



# 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

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## ABSTRACT

The main psychoactive substance,  $\Delta^9$ -tetrahydrocannabinol (THC) can be present in highly variable amounts in different cannabis preparations. An increase in THC content in cannabis products has been suggested, and reported from several countries. However, it has not yet been investigated if products with high potency lead to increased human exposure, and thus to higher risk of adverse effects.

In this study, we examined the mean concentrations of THC in whole blood samples from drivers apprehended in Norway in the period between 2000 and 2010 suspected of driving under the influence of drugs. Cases with only THC ( $n = 1747$ ) have been compared to cases with only ethanol ( $n = 38\,796$ ) or amphetamines ( $n = 2493$ ). The increase in mean THC concentration measured from 2000 to 2010 was from  $4.0 \pm 0.3$  to  $6.6 \pm 0.4$  ng/ml (58%), compared to 3% for ethanol and 16% for the amphetamines. This increase in THC concentrations was to some extent paralleled by an increase in the percentage of drivers which were judged as lightly impaired by a physician.

Monitoring concentrations of drugs of abuse in blood from apprehended drivers indicated an increasing exposure to THC in Norway. If similar trends are observed globally, it should be further explored if this type of information could be used to elucidate the drug consumption patterns in a population and accordingly the consequences with regard to adverse effects of cannabis from a public health perspective.

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## 1. Introduction

*Cannabis sativa* derivatives, like hashish and marijuana, are the most commonly consumed illegal drugs worldwide. The adverse health effects of cannabis have been debated, but cannabis has been considered to have a low toxicity and abuse potential [1,2]. Nevertheless, accumulating and converging evidence during the last decade has, revealed that cannabis use may be a risk factor for psychotic symptoms [3,4]. The reason for the increased number of such reports is not clear. There has, however, been great interest in whether the concentration of  $\Delta^9$ -tetrahydrocannabinol (THC), the psychoactive compound in cannabis, has increased in illegal cannabis products, leading to more frequent adverse effects [2,5,6]. Different cannabis products coexist in Europe, like resin, herbal cannabis and sinsemilla [5]. The typically THC content of resin and herbal cannabis is reported to be between 2 and 8%. Sinsemilla is herbal cannabis grown from selected seeds by intensive indoor methods, and the potency might be twice as high as herbal

cannabis [5]. A study monitoring the cannabis preparations sold in Dutch coffee shops in 2004 revealed that the average THC concentrations in Dutch (39.3% THC) and imported hashish (18.2% THC) were nearly doubled over 5 years [6]. The situation in the Netherlands is, however, probably not representative, since sinsemilla dominates the market. A meta-analysis by Cascini et al. have recently reported that the herbal cannabis market has changed towards increased THC contents in the period from 1979 to 2009, but data concerning the diffusion of more potent varieties to the illicit market is poor [7]. In California, the median THC-level in seizures has increased from 4.56% in 1996 to 11.75% in 2008 [8].

Besides, the question of whether the content of THC in cannabis products has increased, is mainly interesting to explore if this leads to an increase in human exposure to THC, defined as the amount of THC delivered to the human body, and, further, in possible subsequent negative repercussions for public health. Di Forti et al. reported that patients with first episode of psychosis had smoked higher-potency cannabis, for longer periods, and with greater frequency, than a healthy control group [3]. Frequent use of cannabis has also been associated, in a dose-related manner, with increased risk of psychotic symptoms later in life [9] and continued use was reported to increase the risk of persistent psychotic symptoms [4]. To our knowledge, THC concentrations in blood have not been measured in any studies investigating the risk of

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cannabis induced psychosis. It is still unknown if cannabis smokers titrate the dose according to the subjective pharmacological effects experienced during smoking, or whether those who smoke higher potency cannabis will obtain higher blood levels of THC. Cannabis products contain multiple cannabinoids, and other substances, like cannabidiol (CBD), might also affect the risk of psychosis [8].

The best measure of human THC exposure after smoking would be the Area Under the Curve (AUC) for blood THC-concentration over time, but such data are very difficult to obtain for regular users. Cannabis users are however reported to drive after smoking [10], and analyses of blood samples from apprehended drivers suspected of driving under the influence of drugs (DUID) might therefore provide important information regarding pattern of drug use and might elucidate changes with time.

