



THC and CBD in blood samples and seizures in Norway: Does CBD affect THC-induced impairment in apprehended subjects?



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ABSTRACT

Background and aims: Several publications have suggested increasing cannabis potency over the last decade, which, together with lower amounts of cannabidiol (CBD), could contribute to an increase in adverse effects after cannabis smoking. Naturalistic studies on tetrahydrocannabinol (THC) and CBD in blood samples are, however, missing. This study aimed to investigate the relationship between THC- and CBD concentrations in blood samples among cannabis users, and to compare cannabinoid concentrations with the outcome of a clinical test of impairment (CTI) and between traffic accidents and non-accident driving under the influence of drugs (DUID)-cases. Assessment of THC- and CBD contents in cannabis seizures was also included.

Methods: THC- and CBD concentrations in blood samples from subjects apprehended in Norway from April 2013–April 2015 were included ($n=6134$). A CTI result was compared with analytical findings in cases where only THC and/or CBD were detected ($n=705$). THC- and CBD content was measured in 41 cannabis seizures.

Results: Among THC-positive blood samples, 76% also tested positive for CBD. There was a strong correlation between THC- and CBD concentrations in blood samples (Pearson's $r=0.714$, $p<0.0005$). Subjects judged as impaired by a CTI had significantly higher THC- ($p<0.001$) and CBD ($p=0.008$) concentrations compared with not impaired subjects, but after multivariate analyses, impairment could only be related to THC concentration ($p=0.004$). Analyzing seizures revealed THC/CBD ratios of 2:1 for hashish and 200:1 for marijuana.

Conclusions: More than $\frac{3}{4}$ of the blood samples testing positive for THC, among subjects apprehended in Norway, also tested positive for CBD, suggesting frequent consumption of high CBD cannabis products. The simultaneous presence of CBD in blood does, however, not appear to affect THC-induced impairment on a CTI. Seizure sample analysis did not reveal high potency cannabis products, and while CBD content appeared high in hashish, it was almost absent in marijuana.

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1. Introduction

Cannabis is the most frequently used illicit drug worldwide. Different types of products can be derived from the *Cannabis sativa* plant, with the main types being herbal cannabis (marijuana) and resin (hashish). The plant contains almost 500 compounds, including 104 cannabinoids [1], and Δ^9 -tetrahydrocannabinol (THC) is considered to be the main psychoactive constituent [2].

A substantial number of publications have reported disruption of cognitive- and psychomotor effects after cannabis exposure [3–6]. Due to cognitive- and psychomotor impairment, in addition to altered judgment, cannabis use has been associated with an increased risk of traffic accidents [7,8]. In a study by Khiabani et al. in 2006 [9], a higher number of apprehended drivers were judged as impaired than not impaired by a physician, while being under the influence of THC, and with increased consistency at higher THC concentrations.

Since 1982, there have been several studies investigating the effects of another cannabis compound: cannabidiol (CBD) [10]. The main question has been if this compound could protect against adverse psychological effects of THC [11]. The exact mechanism of action for CBD is not known, but it might be mediated through its inhibiting effect on the degradation of the endogenous

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cannabinoid anandamide; prolonging anandamide's effect and thereby preventing THC from interacting with the cannabinoid receptor [11].

Several studies have also focused on the levels of THC and CBD in cannabis over time and increasing levels of THC content have been reported worldwide. Large-scale analyses for THC- and CBD content in cannabis seizures covering the past two decades have been performed in the United States [1,12,13]. Other countries, like England [14] and Australia [15], have also published data on cannabinoid content in cannabis seizures, but not consistently. In the Netherlands, cannabinoid content in cannabis samples from coffee shops has been monitored since the beginning of 2000 [16,17]. A systematic review and meta-analysis from 2012 by Cascini et al. [18], including 21 studies with 75 total mean THC observations from 1979–2009, showed a recent and consistent increase in cannabis potency worldwide.

Simultaneous to reports on increased cannabis potency, an increase in cannabis-related health problems has been reported [19], but it is not understood if this could be due to an increase in THC and/or decrease in the amounts of CBD in cannabis products.

Our laboratory has previously found that concentrations of THC in blood samples from driving under the influence of drugs (DUID)-cases, where only cannabis products had been consumed, increased significantly from 2000–2010 [20]. Analysis for CBD was not available during this time period.

