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A two-sample approach to retrograde extrapolation of blood THC concentrations – Is it feasible?

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ABSTRACT

Background: Retrograde extrapolation of drug concentrations in blood can be relevant in cases of drug-impaired driving and is regularly used in forensic toxicology in Norway. Δ^9-tetrahydrocannabinol (THC) has complex, multi-compartmental pharmacokinetics, which makes retrograde extrapolation of blood THC concentrations problematic. In the present study, we evaluated an approach to retrograde extrapolation in which momentary rates of decrease of THC were estimated from two consecutive blood samples in apprehended drivers.

Material and methods: Data were collected from apprehended drivers in Norway 2000–2020. We included 548 cases in which THC was detected in two consecutive blood samples collected $\geq$ 20 min apart. THC concentrations were measured by GC-MS and UHPLC-MS/MS. In each case, THC concentrations and the time between the two sampling points (Δt) were used to estimate the rate constant k. The relationship between THC concentration and k was modelled by linear regression.

Results: The median Δt was 31 min (interquartile range, $IQR = 9$). The median blood THC concentration was 2.4 μg/L ($IQR = 3.4$) at the first sampling point and 2.3 μg/L ($IQR = 3.1$) at the second. The concentration decreased in 62% and increased in 38% of all cases. However, considering measurement uncertainty, the changes were not statistically significant in 87% of cases. The mean of k was 0.12 h^{-1}, corresponding to an apparent $t_{1/2}$ of 6.0 h. The $t_{1/2}$ predicted from linear regression of k against THC concentration ranged from 0.93 to 13 h for the highest and lowest concentrations observed (36 and 0.63 μg/L, respectively). The time from driving to blood collection had a median of 1.7 h ($IQR = 1.5$), and did not correlate with k.

Conclusions: The apparent $t_{1/2}$ of THC calculated from the mean of k was 6.0 h, which is shorter than the terminal elimination $t_{1/2}$ suggested in previous population studies. This indicates that blood samples were often taken during the late distribution phase of THC. Because Δt was short relative to the rates of decrease expected in the late distribution and elimination phases, the underlying *true* concentration changes related to *in vivo* pharmacokinetics were small and masked by the relatively larger "false" changes introduced by random analytical and pre-analytical error. Therefore, individual values of k calculated from only two blood samples taken a short time apart are unreliable, and a two-sample approach to retrograde extrapolation of THC cannot be recommended.

1. Introduction

Second to alcohol, THC (Δ^9-tetrahydrocannabinol, the main psychoactive compound in cannabis) is by far the most frequently detected substance in cases of suspected of driving under the influence (DUI) of drugs in Norway. THC was present in 34% of all drug-positive blood samples from Norwegian drivers in the period 1990–2015 [1] increasing to 42% in 2021 [2], and in the same period we received an increasing number of samples from suspected DUI cases. Acute cannabis intoxication impairs driving ability [3–6], and is associated with increased motor vehicle crash risk [7–13]. The magnitude, duration and inter-individual variability of cannabis impairment are subjects of ongoing research.

Norway introduced legislative limits for DUI of non-alcohol drugs

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including THC in 2012 [14]. Although there is no strong correlation between blood THC concentration and driving impairment [15,16], whole blood THC concentrations of 1.3, 3.1 and 9.4 μg/L are considered by Norwegian law to be *legally* equivalent to blood alcohol concentrations of 0.02%, 0.05% and 0.12%, respectively, regardless of individual sensitivity or tolerance. The limits apply not only to drug concentrations in the driver's blood at the time of blood sampling, but also to concentrations that can be assumed with an acceptable level of confidence to have been present at the time of driving. For some drugs, especially ethanol, previous blood concentrations can be estimated by *retrograde extrapolation* (i.e., *back-calculation*) under certain conditions that will not be detailed here). In Norway, the prosecution often requests retrograde extrapolation as part of forensic toxicology expert statements in criminal procedures. However, while *per se* legislative limits entail that the legal outcome can be changed by retrograde extrapolation, actual traffic-relevant impairment cannot necessarily be retrogradely extrapolated because the relationship between drug concentrations and impairment may be inconsistent, perhaps especially in the case of THC [15,16]. Therefore, retrograde extrapolation may be less relevant in countries where *per se* limits have not been established.