In this study we investigated if the mean concentration of THC in blood samples from apprehended Norwegian drugged drivers has changed over the last 11 years.

## 2. Materials and methods

### 2.1. Samples

During the latter 10–15 years, the Norwegian police has apprehended about 10 000 drivers per year (of a population close to 5 million people) suspected of DUID. Blood samples have been collected from the drivers, usually within 1–2 h after apprehension, and sent to the Norwegian Institute of Public Health for drug analyses. In this study, we have selected blood samples for the years 2000–2010 containing only THC. Samples containing only ethanol or only amphetamines (defined as the sum of amphetamine and/or methamphetamine) during the same period were used as references.

Whole blood was collected in 5 ml Vacutainer® tubes containing 20 mg sodium fluoride and 143 IU heparin (BD Vacutainer Systems, Belliver Industrial Estate, Plymouth, UK).

### 2.2. Analysis

All blood samples were analysed shortly after reception at the institute. All samples were screened for ethanol by an enzymatic method [11], for THC, amphetamine and/or methamphetamine, benzodiazepines, cocaine, and opiates by immunological methods, and for 16 frequently used sedatives, hypnotics and analgesics by liquid chromatography–mass spectrometry (LC–MS) until 2009. From 2009, screening by LC–MS/MS was used for drugs of abuse, sedatives, hypnotics and analgesics [12]. The confirmatory analyses for THC [13] and amphetamine/methamphetamine [14] were performed by GC–MS, and by headspace GC–FID for ethanol throughout the study period [15].

### 2.3. Clinical test of impairment (CTI)

In Norway, drivers suspected of DUID are usually examined by a physician shortly after driving to assess drug impairment. The Norwegian CTI consists of 25 tests and observations related to common signs of drug impairment [16]. The physician concludes if the driver is considered not impaired or impaired, and if so, the degree of impairment is also indicated. The CTI was undertaken at the same time as when the blood sample was collected.

### 2.4. Calculations

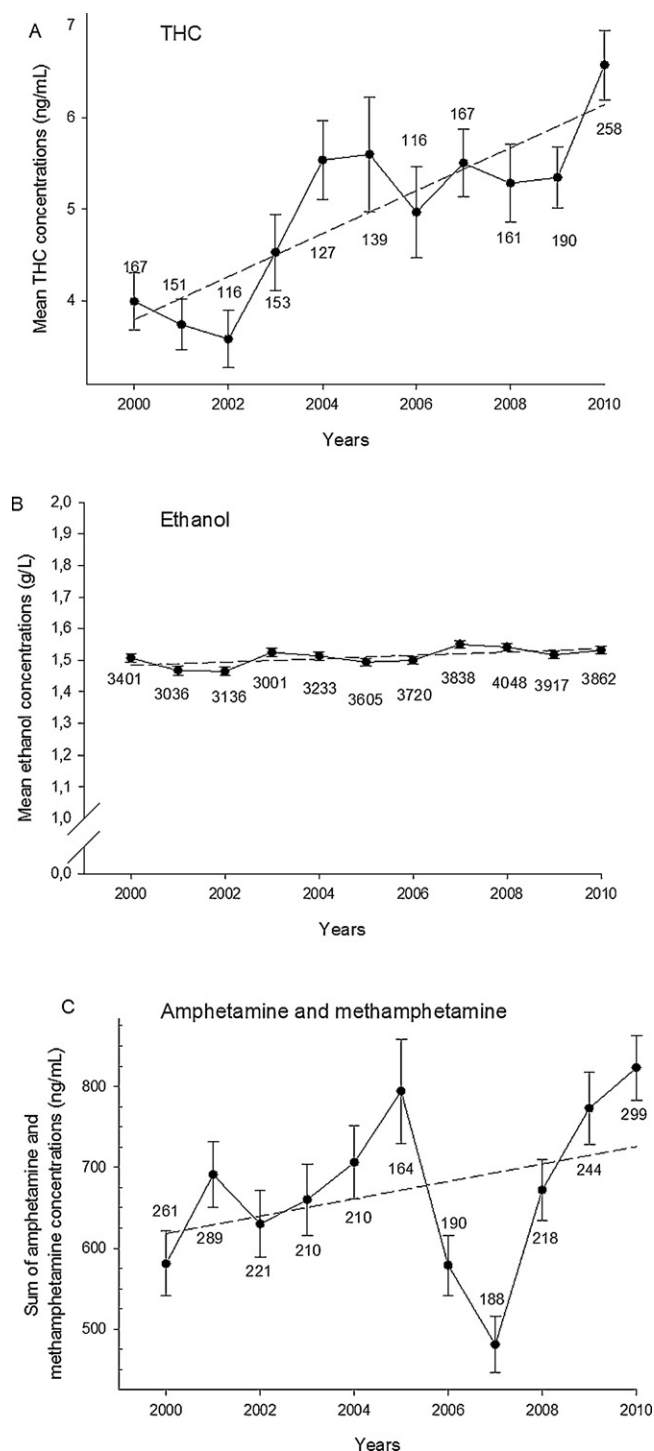
The changes in concentrations over the years were calculated as percentage for each drug. A regression line was drawn for each drug, and from this line, the change in mean concentrations from 2010 to 2000 was divided by the mean drug concentration in 2000, reported as percentage.