The purpose of this study was to investigate the relationship between the THC- and CBD concentrations in blood samples from subjects apprehended by the police in Norway, from April of 2013 to April of 2015. Furthermore, it was to compare the concentrations of THC and CBD in blood samples with the findings from a concurrent clinical test of impairment (CTI) and between DUID cases resulting in a traffic accident with those that did not. Analysis of THC- and CBD content in 41 Norwegian cannabis seizure samples from the same time period was also included.

2. Materials and methods

2.1. Blood samples

2.1.1. Blood samples

When subjects are apprehended by the police in Norway on suspicion of drug use in connection to a crime, they are usually subjected to a blood test. The blood samples included in this study were whole blood drained into 5 mL BD Vacutainer[®] evacuated blood collection tubes, containing 20 mg of sodium fluoride and 143 IU of heparin (BD Diagnostics, Plymouth, UK). The blood samples were sent to our laboratory by mail or by road transportation services and stored at 2–8 °C until analyzed. In general, blood samples are analyzed shortly after arrival at our laboratory, normally being completed within two weeks.

The blood samples were screened for ethanol by an enzymatic method [21]. High-performance liquid chromatography with tandem mass spectroscopy (LC–MS/MS) was used to analyze for a selection of illicit drugs, sedatives, hypnotics and analgesics [22]. The confirmation analyses of THC along with CBD were performed by gas chromatography mass spectrometry (GC–MS) (modified from Christophersen [23]). GC–MS was operated in specific ion monitoring (SIM) mode. The administrative cut-off limits in whole blood were set at 0.16 ng/mL for CBD and 0.31 ng/mL for THC. Standard curves were linear with coefficients of determination greater than 0.998 for both analytes. QC-samples (four concentration levels) had less than 14% deviation from nominal values. The method has also been evaluated by proficiency testing (LGC quant Tox case) with pleasing results for THC.

2.1.2. Categories of cases

The blood samples received at our laboratory from the police are divided into two main categories: traffic-related cases (suspected DUID cases), which include random traffic controls, suspicious driving, traffic accidents etc.; and other types of cases, which include assaults, rape, manslaughter etc. Traffic-related cases comprise, by far, the majority of cases. In this study, the two main categories of cases were handled as one, except for in the last part of the study, where traffic accident cases were compared with non-accident cases.

2.1.3. Clinical test of impairment (CTI)

In Norway, subjects apprehended by the police in relation to a crime, with suspected drug use, are usually subjected to a clinical test of impairment (CTI), in addition to the blood test. The CTI is performed by a physician and aims to reveal signs of impairment related to drug intoxication. The CTI consists of three parts. First, the physician performs a short interview, asking the apprehended subject about drinking habits and drug history, including recent drug use. Second, a set of twenty-seven observations and tests is performed (including seven tests on alertness, cognitive function, and vestibular function; four observations of the eyes; two observations of cardiac action; two observations pertaining to signs of intravenous drug use; four tests on motor activity/coordination; and eight observations of appearance) [24]. Finally the physician must conclude on whether the subject appears impaired or not. The conclusion of the CTI is based on the physician's overall impression of the apprehended subject and not solely on the total score of the individual tests included in the CTI. The level of impairment is further subdivided into three categories: "slightly", "moderately", and "obviously" impaired. There is also the option to conclude that it was "impossible" to decide on whether the subject appeared impaired or not. This final option should be reserved for subjects with severe disabilities and cases where a traffic accident has rendered the subject unconscious etc. The results ("impaired" or "not impaired") of the CTIs for the corresponding set of blood samples were included in this study.

2.1.4. Driving under the influence of drugs (DUID) in Norway

In Norway, as of February 2012, legislative DUID limits were given for 20 different drugs, other than alcohol [25]. These new limits are drug concentrations that correspond to the legal DUID limits for alcohol, which in Norway are blood alcohol concentrations (BAC) set at 0.02%, 0.05%, and 0.12%. For THC, the corresponding legal DUID limits are 1.3 ng/mL, 3.1 ng/mL, and 9.4 ng/mL. Different sanctions are given to subjects presenting THC levels detected above these limits.

2.1.5. Data sets

Our database was searched for a set of data among forensic toxicological cases, including data from subjects apprehended by the police testing positive for THC and/or CBD in blood between April of 2013 and April of 2015. The dataset included all the THC and/or CBD positive cases, regardless of the detection of other drug (mostly narcotic/psychoactive substances) findings, providing details on age, gender, date and time of incident, date and time of blood sampling, calculated time interval between incident and blood sampling, arrest category, accident outcome in traffic-related cases, THC concentration, and CBD concentration. A subset of data included those cases testing positive for THC and/or CBD only, providing details on age, gender, date and time of incident, date and time of blood sampling, calculated time interval between incident and blood sampling, arrest category, accident outcome in traffic-related cases, clinical test of impairment (CTI) conclusion, THC concentration, and CBD concentration.