For drugs with first-order elimination kinetics, retrograde extrapolation requires the rate of decrease to be specified, typically in the form of a half-life ($t_{1/2}$) or rate constant (k). In a legal setting, it is important to avoid overestimation of past blood concentrations. Therefore, a reasonably long $t_{1/2}$ should be selected based on population data for the drug in question.

For THC, however, choosing an appropriate $t_{1/2}$ is far from straightforward. Due to complex, multi-compartmental kinetics, the blood concentration of THC decreases at a progressively lower rate as various phases of distribution and elimination are reached [17–20]. The apparent $t_{1/2}$ of THC can be minutes or hours in the distribution phases [18,19] and in the order of days during the terminal elimination phase [19,21]. The relationship between THC concentration and the rate of decrease is strongly influenced by factors such as the route of administration, the time that has elapsed after intake, and possibly other factors influencing drug distribution to various tissues [22,23]. Because those variables are often unknown in individual cases, it has been suggested that retrograde extrapolation of THC simply should not be done [24].

However, if the momentary rate of decrease of THC present at the time of blood sampling could be determined directly, conservative retrograde extrapolation would indeed be possible. Truthful prediction of previous blood concentrations would require knowledge of the entire multi-exponential pharmacokinetic course of THC in the blood of each driver. This is obviously impossible. However, although the true concentrations may be out of reach, this does not mean that retrograde extrapolation must be rejected altogether. Extrapolation assuming mono-exponential decay and using the momentary rate of decrease will predict past concentrations better than no extrapolation at all. Moreover, due to the underlying multi-exponential pharmacokinetics, the momentary rate of decrease at a given point in time will always be lower than at any previous time. Therefore, a mono-exponential approximation effectively prevents overestimation. Emphatically, these considerations are only true if the momentary rate itself can be determined to a high level of accuracy.

In current Norwegian forensic toxicological practice, retrograde extrapolation of blood alcohol concentrations is routine practice. It can be individualised by estimating the driver's elimination rate from two consecutive blood samples (assuming zero-order kinetics). The samples are usually taken approximately 30 min apart, and rarely more than an hour apart because that would be impractical and time-consuming for the police and healthcare professionals involved.

While a two-sample approach to retrograde extrapolation is not presently used for drugs other than alcohol, paired blood samples intended for alcohol calculations are sometimes analysed for other substances as well. Having access to the analytical results of numerous paired blood samples taken from apprehended drivers suspected of DUI during the past two decades, we looked into those analysed for THC.

The aims of the present study were to estimate individual, momentary rates of decrease of blood THC concentrations via paired blood samples taken from apprehended drivers (assuming mono-exponential, first-order kinetics), and to evaluate the feasibility of using those estimates for retrograde extrapolation.

2. Material and methods

2.1. Study population

In Norway, all blood samples taken from drivers suspected of drug-impaired driving are currently analysed by the Department of Forensic Sciences, Oslo University Hospital. Prior to 2017, the department belonged to The Norwegian Institute of Public Health. All data used in this study were retrieved from the department's database. We included all cases in the period 2000–2020 in which THC was detected above the cut-off value (i.e., the threshold concentration above which THC was reported as "detected") in two consecutive blood samples taken at least 20 min apart. Cases were excluded if THC concentrations or sampling times contained missing values or errors that could not be corrected. Sex and age were registered in all cases. The time from driving to blood collection was available in all but 57 cases; those cases were still included. Information about the time of intake and the route of administration were not available. 8 cases were excluded because the concentration differences between the first and the second blood sample were implausibly large and suggestive of either pre-analytical errors or that the blood samples had been taken during the absorption phase of THC. In the end, 548 cases were included.

2.2. Collection, transportation and storage of blood samples

Venous blood was collected in 5 mL Vacutainer tubes (BD Vacutainer Systems, Belliver Industrial Estate, Plymouth, UK), containing sodium fluoride (4 mg/mL) as a preservative and sodium heparin (28 IU/mL) as an anticoagulant. The blood samples were transported to the laboratory of the Department of Forensic Sciences by the Norwegian public postal system. In the laboratory, the samples were stored in a refrigerator room with a temperature of 4 °C. During the analytical procedures, the blood samples were handled in room temperature.