### 2.5. Statistics

In order to examine if changes over time were statistically significant for the different drugs over the years, the mean concentrations of THC, ethanol and amphetamines for each year were compared using ANOVA and Bonferroni post hoc tests. Ratio of impaired vs. not impaired was tested using chi-square. Statistical analyses were conducted using the statistical package SPSS 17.0.

## 3. Results

A total of 1748 samples were positive only for THC, 38 796 for ethanol and 2493 for amphetamines. The mean concentrations of THC, ethanol and amphetamines from 2000 to 2010 are shown in Fig. 1a–c.



**Fig. 1.** The mean concentrations  $\pm$  s.e.m. of THC (a), ethanol (b) and amphetamines (c) in whole blood samples from drivers apprehended by the police suspected of driving under the influence, are shown. ANOVA showed statistical significant differences between the years for all three drugs: THC [ $F(10, 1738) = 5.63, p < 0.001$ ], amphetamines [ $F(10, 2483) = 5.05, p < 0.001$ ] and ethanol [ $F(10, 38\,786) = 4.72, p < 0.001$ ]. Post hoc comparisons revealed that the mean THC concentrations from 2000, 2001, 2002 and 2003 were statistically significantly lower when compared to concentrations in 2010 ( $p < 0.05$ ). For ethanol post hoc comparison showed that the mean concentrations in 2001 and 2002 were significantly different from 2010 ( $p < 0.05$ ). For the amphetamines post hoc comparisons revealed that the mean concentrations in 2000, 2006 and 2007 were statistically significantly different from the 2010 concentration ( $p < 0.05$ ). The regression line illustrates the change in percentage during this period.

**Table 1**

Mean  $\pm$  s.e.m. THC concentrations in blood, mean time in hours between driving and blood sampling, mean  $\pm$  s.e.m. age of the drivers, the number of THC positive cases, and the ratio of drivers judged as impaired versus not impaired from the clinical test of impairment. Data is shown for each year during the study period for the THC positive cases where no other drugs have been detected.