2.2. Seizures

A random sample of forty-one cannabis products, seized in Norway sometime during 2013 and 2014, were donated from the Norwegian National Criminal Investigation Service (otherwise known as KRIPOS in Norway) to our laboratory in the spring of 2015. KRIPOS categorizes cannabis seizures as hashish or marijuana/cannabis plant products, making no distinction between the different types of products in the latter category, leaving high THC-containing products, like sinsemilla (female seedless plants producing high amounts of THC), to be grouped together with marijuana.

Upon arrival at our laboratory, the seizures were categorized as either hashish (resin) or marijuana (herbal cannabis) samples, based on their appearance. The seizures were homogenized, and aliquots of approximately 50 mg were weighted and solved with ethanol in 10 volumetric flasks, agitated in an ultrasonic bath for approximately 30 min, and allowed to stand in a refrigerator until analysis. 25 μL of the internal standard solution (30 $\mu\text{g/L}$ THC- d_3 and cannabidiol- d_3 in ethanol/Type 1 water mixture (1:2 v/v)) was added to a sample aliquot of 250 μL and evaporated to dryness, followed by derivatization with 20 μL BSTFA/acetonitrile mixture (1:2 v/v). The samples were consequently analyzed for their THC and CBD content, applying the same analytical technique as for the blood samples (see above).

2.3. Statistical analyses

For the cases testing positive for THC and/or CBD, regardless of other drug findings, mean THC and CBD concentrations, mean ratio, and mean age were calculated. Mean time interval between incident and blood sampling was also calculated, excluding all values below or above 0–24 h (providing reliable values for 89% of the cases). The relationship between the THC and CBD concentrations was investigated using Pearson product–moment correlation coefficient. Preliminary analyses were performed to ensure no violation of assumptions of normality, linearity and homoscedasticity. The data set was divided according to the legislative DUID limits for THC: equal to or below the 1.3 ng/mL legal limit; above 1.3 ng/mL and below or equal to the 3.1 ng/mL legal limit; above the 3.1 ng/mL and below or equal to the 9.4 ng/mL legal limit; and finally, above the 9.4 ng/mL legal limit. The number of THC positive cases, the number of CBD positive cases, the mean CBD concentrations, the mean THC/CBD ratios, and the mean time intervals were calculated for each legal limit group. Independent samples t-test were conducted to compare CBD concentrations, THC/CBD ratios, and time intervals, while Pearson Chi-Square test was used to compare CBD positive case frequencies.

For the subset of cases testing positive for THC and/or CBD only, mean THC and CBD concentrations, mean ratio, and mean age were calculated. Mean time interval between incident and blood sampling was also calculated, excluding all values below or above 0–24 h (providing reliable values for 89% of the cases). The cases in this subset were grouped based on the result of the CTI as “impaired”, including the “slightly”, “moderately”, and “obviously” impaired cases, and “not impaired”; excluding those cases deemed as “impossible” to conclude and where no CTI was performed. The differences in THC- and CBD concentrations and the ratios between the impaired and the not impaired subjects were first studied using independent samples t-test. Further, a logistic regression was performed, applying impairment as the dependent variable and the concentrations of THC and CBD, together with age and sex, as the independent variables. Differences in THC and CBD concentrations, THC/CBD ratios, and time interval between the non-accident group of traffic cases and the accident group were assessed using the independent samples t-test.

Mean and SD for the continuous variables and frequency distributions for the categorical variables are reported throughout the results section.

The forty-one seizures were studied based on category, calculating separate mean THC- and CBD contents and THC/CBD ratios for the hashish- and marijuana samples.

2.4. Ethics

An ethical committee approval was not required to perform this study. The study was conducted according to the data processing agreement with the Higher Prosecuting Authority, which stands as the owner of forensic materials in Norway. In accordance with this agreement, only anonymous data were used in the present study.

3. Results

3.1. Concentrations of THC and CBD in blood samples

3.1.1. All cases

In total, 6134 cases tested positive for THC and/or CBD, including the detection of other narcotic/psychoactive substances, in the given time period (Table 1).

