subjects could be punished by law due to their therapy; while it seems necessary to distinguish patients who consume cannabis under medical prescription from subjects who take the substance as a recreative drug, patients must be instructed not to drive after recent consumption of medical cannabis, as it happens with opioid and opiate medicinal drugs.

If a policy based on thresholds was effective in Italy, a smaller number of drivers would be punished by law. For instance, with a threshold value of 3 ng/mL, 83 drivers in our study would not have been charged. This number drops to 52 subjects if a threshold of 2 ng/mL is applied, and to 15 with a threshold of 1 ng/mL. We highilight once more that these THC concentrations refer to blood samples taken in the hospital, usually a few hours after the RTA, and therefore do not correspond to the exact THC levels present at the time of the incident. Considering the discussion above, we can affirm that adopting different state laws has an unequivocal impact on the criminal consequences for drivers consuming cannabinoids, who may behave differently depending on the Country, perhaps putting road safety at risk.

Another approach for assessing and controlling drugged driving is "effect-based," by which prosecutors have to prove the drug impaired the driver's ability to operate a vehicle. The main criticism of this approach is the lack of standardization, since it depends both on the type of drug used and on the judgement of the prosecutor.[23] In this regard, it seems necessary to rely on a forensic toxicologist being familiar with typical signs of impairment due to THC, who has the expertise to assess the effective condition of the offender and to guide the prosecutor in the most appropriate judgement.

Forty-one of 145 (28.3%) THC-positive drivers also had traces of alcohol in their blood. Of these, 35 drivers (24.1% of the total) had levels above the limit established by law (0.5 g/L). We also found a slightly lower percentage (28.1%) of alcohol positivity in subjects with THC-COOH alone, without observing statistically significant differences between the groups. An acute combination of alcohol and cannabinoids tends to produce additive effects, especially among infrequent cannabis users, while chronic cannabis use, without acute administration, does not potentiate the effects of alcohol.[29] It has previously been described that, among alcohol users, simultaneous alcohol-cannabis intake is more common than smoking cannabis alone.[30] Besides alcohol, other drugs were also detected in the blood of THC-positive drivers. Cocaine and metabolites were the most frequently detected substances. Benzodiazepines, amphetamine, ketamine, and opioids were found to a lesser extent. These findings were similar to those observed by the above-mentioned authors in their research [31].

In our study, we also evaluated 176 cases in which THC-COOH was found in blood in the absence of THC. As expected, in this group of subjects, blood concentrations of THC-COOH were significantly lower, evidencing that metabolism and excretion of the substance occurred. The same result was found in the urinary concentrations of the metabolite. Since THC-COOH is an inactive metabolite of THC, and does not possess psychotropic properties, its blood presence does not entail neuropsychological and behavioural alterations at the time of collection of the sample.[32],[5] However, Cocchetto et al. stated that plasma THC concentration is a poor predictor of simultaneously occurring physiological and psychological effects, as illustrated by hysteresis plots.[33] Therefore, the absence of THC in the blood is not necessarily associated with a lack of disabling effects when driving. In Italy, by law,[34] the presence in the blood and/or urine of THC-COOH alone does not *per se* entail a felony but can impose administrative sanctions (fines, driving licence provisional suspension) on drivers.

It would also be questionable whether the sole discovery of THC-COOH is a consequence of actual consumption of cannabinoids that occurred in previous days without altering driving skills, or whether the time elapsed between the event (RTA or police control) and withdrawal was too long to properly examine the state of the subject at the time of the event, as previously stated. The above-mentioned models for estimating the time of cannabinoid exposure based on plasma concentrations of THC and THC-COOH proposed by Huestis et al.[15] is not applicable in these cases due to the lack of THC concentrations. Hence, in these cases, it is not possible to accurately establish the neuro-psychic state of the driver at the time of the event based on recent or remote consumption. To overcome this, Stevenson et al.[35] proposed a method to assess the presence of THC in saliva as an on-the-road screening, which could represent an additional tool to more precisely evaluate the driver's status within a short timeframe.

In conclusion, driving under the influence of drugs remains a danger to drivers and passengers, as it increases the risk of deaths and injuries caused by traffic accidents.[36] To reduce these risks, due to the rapid onset of impairing effects after smoking cannabis and to THC pharmacokinetics, we believe that strategies, such as an extensive network of roadside controls at night and state-sponsored awareness campaigns aimed primarily at young people as well as the implementation of specific laws, could improve road safety.

CRediT authorship contribution statement

Donata Favretto: Conceptualization, Methodology, Supervision, Writing – review & editing. **Alessandro Cinquetti**: Data curation, Writing – original draft. **Claudio Terranova:** Formal analysis, Supervision, Statistics. **Anna Aprile:** Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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