Years	Mean THC concentrations $\pm$ s.e.m. (ng/mL)	Median THC concentrations (ng/mL)	Maximum concentration (ng/mL)	Mean time between driving and blood sampling (h)	Mean age THC-drivers	Numbers of cases with THC only (total number of cases in brackets)	Ratio impaired/not impaired from CTI**
2000	4.0 $\pm$ 0.3	2.83	31.45	*	25.1 $\pm$ 0.49	167 (7249)	0.83
2001	3.7 $\pm$ 0.3	2.83	22.01	*	25.7 $\pm$ 0.56	151 (7409)	0.97
2002	3.6 $\pm$ 0.3	2.20	21.07	2.01	26.4 $\pm$ 0.75	116 (8211)	1.11
2003	4.5 $\pm$ 0.4	2.83	31.14	1.95	26.5 $\pm$ 0.65	154 (7428)	1.16
2004	5.5 $\pm$ 0.4	4.09	22.01	1.90	25.0 $\pm$ 0.70	127 (6974)	1.17
2005	5.6 $\pm$ 0.6	3.46	49.69	1.84	25.5 $\pm$ 0.59	139 (7087)	1.37
2006	5.0 $\pm$ 0.5	3.46	37.11	1.86	26.0 $\pm$ 0.69	116 (7329)	1.19
2007	5.5 $\pm$ 0.4	4.09	25.47	1.80	26.1 $\pm$ 0.59	167 (7469)	0.94
2008	5.3 $\pm$ 0.4	3.77	48.12	1.76	26.1 $\pm$ 0.62	161 (7786)	0.88
2009	5.3 $\pm$ 0.3	4.40	24.53	1.77	26.0 $\pm$ 0.59	192 (7812)	1.21
2010	6.6 $\pm$ 0.4	4.72	41.83	1.73	25.2 $\pm$ 0.47	258 (7861)	1.44

\* No registrations in our database for these years.

\*\* No statistically significant change in the ratio was seen over the years ( $p=0.076$ ) using chi-square Mantel–Haenszel linear-by-linear association.

THC concentrations gradually increased from  $4.0 \pm 0.3$  in 2000 to  $6.6 \pm 0.4$  ng/ml in 2010. Median concentration in 2000 was 2.83 ng/ml and 4.72 ng/ml in 2010. Statistical significant differences between the years were seen for all three drugs: THC [ $F(10, 1738) = 5.63$ ,  $p < 0.001$ ], amphetamines [ $F(10, 2483) = 5.05$ ,  $p < 0.001$ ] and ethanol [ $F(10, 38786) = 4.72$ ,  $p < 0.001$ ]. Post hoc comparisons revealed that the mean THC concentrations from 2000, 2001, 2002 and 2003 were statistically significantly lower when compared to concentrations in 2010 ( $p < 0.05$ ). For ethanol post hoc comparison showed that the mean concentrations in 2001 and 2002 were significantly different from 2010 ( $p < 0.05$ ). For the amphetamines post hoc comparisons revealed that the mean concentrations in 2000, 2006 and 2007 were statistically significantly different from the 2010 concentration ( $p < 0.05$ ).

Looking at the gradient for changes in concentrations over the study period, the increase in THC concentrations was 58%, compared to 3% for ethanol and 16% for the amphetamines.

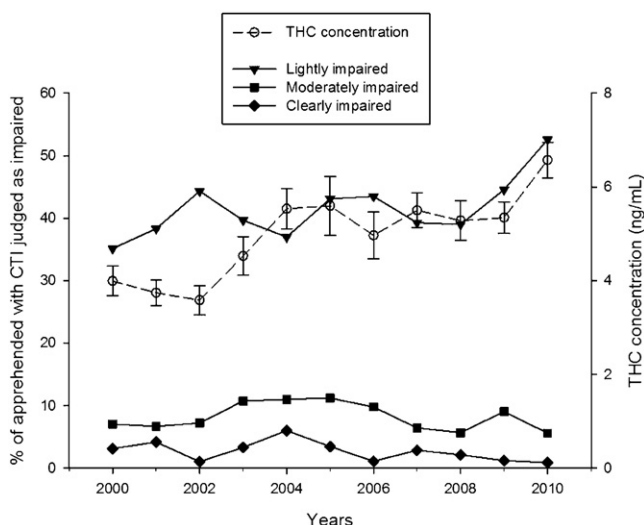
The mean age of the drivers was  $25.7 \pm 0.2$  years in the THC group, and did not show any significant change during the study period (Table 1). For ethanol the mean age was  $36.0 \pm 0.1$  years and in the amphetamines group  $32.2 \pm 0.2$ . The percentage of males in each

group was 95% for THC, 89% for ethanol and 87% for amphetamine/methamphetamine. Table 1 shows a gradual decline in the time from driving to blood sampling during our study period. A reduction of around 17 min, from 2.01 h in 2000 to 1.73 h in 2010, was seen.