Increasing numbers of CBD positive cases, CBD concentrations, and THC/CBD ratios were observed with increasing THC concentrations (Table 2). In addition, time intervals between incident and blood sampling decreased, with increasing THC concentrations. There was a strong correlation between the concentrations of THC and CBD (Pearson's $r = 0.714$, $n = 6134$, $p < 0.0005$), associating high THC concentrations with high CBD concentrations.

3.1.2. Cases testing positive for THC and/or CBD only

A subset of 890 cases tested positive for THC and/or CBD only, meaning no other drugs were detected (Table 3).

The relationship between impairment and concentrations of THC and CBD is presented in Table 4. The impaired subjects had significantly higher THC- ($p < 0.001$) and CBD ($p = 0.008$) concentrations compared with the not impaired subjects, when conducting an independent samples t-test. There was no difference in the THC/CBD ratio between the impaired and the not impaired subjects ($p = 0.229$). When a logistic regression analysis was performed, it showed a significant effect of the concentration of THC on impairment, after correcting for the concentration of CBD, age, and sex ($p = 0.004$). There was, however, no significant effect of the concentration of CBD on impairment, after correcting for the concentration of THC, age, and sex ($p = 0.710$). The model in itself containing all the predictors was statistically significant, $\chi^2(4) = 23.17$, $p < 0.001$.

Among the DUID cases, significantly higher THC concentrations ($p < 0.001$) and THC/CBD ratios ($p = 0.011$) were found in the non-accident group of cases compared with the traffic accidents (Table 5). The time interval between incident and blood sampling was, however, significantly shorter among the non-accident cases

Table 1

Descriptive for all cases testing positive for THC and/or CBD (n gives the number of valid cases and % gives the percentage of all cases).

All cases, n	6134
THC positive cases, n (%)	6121 (99.8%)
THC concentration (ng/mL), mean \pm SD	4.33 \pm 5.89
CBD positive cases, n (%)	4632 (76%)
CBD concentration (ng/mL), mean \pm SD	0.98 \pm 1.45
THC/CBD ratio, mean \pm SD	5.6 \pm 10.6
Age (years), mean \pm SD	31 \pm 10
Male, n (%)	5613 (92%)
Time interval in minutes, mean \pm SD	135 \pm 161

Table 2

THC concentrations categorized according to the Norwegian legislative laws on DUID, with the corresponding number of THC positive cases, CBD positive cases, mean CBD concentrations, THC/CBD ratios, and time intervals, for all cases testing positive for THC and/or CBD (*n* gives the number of valid cases and % gives the percentage of all THC positive cases).

THC concentrations according to Norwegian DUID limits (ng/mL)	≤1.3	1.3–3.1	3.1–9.4	≥9.4
<i>N</i>	2245	1520	1672	697
CBD positive cases, <i>n</i> (%)	1100 (49%)	1330 (88%)*	1549 (93%)*	653 (94%)*
CBD concentrations (ng/mL), mean ± SD	0.18 ± 0.24	0.64 ± 0.45*	1.41 ± 1.02*	3.21 ± 2.79*
THC/CBD ratio, mean ± SD	3.0 ± 1.2	4.0 ± 2.6*	5.7 ± 5.9*	13.1 ± 25.0*
Time interval in minutes, mean ± SD	152 ± 173	147 ± 170	121 ± 146**	90 ± 121**

* Significantly ($p < 0.05$) more CBD positive cases, higher CBD concentrations, and/or higher THC/CBD ratios compared with the group with lower THC concentrations.

** Significantly ($p < 0.05$) lower time interval compared with the group with lower THC concentration.

Table 3

Descriptive for cases testing positive for THC and/or CBD only (*n* gives the number of valid cases and % gives the percentage of all THC and/or CBD only cases).

THC and/or CBD only cases, <i>n</i>	890
DUID cases, <i>n</i> (%)	791 (89%)
Traffic accident, <i>n</i> (%)	71 (9%)
THC positive cases, <i>n</i> (%)	890 (100%)
THC concentration (ng/mL), mean ± SD	7.08 ± 8.14
CBD positive cases, <i>n</i> (%)	662 (74%)
CBD concentration (ng/mL), mean ± SD	1.16 ± 1.73
THC/CBD ratio, mean ± SD	10.5 ± 21.7
Age (years), mean ± SD	26 ± 8
Male, <i>n</i> (%)	852 (96%)
Time interval in minutes, mean ± SD	107 ± 126

($p < 0.001$). No difference was found for the CBD concentrations between the two groups.