2.3. THC analysis

Whole blood THC concentrations were determined by gas chromatography mass spectrometry (GC-MS) in the period 2000–2016, and by ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) from 2017 onwards [25]. Both methods were fully validated for use in forensic toxicology. Both analytical methods had a specified cut-off concentration of 0.6 μg/L and imprecision with a coefficient of variation (CV) of approximately 9%.

2.4. Data preparation, calculations and statistical analyses

Microsoft Excel 2016 was used for some manual data preparation and correction of obvious typographical or logical errors in the registered dates or times.

R version 4.2.1 and RStudio 2022.07.1–554 was used for all calculations, statistical analyses, and figures.

The time interval between the first sampling point (t_1) and the second (t_2), hereafter referred to as Δt, and the time between driving and t_1 were notified. Blood THC concentrations at t_1 and t_2 are referred to as C_1 and C_2, respectively.

Taking measurement uncertainty into consideration, we assessed whether apparent differences between individual instances of C_1 and C_2 were statistically significant. Based on the coefficient of variation (CV) of the THC analysis (approximately 9%) and the method described in a

paper by Jones [26], the critical value required for any apparent concentration difference to be significant with $p < 0.05$ was determined. Decreases of at least 22.3% or increases of at least 28.8% were considered significant. It is important to note that in this context, a "significant" difference does not necessarily indicate a "true" difference. We used Jones' method as a kind of Fisher's significance test in which the *p*-value simply indicates the unusualness or surprisingness of the data in relation to a specific statistical model [27]. It is a frequentist statistical approach that does not account for the fact that for exogenous substances like THC, the prior probability of concentration decrease is (presumably) much higher than the prior probability of no change or increase. Specifically, the *p*-value in Jones' method is the probability of observing measured differences at least as large as the one in question if the true difference were actually zero. By itself, it does not signify the likelihood that an *apparent* difference is *true* [28,29]. Unfortunately, there is no straightforward, objective way to determine whether a concentration difference is true. We used the method only to demonstrate the impact of analytical imprecision on our data. The 8 cases excluded from our data (mentioned in Section 2.1) were done so on the basis of a discretionary, Bayesian-like assessment.

Assuming mono-exponential first-order decay (the rationale for which is explained in the introduction), the rate constant k was calculated as follows:

$$C_2 = C_1 \cdot e^{-k \cdot \Delta t} \Longleftrightarrow k = \frac{\ln C_1 - \ln C_2}{\Delta t}$$

$t_{1/2}$ was calculated from k:

$$t_{1/2} = \frac{\ln 2}{k}$$

Normality of the variables was assessed visually on a Q–Q plot and using the Shapiro-Wilk test. k was the only normally distributed variable. Descriptive statistics consisting of median, interquartile range (*IQR*) and range was used for all other variables.

C_1 and C_2 were compared using Wilcoxon signed rank test, and sex difference in k-values using Student's t-test.

Correlations between the following variables were calculated using Pearson's product moment correlation: age and k; C_1 and k; Δt and k; and the time from driving to blood sampling and k. Because C_1 was not normally distributed, the correlation between time from driving to blood sampling and C_1 was calculated using Spearman's rank correlation.

The relationship between C_1 and k was modelled by simple linear regression. The conditional mean values of k and their uncertainty (95% confidence bands) predicted by the regression model were translated into the corresponding values of $t_{1/2}$ using the formula above (ln 2 / k).

3. Results

A total of 548 cases were ultimately included. In 94% of the cases, the drivers were male. Median values, *IQR* and range for age, THC concentrations (C_1 and C_2), the time between blood samples (Δt), and the time from driving to the first blood sample are presented in Table 1. A summary of all other analyses is presented in Table 2.

Table 1
Median, interquartile range (*IQR*) and range (min–max) for age, THC concentrations (C_1 and C_2), the time between blood samples (Δt), and the time from driving to the first blood sample.

	Median	*IQR*	Range
Age (years)	28	12	17–62
C_1 (μg/L)	2.4	3.4	0.63–36
C_2 (μg/L)	2.3	3.1	0.63–27
Δt (minutes)	31	9	20–132
Time from driving to t_1 (hours)	1.7	1.5	0.083–22

Table 2
A summary of the main variables/relationships investigated, the methods used, and the findings.