The ratios of drivers judged as impaired versus not impaired for each year (Table 1) shows a slight increase during the study period which did not reach statistical significance ( $p = 0.076$ , chi-square Mantel–Haenszel linear-by-linear association). This ratio was below 1 for the two first years (2000 and 2001), and above 1.2 for the two last years studied (2009 and 2010). Fig. 2 shows the percentage of drivers judged as impaired and the mean THC concentrations for each year. The increase in THC concentrations was to some extent paralleled by an increase in the percentage of drivers which were judged as lightly impaired by a physician. The percentages judged as moderately and clearly impaired did not increase during the period.

#### 4. Discussion

Our study indicates that THC concentrations in blood samples from Norwegian drivers suspected of DUI have increased substantially over the last years, a phenomenon not seen for the amphetamines or ethanol. Methodological changes in our laboratory cannot explain the increase observed, but changes in the procedures by which the police handle impaired drivers could be a possible cause. Thus, the percentage of drivers with only THC in the blood sample judged as impaired by a physician varied over time, but a slight increase might be observed. However, the number of drivers apprehended each year did not change markedly from year to year, indicating that the police activity against the group of impaired drivers was rather constant during the study period. On the other hand, the mean time from driving until blood sampling was reduced with around 17 min during this 11 years study period, mostly due to the reduction in the interval in those cases where the time to collection was longer than 1 h. Smoking cannabis leads to maximum THC concentrations within few minutes, with a rapid decrease in concentrations within the next hour (alpha-phase) followed by a period (beta-elimination phase) with longer half-life and slower disappearance of THC from the blood [17]. If we assume that smoking took place up to the time of driving, only small changes of the THC concentration would be expected to occur around the time of sampling approximately 2 h later. The shortest mean time sample collection, observed in the last year of the period studied, was of 1 h and 45 min after driving, representing the minimum mean time between smoking and sampling, indicated that the time of sampling was located within the



**Fig. 2.** The percentages of drivers judged as lightly, moderate or clearly impaired are plotted against the mean THC concentrations for each year. The clinical test of impairment (CTI) is performed by a physician when a driver has been apprehended by the police, suspected of driving under the influence of drugs.

beta-elimination phase. Furthermore, the mean concentrations of THC for each year found in our study are within concentration levels normally seen some time after the first hour subsequent to cannabis smoking [17,18]. All this together implies that most part of the samples analysed were taken during the beta-elimination phase. In this late beta-elimination phase, a half live of THC concentrations around 24 h has been reported [17]. Therefore, a 17 min reduction in the time from driving to sampling blood, representing an increase of the THC level of less than 1%, cannot explain a 58% increase in the THC concentrations. For some of the cases, it cannot be ruled out that smoking took place just before apprehension, and that blood was collected within 1 h after driving. However, for this collection interval the mean reduction in time from driving to blood sampling was only of around 1 min. For the majority of the samples it is thus likely that they were collected in the elimination phase, and the change in time from driving to blood sampling over the years will only increase the THC concentrations by a small degree.

There are no systematic analyses of the THC content in all cannabis seizures in Norway, but analyses from different products over the years have shown great variability (whole plants between 3 and 7%, flowering tops 11–22%) [19]. Hashish dominates the Norwegian market, and the mean THC content have been around 7% for several years, but has increased to 8–10% the last years [19]. THC content up of 25–35% has only been seen in some particular products. The findings from Norwegian seizures might thus explain the increase in THC concentrations observed in our study, but since the seizures are not systematically analysed more data are warranted. Studies from other countries have found increasing content of THC in seizures, but it has been commented that some of the information might not be based on scientific evidence, and systematic analyses of illicit products are scarce [7,8].

The legislation in Norway for driving under the influence of non-alcohol drugs did not change during our study period. No legislative limits were established for these drugs, and for the whole period impairment was evaluated individually. For alcohol the impairment limit was 0.5 per mille up to 2000, but was lowered to 0.2 per mille in 2001.