3.2. Seizures

Of the forty-one seizures received from KRIPOS, 21 were categorized as hashish seizures and 20 as marijuana seizures (Table 6).

4. Discussion

Of the 6134 cases testing positive for THC and/or CBD in blood, in addition to other narcotic/psychoactive substances, 6121 cases tested positive for THC, and 4632 cases tested positive for CBD, leaving 13 cases testing positive for CBD only (THC not detected above the analytical cut-off limit). The high detection rate of CBD in blood (76%) was at first surprising. Previous studies have

given a detection time for CBD in blood of less than 1 h after smoking [26–28]. The CBD detection rate was expected to be low because the mean time interval between incident and blood sampling was more than 2 h (135 min). Incidentally, the mean time interval for the CBD positive cases was also found to be more than 2 h (133 min). It should, however, be noted that the analytical cut-off limit used for CBD (LOQ 0.16 ng/mL) in this study was lower than those used in other studies (LOQ 0.5–1.0 ng/mL) [26–28], which could lead to a longer detection time for CBD in blood. In addition, the subjects in these other studies smoked marijuana, which contained only small amounts of CBD (0.20%–0.25%). In Norway, hashish appears to be more common than marijuana. By example, in 2015 hashish seizures totaled around 2000 kg while marijuana seizures weighed roughly 300 kg in all [29]. Because hashish in general contains substantially higher amounts of CBD than marijuana, this could also explain the higher detection rate.

Grouping the cases according to THC blood concentrations, it became obvious that with increasing THC concentrations, there was an increased likelihood of detecting CBD in blood; among the cases with the highest THC concentrations (above 9.4 ng/mL THC in blood), 94% also tested positive for CBD. In addition, the mean CBD concentrations increased significantly with each THC concentration group increment. The strong correlation calculated between the THC- and CBD concentrations (Pearson's $r = 0.714$, $n = 6134$, $p < 0.0005$), in this study, is likely due to a proximity to cannabis intake among these cases. Recalling the smoking pharmacokinetics of THC [30] and CBD [31], both cannabinoids reach their maximum concentrations in blood during or shortly after smoking a cannabis product, before falling quickly and exponentially during the first hour and then tapering off to a more gradual decline. The CBD concentrations should therefore be at their highest and the

Table 4

THC- and CBD concentrations for the impaired and the not impaired subjects, among cases testing positive for THC and/or CBD only (*n* gives the number of valid cases).

CTI result (<i>n</i> = 705)	THC concentration (ng/mL), mean ± SD	CBD concentration (ng/mL), mean ± SD
Impaired (<i>n</i> = 373)	8.65 ± 9.15	1.32 ± 1.98
Not impaired (<i>n</i> = 332)	6.28 ± 7.18	0.98 ± 1.39
<i>p</i> (regression analysis)	0.004 [†]	0.710 ^{**}

The italic values are *p*-values.

[†] Corrected for CBD concentration, age, and sex.

^{**} Corrected for THC concentration, age, and sex.

Table 5

THC- and CBD concentrations, ratios, and time intervals, for the different types of cases testing positive for THC and/or CBD only.

THC and/or CBD only cases	THC concentrations (ng/mL), mean ± SD	CBD concentrations (ng/mL), mean ± SD	Ratios, mean ± SD	Time interval in minutes, mean ± SD
DUID cases	7.51 ± 8.34	1.21 ± 1.79	11.1 ± 22.8	95 ± 90
No traffic accident	7.79 ± 8.58	1.24 ± 1.83	11.5 ± 23.6	92 ± 85
Traffic accident	4.66 ± 4.42	0.96 ± 1.36	7.0 ± 10.7	134 ± 124
<i>p</i> (t-test)	0.000	0.112	0.011	0.000
Other cases	3.70 ± 5.24	0.70 ± 0.99	5.3 ± 4.8	242 ± 290

The italic values are *p*-values.

Table 6

THC- and CBD content in hashish and marijuana seizures from 2013–2014 (*n* gives the number of seizures).

	THC content (%)	CBD content (%)	THC/CBD ratio
Hashish seizures (<i>n</i> = 21)			
Mean (median)	3.8 (2.0)	2.1 (1.6)	2:1
Min	0.15	0.54	
Max	17.3	7.2	
Marijuana seizures (<i>n</i> = 20)			
Mean (median)	1.9 (2.0)	0.010 (0.005)	200:1
Min	0.0064	0.0009	
Max	3.6	0.090	

likelihood of detecting CBD should be at its greatest along with the highest THC concentrations, regardless of the contents of the product smoked. Significantly shorter time intervals between incident and blood sampling were also observed with increasing THC concentrations, supporting this assumption of proximity to intake.