What was investigated	Method	Results
Relative differences between C_1 and C_2	Mean, *SD*, descriptive	Mean C_2/C_1-ratio was 0.96 ($SD = 0.15$). $C_1 > C_2$ in 61.7% of cases, $C_1 < C_2$ in 37.6% and $C_1 = C_2$ in 0.7%
Difference between the individual values of C_1 and C_2	A significance test developed by G.R. Jones[26]	Decreases of ≥ 22.3% or increases of ≥ 28.8% were considered significant. The difference was not significant in 87.2% of cases.
Significance of the overall difference between C_1 and C_2	Two-sided paired Wilcoxon signed rank test	C_1 was significantly greater than C_2 ($p < 0.001$).
Relationship between age and k	Pearson's r	No correlation (Pearson's $r(546) = -0.0493$, $p = 0.249$).
Sex difference in k	Two-sided student's t-test	No significant difference ($t(546) = 0.123$, $p = 0.902$).
Relationship between C_1 and k	Pearson's r Linear regression	Positive correlation (Pearson's $r(546) = 0.280$, $p < 0.001$). C_1 significantly predicted k ($R^2 = 0.0770$, $p < 0.001$). Predicted values of k ranged from 0.0456 h^{-1} ($t_{1/2} = 13$ h) for the minimum C_1 (0.63 μg/L) and 0.759 h^{-1} ($t_{1/2} = 0.93$ h) for the maximum (36 μg/L).
Relationship between Δt and k	Pearson's r Graphical/visual assessment	Very weak, negative correlation (Pearson's $r(546) = -0.0963$, $p = 0.0242$). Variance of k increased with decreasing Δt.
Relationship between the time from driving to blood sampling and C_1	Spearman's ρ	Very weak correlation ($\rho = -0.0991$, $p = 0.0280$)
Relationship between the time from driving to blood sampling and k	Pearson's r	No correlation (Pearson's $r(489) = -0.00911$, $p = 0.840$)

3.1. Concentration differences

The median C_1 was higher than the median C_2 (two-sided paired Wilcoxon signed rank test, $p < 0.001$). The mean C_2/C_1-ratio was 0.96 ($SD = 0.15$). In 61.7% of cases, C_1 was higher than C_2; in 37.6%, C_1 was lower than C_2; and in 0.7%, they were equal. However, in 87.2% of the cases, the relative difference between C_1 and C_2 was not significant (as explained in Section 2.4).

3.2. Rate constant k

k appeared normally distributed (Shapiro-Wilk test, $W = 0.996$, $p = 0.235$) with a mean of 0.12 h^{-1} (corresponding to a $t_{1/2}$ of 6.0 h) and SD 0.31 h^{-1}.

k did not correlate with age (Pearson's $r(546) = -0.0493$, $p = 0.249$), and did not differ between the sexes (two-sided Student's t-test: $t(546) = 0.123$, $p = 0.902$).

There was a very weak negative correlation between Δt and k (Pearson's $r(546) = -0.0963$, $p = 0.0242$). As visualised in Fig. 1, both the mean and the variance of k decreased when Δt increased.

3.3. Time from driving to blood sampling

The time from driving to blood sampling correlated very weakly with C_1 (Spearman's $\rho = -0.0991$, $p = 0.0280$), but not with k (Pearson's $r(489) = -0.00911$, $p = 0.840$). Please note that the time of driving does not reflect the time of cannabis intake, as explained at the end of the Discussion section.

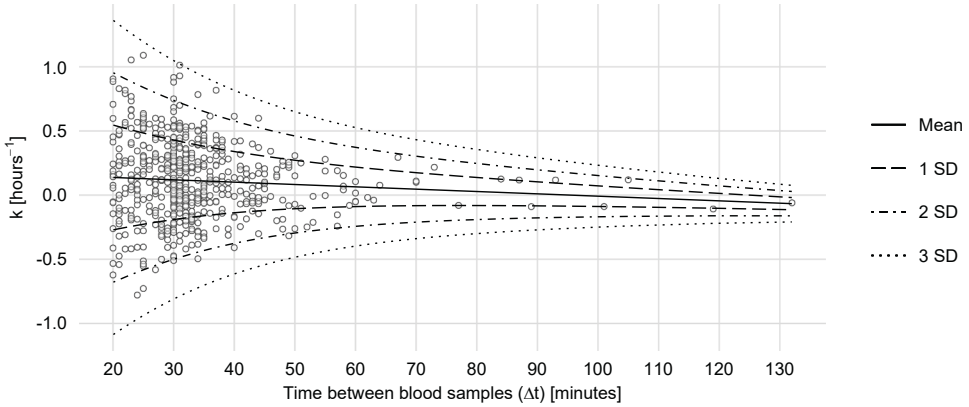

Fig. 1. Plot of k against Δt. The lines represent the conditional mean and conditional standard deviations.