One reason for the increased blood THC-concentrations observed could be that this group of drivers over time had developed tolerance to THC and, accordingly, were driving with much higher THC-concentrations. The lack of change in the age of cannabis drivers over time might speak against this. Furthermore, the ratio for drivers judged as impaired versus not impaired by the physician performing the CTI, despite varying over time, demonstrated a slight increase, indicating that the higher THC concentrations lead to reduced driving skills. Thus the increase in THC concentration was accompanied by an increase in the percentage of apprehended which were judged as lightly impaired (Fig. 2). This implies that the increase in THC concentration translated into more visible impairment which again could have consequences for traffic safety. The CTI is, however, not very sensitive to cannabis impairment [25], making a possible risk increase difficult to assess.

It is difficult to generalise from the group of drivers selected by the police under the suspicion of DUID to the total group of subjects using cannabis. It could be assumed that subjects with higher blood THC-concentrations to a larger extent would refrain from driving than those with lower blood THC-concentrations, but our data do not support this suggestion, since the number of cases where only THC could be detected increased during this period. The results might therefore point at a general increase in blood THC levels among cannabis users. This would be consistent with increased potency of cannabis products as reported [6]. The increase in blood THC concentrations contrasts with the stability seen over time on blood ethanol and the slight increase in the concentration of amphetamines measured in comparable groups,

and might point at a cannabis specific phenomenon taking place. This might be an indicator of higher THC-exposure among cannabis users with accompanying increased risk of intoxication, impairment, and short- and long-term psychosis [4,9]. In an experimental study, Mensinga et al. have measured the blood concentrations after smoking cannabis with higher THC content, and revealed a dose-related increase in serum concentration [20]. A similar relation was also seen for physiological effects (like heart rate and decrease of blood pressure) and psychomotor effects (such as reacting more slowly, being less concentrated and making more mistakes during performance testing). This phenomenon is well known for most drugs.

Ethanol and amphetamines were chosen as control groups because they are frequently used drugs of abuse in Norway, one legal and one illegal, and the numbers of positive samples containing only one drug are high enough to make comparisons over the years. For cases with only opiates, the numbers for each year would have been too small. The stable mean concentration of ethanol during the study period indicates that the pattern of use of ethanol in relation to driving was rather unchanged. For the amphetamines, the mean concentrations fell from 2005 to 2007, and the lowest number of cases with only amphetamines was found in this period. Compared to methamphetamine, amphetamine was found in the majority of our cases in the beginning of 2000, but the Norwegian drug market has changed towards more methamphetamine and less amphetamine [21]. To be able to investigate if there has been a change in the pattern of drug intake of amphetamines, the concentrations of amphetamine and methamphetamine were summed. Amphetamine is a metabolite of methamphetamine, and will thus be detected in blood after ingestion of methamphetamine, although in a lower concentration [22]. If amphetamine and methamphetamine are sold and ingested in similar doses, it would thus be expected that with more methamphetamine on the market, the mean concentration of the sum of both amphetamines would increase. The mean concentration of amphetamines varies, however, during the study period, and such trend cannot be seen from our data. Our findings might be explained by changes in the Norwegian illicit drug market, and which central stimulants are available at each time.

After ingestion of cannabis, other substances than THC might contribute to impairment [23]. For DUID cases, such substances have not regularly been measured, despite an increasing number of studies claiming that they might influence the degree of impairment observed after cannabis intake. Thus, CBD has i.e. been shown to counteract cognitive impairment and risk of developing psychotic symptoms experienced by users, as well as it seems to confer a neuroprotective effect [24].

To our knowledge, this is the first population study with laboratory based findings of increased THC-exposure during the last decade. Similar studies from other countries are necessary to investigate if this trend is also observed in other countries than Norway.

## 5. Conclusion

Monitoring concentrations of drugs of abuse in blood from drug users over the years may represent a marker to elucidate the drug consumption patterns in the population. Such data are however difficult to achieve, but samples from apprehended drivers can provide important information. This study shows a significant increase in THC concentrations in blood from apprehended drivers over the last decade. Similar data from other countries would be of great importance. If future findings from other countries are consistent with the present study, the consequences of higher THC-exposure should be further explored.



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