In the subset of the 890 cases testing positive for THC and/or CBD only, all cases tested positive for THC, while 662 of the cases also tested positive for CBD (74%). Almost all were young (mean 27 years) men (96%), and most were apprehended in relation to traffic violations (89%), of which 9% had resulted in a traffic accident. The mean THC concentration in this subset of cases (7.08 ng/mL) was almost twice as high as the mean for all the cases (4.33 ng/mL), while the CBD concentrations remained similar. This finding suggests in general a shorter time interval between cannabis intake and apprehension, in this subset of cases. In addition, the mean time interval between apprehension and blood sampling in this subset was shorter than for all cases, which should increase the likelihood of detecting higher cannabinoid concentrations. The higher THC concentrations could also imply a greater use of high potency products, among this group of subjects.

In 705 cases (79%), of the subset of cases testing positive for THC and/or CBD only, a CTI with a valid conclusion was performed. In total, 53% of these apprehended subjects were judged as impaired. There were significantly higher concentrations in blood in the impaired group of subjects compared with the not impaired, both for THC ($p < 0.001$) and for CBD ($p = 0.008$), while no difference was found in the THC/CBD ratio ($p = 0.229$). Because these subjects tested negative for other drugs in blood, one would expect the impairment observed on the CTI to be related to the THC concentration, which was shown to be significant ($p = 0.004$), with the results being corrected for concentrations of CBD, age, and sex. Further, one could suspect the simultaneous presence of CBD to affect the likelihood of being judged as impaired. There was, however, no effect of the CBD concentration on impairment, with the results being equally corrected for concentrations of THC, age, and sex. A previous study on the relationship between THC concentrations in blood and impairment, as judged by a CTI in apprehended drivers, showed that the drivers who were judged as impaired had higher THC concentrations in blood than the drivers who were judged as not impaired [9]. Conversely, a number of studies have been unable to show signs of intoxication with CBD use [32–36]. Our results support these previous findings, showing that CBD alone does not cause impairment while THC does, and further that CBD does not appear to protect against THC-induced impairment, as measured by a CTI among apprehended subjects.

Information on arrest category and traffic accident outcome allowed us to study the difference in THC- and CBD concentrations between traffic accidents and non-accident groups of DUID cases, in the subset of cases testing positive for THC and/or CBD only. One could expect the accident cases to reveal higher THC concentrations, leading to impairment and possibly increasing the risk of being

involved in a traffic accident. The concentration of THC and the THC/CBD ratio were, however, significantly higher in the non-accident group of cases compared with the accident cases. Meanwhile the CBD concentration was not significantly higher in the non-accident cases. The time elapsed between the incident and the blood sampling was conversely significantly higher in the accident group of cases compared with the non-accident cases ($p < 0.001$), which could in part explain the decrease in THC concentration and ratio in this former group of cases. Traffic accidents require time for the police and ambulance workers to perform other tasks, such as assessing and documenting the scene, in addition to triaging the driver and possible victims, delaying the police in collecting a blood sample. Clearly the shorter mean time interval (95 min) between apprehension and blood sampling for the non-accident group of cases would increase the likelihood of detecting higher THC concentrations. Other factors, which could also explain the higher THC- and CBD concentrations in the non-accident cases, in addition to impairment causing aberrant driving, could be the observation, by the police or others, of the subject smoking a cannabis joint or the presence of a butt in the car, or simply recognizing the subject or his/her car from a previous drug bust.

Among the hashish seizure samples analyzed in this study, the THC- and CBD content varied greatly, ranging from 0.15–17.3% for THC and 0.54–7.2% for CBD, with the highest THC- and CBD contents found in the same sample. The mean THC/CBD ratio of around 2:1 indicates a mean high CBD content among these seizures. In fact, in 11 of the 21 hashish seizures the CBD content was the same or, even more commonly, higher than the THC content. In comparison, the mean THC/CBD ratio for the marijuana seizures was 200:1, indicating a mean low CBD content. These findings of varying THC content and high CBD content in the hashish samples are consistent with previous findings in other parts of Europe [14,17]. It should be noted that the original age and storage conditions of the samples were unknown, meaning that some samples could have been subject to degradation with decreasing cannabinoid content. However, the findings from the cannabis seizures are in accordance with previous findings of higher THC- and CBD content in hashish compared with that of marijuana, and almost a complete absence of CBD in marijuana [13,14,17]. Furthermore, the number of seizures analyzed was low and covered a short time period, prohibiting any conclusions on changes in potency. A previous Norwegian study from 2013 revealed increasing THC concentrations in blood samples from 2000–2010, indicating increased potency in cannabis products consumed in Norway [20].