3.4. Relationship between THC concentration and k

There was a positive correlation between THC concentration (C_1) and k (Pearson's $r(546) = 0.280$, $p < 0.001$), i.e., the rate of decrease tended to be higher when blood THC concentrations were higher. Simple linear regression was used to model k as a function of blood THC concentration (C_1). With C_1 measured in μg/L, the fitted regression model was:

$$\widehat{k}_i = 0.0395 + 0.0198 \cdot C_{1i}$$

The overall regression was statistically significant ($R^2 = 0.0770$, $F(1, 546) = 46.63$, $p < 0.001$). C_1 significantly predicted k ($\widehat{\beta} = 0.0198$, $p < 0.001$).

The predicted conditional mean values of k were 0.0456 h^{-1} ($t_{1/2} =$ 13 h) for the minimum observed value of C_1 (0.63 μg/L) and 0.759 h^{-1} ($t_{1/2} = 0.93$ h) for the maximum (36 μg/L). Conditional mean values of k for the entire concentration range are visualised as the regression line in Fig. 2A. In Fig. 2B, the conditional mean values of k have been translated into the corresponding values of $t_{1/2}$. To avoid confusion, we emphasise that the grey areas in the figures do not signify the range within which k and half-lives are expected to fall on a population level. They are simply 95% confidence bands showing the uncertainty of the conditional means. The data did not allow for determination of the actual range of possible half-lives in the population.

4. Discussion

We measured THC concentrations in 548 pairs of blood samples from apprehended drivers, and found that the mean rate constant k corresponded to a $t_{1/2}$ of 6.0 h; that the blood THC concentration decreased more rapidly at higher THC concentrations than lower; that the time between driving and blood sampling did not correlate with k; that the length of Δt influenced both the mean and variance of k; and that most of the concentration differences used to calculate the individual estimates of k were not significant with respect to measurement uncertainty.

Most pharmacokinetic studies use serial blood sampling in a highly controlled setting. This allows for accurate estimation of pharmacokinetic parameters. There are examples of studies in which only one or two blood samples were used in conjunction with various statistical methods to estimate pharmacokinetic parameters with a decent level of accuracy [30–33]. Bayesian strategies for limited sampling parameter estimation have been developed [34]. However, such approaches are possible because the dosage and the time and route of administration are known; blood collection is timed strategically; and prior population data are used to inform and narrow down the estimates through Bayesian inference. Using only two blood samples taken by external personnel in a non-controlled setting obviously poses some challenges, especially when no information about dosage or the time and route of administration is available. Acknowledging the many uncertainties and limitations implicit in such a study design, our main findings can be interpreted as follows.

k had an overall mean of 0.12 h^{-1}, corresponding to a $t_{1/2}$ of 6.0 h. Linear regression was used to predict the conditional mean of k as a function of blood THC concentration (C_1). The $t_{1/2}$ corresponding to the predicted values of k ranged from 0.93 h for the highest (36 μg/L) to 13 h for the lowest (0.63 μg/L) concentrations. Thus, k did depend on blood THC concentration. This is compatible with multi-exponential pharmacokinetics, as expected, since concentration is related to time after intake, which influences k as found in previously published population studies [18–20].