5. Conclusions

Among subjects apprehended in Norway from April of 2013 to April of 2015, more than $\frac{3}{4}$ of the blood samples that tested positive for THC also tested positive for CBD, suggesting frequent consumption of high CBD cannabis products, which is consistent with the high hashish seizure rate in Norway.

For the subjects testing positive for THC and/or CBD only in blood, impairment, as measured by a CTI, could be related to THC concentrations but not to CBD concentrations. Our results indicate that CBD alone does not cause impairment while THC does, and that CBD does not appear to protect against THC-induced impairment, in a naturalistic setting.

Comparing traffic accidents with non-accident DUID cases, we found significantly higher mean THC concentration and THC/CBD ratio in the non-accident group of cases compared with the accident cases. The time elapsed between incident and blood sampling was conversely significantly higher in the accident cases, which could in part explain this finding.

Although former studies have suggested CBD as a marker of cannabis smoking within the last hour, our findings also incidentally revealed that CBD may be detected in blood for more than 2 h after intake.

The hashish- and marijuana seizure samples included in this study did not reveal high potency cannabis products, but the sample size was limited and some samples could have been subject to degradation. The twice as high THC content along with the considerably higher CBD amount in the hashish samples compared with the marijuana samples is consistent with previous findings.

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References

- [1] M.A. ElSohly, Z. Mehmedic, S. Foster, C. Gon, S. Chandra, J.C. Church, Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States, *Biol. Psychiatry* 79 (7) (2016) 613–619.
- [2] R. Mechoulam, Y. Gaoni, A total synthesis of dl-delta-1-tetrahydrocannabinol, the active constituent of hashish, *J. Am. Chem. Soc.* 87 (1965) 3273–3275.
- [3] 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.
- [4] M. Ranganathan, D.C. D'Souza, The acute effects of cannabinoids on memory in humans: a review, *Psychopharmacology* 188 (4) (2006) 425–444.
- [5] K.B. Bocker, J. Gerritsen, C.C. Hunault, M. Kruidenier, T.T. Mensinga, J.L. Kenemans, Cannabis with high delta9-THC contents affects perception and visual selective attention acutely: an event-related potential study, *Pharmacol. Biochem. Behav.* 96 (1) (2010) 67–74.
- [6] D.C. D'Souza, E. Perry, L. MacDougall, Y. Ammerman, T. Cooper, Y.T. Wu, et al., The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis, *Neuropsychopharmacology* 29 (8) (2004) 1558–1572.
- [7] F. Grotenhermen, G. Leson, G. Berghaus, O.H. Drummer, H.P. Kruger, M. Longo, et al., Developing limits for driving under cannabis, *Addiction (Abingdon, England)* 102 (12) (2007) 1910–1917.
- [8] B. Laumon, B. Gadegbeku, J.L. Martin, M.B. Biecheler, Cannabis intoxication and fatal road crashes in France: population based case-control study, *BMJ* 331 (7529) (2005) 1371.
- [9] 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.
- [10] D. Rottanburg, A.H. Robins, O. Ben-Arie, A. Teggin, R. Elk, Cannabis-associated psychosis with hypomanic features, *Lancet (London, England)* 2 (8312) (1982) 1364–1366.
- [11] R.J. Niesink, M.W. van Laar, Does cannabidiol protect against adverse psychological effects of THC? *Front. Psychiatry* 4 (2013) 130.
- [12] M.A. ElSohly, S.A. Ross, Z. Mehmedic, R. Ararat, B. Yi, B.F. Banahan 3rd, Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980–1997, *J. Forensic Sci.* 45 (1) (2000) 24–30.
- [13] Z. Mehmedic, S. Chandra, D. Slade, H. Denham, S. Foster, A.S. Patel, et al., Potency trends of Delta9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008, *J. Forensic Sci.* 55 (5) (2010) 1209–1217.
- [14] D.J. Potter, P. Clark, M.B. Brown, Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology, *J. Forensic Sci.* 53 (1) (2008) 90–94.
- [15] W. Swift, A. Wong, K.M. Li, J.C. Arnold, I.S. McGregor, Analysis of cannabis seizures in NSW, Australia : cannabis potency and cannabinoid profile, *PLoS One* 8 (7) (2013) e70052.
- [16] F.T. Pijlman, S.M. Rigter, J. Hoek, H.M. Goldschmidt, R.J. Niesink, Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops, *Addict. Biol.* 10 (2) (2005) 171–180.
- [17] R.J. Niesink, S. Rigter, M.W. Koeter, T.M. Brunt, Potency trends of Delta9-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005–15, *Addiction (Abingdon, England)* 110 (12) (2015) 1941–1950.
- [18] 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.
- [19] W. Hall, L. Degenhardt, The adverse health effects of chronic cannabis use, *Drug Test. Anal.* 6 (1–2) (2014) 39–45.
- [20] V. Vindenes, D.H. Strand, L. Kristoffersen, F. Boix, J. Morland, Has the intake of THC by cannabis users changed over the last decade? Evidence of increased exposure by analysis of blood THC concentrations in impaired drivers, *Forensic Sci. Int.* 226 (1–3) (2013) 197–201.
- [21] L. Kristoffersen, B. Skuterud, B.R. Larssen, S. Skurtveit, A. Smith-Kielland, Fast quantification of ethanol in whole blood specimens by the enzymatic alcohol dehydrogenase method. Optimization by experimental design, *J. Anal. Toxicol.* 29 (1) (2005) 66–70.
- [22] E.L. Oiestad, U. Johansen, A.M. Oiestad, A.S. Christophersen, Drug screening of whole blood by ultra-performance liquid chromatography–tandem mass spectrometry, *J. Anal. Toxicol.* 35 (5) (2011) 280–293.
- [23] A.S. Christophersen, Tetrahydrocannabinol stability in whole blood: plastic versus glass containers, *J. Anal. Toxicol.* 10 (4) (1986) 129–131.
- [24] J.G. Bramness, S. Skurtveit, J. Morland, Testing for benzodiazepine inebriation—relationship between benzodiazepine concentration and simple clinical tests for impairment in a sample of drugged drivers, *Eur. J. Clin. Pharmacol.* 59 (8–9) (2003) 593–601.
- [25] V. Vindenes, L. Skordal, J. Morland, Fixed limits for central stimulants in traffic, *Tidsskr. Nor. Lægeforen.* 132 (3) (2012) 275–276.
- [26] D.M. Schwowe, 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.
- [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] M.N. Newmeyer, M.J. Swortwood, A.J. Barnes, O.A. Abulseoud, K.B. Scheidweiler, Free and glucuronide whole blood cannabinoids' pharmacokinetics after controlled smoked, vaporized, and oral cannabis administration in frequent and occasional cannabis users: identification of recent cannabis intake, *Clin. Chem.* 62 (12) (2016) 1579–1592.
- [29] KRIPOS, Narkotika- og dopingstatistikk 2015, KRIPOS, 2015 Available from: <http://www.webcitation.org/6oybJbDlh>. (Updated 11 August 2016).
- [30] M.A. Huestis, J.E. Henningfield, E.J. Cone, Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana, *J. Anal. Toxicol.* 16 (5) (1992) 276–282.
- [31] A. Ohlsson, J.E. Lindgren, S. Andersson, S. Agurell, H. Gillespie, L.E. Hollister, Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration, *Biomed. Environ. Mass Spectrom.* 13 (2) (1986) 77–83.
- [32] L.E. Hollister, Cannabidiol and cannabinol in man, *Experientia* 29 (7) (1973) 825–826.
- [33] I.G. Karniol, I. Shirakawa, N. Kasinski, A. Pfeferman, E.A. Carlini, Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man, *Eur. J. Pharmacol.* 28 (1) (1974) 172–177.
- [34] P. Consroe, E.A. Carlini, A.P. Zwickler, L.A. Lacerda, Interaction of cannabidiol and alcohol in humans, *Psychopharmacology* 66 (1) (1979) 45–50.
- [35] A.W. Zuardi, J.A. Crippa, J.E. Hallak, F.A. Moreira, F.S. Guimaraes, Cannabidiol, a *Cannabis sativa* constituent, as an antipsychotic drug, *Braz. J. Med. Biol. Res.* 39 (4) (2006) 421–429.
- [36] S.J. Borgwardt, P. Allen, S. Bhattacharyya, P. Fusar-Poli, J.A. Crippa, M.L. Seal, et al., Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition, *Biol. Psychiatry* 64 (11) (2008) 966–973.