We found that on an individual level, each driver's momentary rate of decrease could not be accurately determined from two blood samples taken a short time apart. When estimating k from only two measurements, analytical precision becomes a major concern [34]. If the time between blood samples (Δt) is short relative to the $t_{1/2}$ of a drug, the true, *in vivo* decrease in blood concentration will be small. For example, for $t_{1/2} = 6$ h, the true concentration will drop by only 5.6% in 30 min. Analytical imprecision of $CV = 9\%$ entails that 95% of measurements will end up somewhere between approximately ± 18% of the true concentration. This means that compared to *in vivo* concentration changes, random analytical error is expected to have a much larger impact on the difference between C_1 and C_2 when the time interval is very short. The shorter the Δt, the steeper become the false concentration slopes introduced by random error, making the values of k more extreme in both the positive and negative direction. This is why the variance of k increased with decreasing Δt (Fig. 1). In addition, pre-analytical factors are also a major source of error [35], making the total uncertainty even greater. All in all, the individually calculated values of k cannot be assumed to accurately estimate each driver's true rate of decrease of THC. Moreover, since the total variance of k comprises pre-analytical and analytical variance in addition to any possible biological variance [36], the biological inter-individual variation of k cannot be determined directly from our data. However, since pharmacokinetic parameters generally are biologically variable, it can safely be assumed that many of the studied drivers had shorter or longer half-lives than what was predicted by linear regression (which only indicates the central tendency and not the variance).

Would increasing Δt be a good way to ameliorate the problem related to analytical precision? A longer Δt would indeed yield a more accurate estimate of the true C_2/C_1-ratio used to calculate k. However, the longer Δt becomes, the more discrepancy there will be between a mono-exponential and a multi-exponential pharmacokinetic model, and the less meaningful a single value of k becomes. Furthermore, increasing Δt makes C_2 more likely to end up below the analytical cut-off. Lastly, increasing Δt is time-consuming and may be impractical.

If the majority of samples were taken shortly after smoking, the

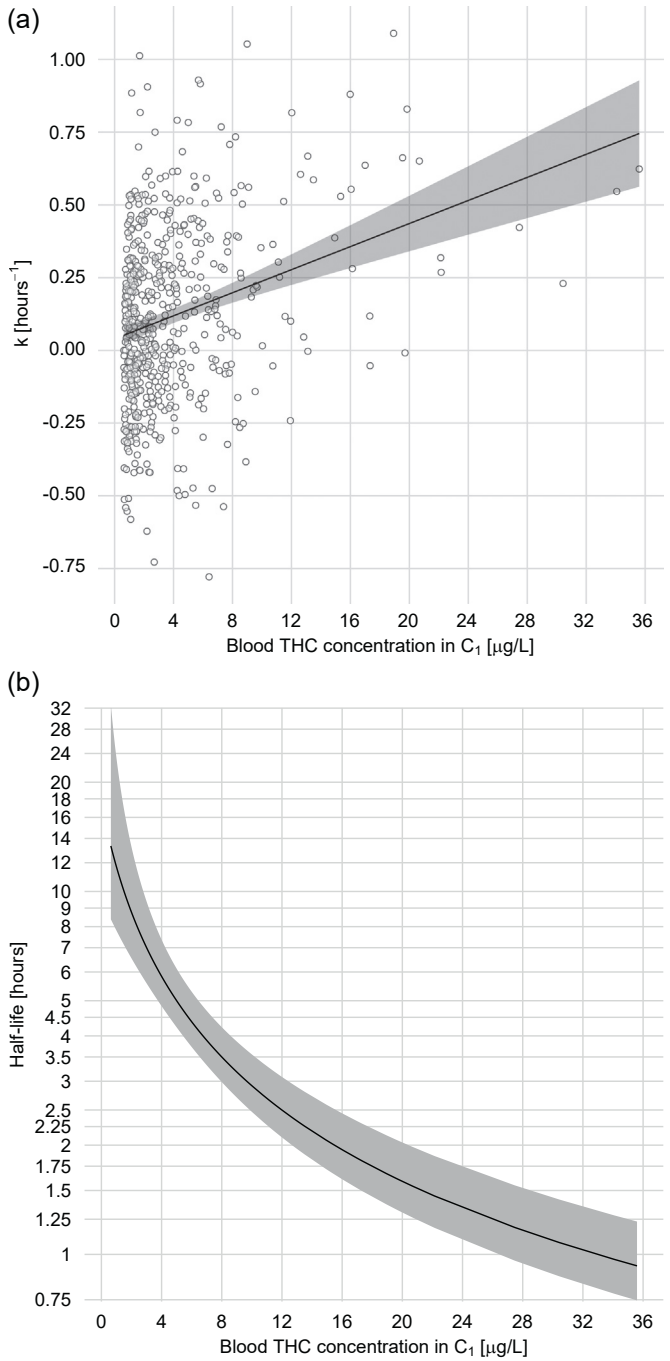

Fig. 2. A. Plot of k against blood THC concentration. The black line shows the conditional mean value of k for each concentration in the range. The grey area shows the uncertainty (95% confidence bands) of the conditional mean. **B.** Semi-logarithmic plot of $t_{1/2}$ against THC concentration. $t_{1/2}$ was translated from conditional mean of k using the formula ln(2) / k. The grey area shows the uncertainty (95% confidence bands) of the estimate. The actual population range of half-lives for each concentration could not be determined.

observed half-lives would be expected to be short and the concentration decreases large. However, in almost 90% of the cases in our data, the concentration differences were not significant with respect to measurement uncertainty and apparently increasing concentrations were observed in almost 40% of the cases. This indicates that very short half-lives were not prevalent and that the majority of the drivers had not smoked cannabis shortly before apprehension and blood sampling.

While the individually calculated values of k and their variance turned out to be unreliable, the mean of k is expected to be less affected by random error due to the relatively large number of samples included in the study. The arithmetic mean may not be the optimal estimator for pharmacokinetic parameters such as k and $t_{1/2}$ (whose population distributions are often assumed to be log-normal and, in which case the expected value is best estimated by the *geometric* mean) [37–39]. Nevertheless, the overall mean of k and the conditional mean predicted by linear regression do provide some useful insight into the general pharmacokinetic tendencies in the driver population.

The $t_{1/2}$ of 6 h found in this study is much shorter than the terminal elimination $t_{1/2}$ reported in previous studies [19,21]. If we exclude the possibility of oral intake, most of the drivers in the present study population would be in a post-absorptive phase, but not in the terminal elimination phase, at the time of blood sampling. A $t_{1/2}$ of 6 h is suggestive of a late distribution phase, since previous population models indicate a $t_{1/2}$ of a few minutes to a few hours in the initial distribution phase and a terminal elimination $t_{1/2}$ of several days [18,19].

With multi-exponential pharmacokinetics, k is expected to correlate with the time interval between cannabis intake and blood sampling. We found no significant correlation between k and the time interval between *driving* and blood sampling. This suggests that the time of driving does not correlate strongly enough with the time of cannabis intake to be useful in terms of retrograde extrapolation.

5. Conclusions

The present study demonstrated that the momentary rate of decrease of THC cannot be accurately determined in individual drivers based on two blood samples taken a short time apart. The true concentration changes that occur *in vivo* during a short time interval will often be smaller than the "false" changes introduced by random analytical and pre-analytical error. Therefore, the suggested two-sample approach to retrograde extrapolation of blood THC concentration is not feasible. Moreover, our data suggest that blood samples may often be taken during the distribution phase of THC, which is another argument against routine retrograde extrapolation of THC, especially in forensic toxicological cases pertaining to DUI.

Credit authorship contribution statement

The study was drafted by JM. All authors participated in planning the study, conceptualisation, formulation of the research aims, and interpretation of the results. POSH was responsible for data curation, programming the R scripts, performing the formal data analyses, visualisation, writing the original draft, and editing subsequent drafts. MCS was the main supervisor and project administrator. All authors reviewed manuscript drafts as they developed, and accepted the final version of the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gudrun Høiseth acts as an expert witness for Norwegian courts in cases and issues regarding forensic toxicology. Liliana Bachs acts as an expert witness for Norwegian courts in cases and issues regarding forensic toxicology. Cecilie H. Thaulow acts as an expert witness for Norwegian courts in cases and issues regarding forensic toxicology. Merete S. Vevelstad acts as an expert witness for Norwegian courts in cases and issues regarding forensic toxicology. Jørg Mørland is member of the Norwegian Board of Forensic Medicine and acts as an expert witness for Norwegian courts in cases and issues regarding forensic toxicology. Maren Cecilie Strand is member of the Norwegian Board of Forensic Medicine, Toxicological group, and acts as an expert witness for Norwegian courts in cases and issues regarding forensic toxicology. Peder Olai Skjeflo Holman has no conflicts of interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.forsciint.2023.111833.

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