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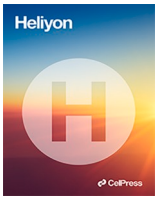

Research article

Concentrations of Delta 9-tetrahydrocannabinol (THC) in oral fluid at different time points after use: An individual participant meta-analysis

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ABSTRACT

Background: Delta 9-tetrahydrocannabinol (THC) concentrations in oral fluid (OF) at different time points after cannabis administration and factors related to these concentrations have not been previously described in a meta-analysis. This information is critical for better understanding of these tests for detection of prior cannabis use and cannabis impairment.
Objectives: 1: To describe the summary statistics of THC concentrations at different time points after cannabis administration. **2:** To describe the relationship between the variables of dose of THC, frequency of using cannabis, route of administration (i.e., inhaled or ingested), OF collection device and sex, with THC concentrations in OF, based on bivariate analyses. **3**: To describe the independent contribution of each of the variables in Objective 2, based on a multivariate analysis of THC concentrations.
Methods: A meta-analysis of studies from two databases (PubMed and Scopus) was conducted. Our inclusion criteria included published empirical articles that administered natural cannabis to subjects in a controlled setting, with OF drug tests showing the exact THC concentrations in OF for each subject (i.e., raw data) for at least two time points after cannabis administration using confirmatory methods. Seven studies of tests with published raw data for OF THC after cannabis administration met these criteria (n observations = 1157).
Results: Summary statistics showed OF THC concentrations by time after use were highly dispersed at every time point, positively skewed, and declined over time. Many positive OF THC concentrations were found after 24-h in one study, but most studies did not conduct observations past 24 h. In a multivariate analysis, we found that increased dose, increased frequency of cannabis use, and inhaled (versus ingested) cannabis were statistically related to higher OF THC concentrations. OF collection with the intercept DOA device was significantly higher than expectorant (i.e. saliva) and being male (versus female) were only significant in a bivariate analysis. Too little data existed to reliably analyze the possible influence of other variables of age, race and body mass index (BMI) on OF THC concentrations.
Discussion: False negatives exist when the tests are used to detect prior use. OF test results are related to confounders of frequency of cannabis use and inhaled (versus ingested) cannabis. OF tests can produce positives at a cut-off 1.0 ng/mL well beyond 24 h. The tests are not valid to detect cannabis impairment. More information is needed on the influence of potential

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confounders for OF concentrations. We do not have a good idea of the degree to which the subjects in these studies are representative of persons who use cannabis. Overall, more research is needed for these tests to be used in workplace settings.

1. Rationale

Oral fluid (OF) tests to detect recent cannabis use or cannabis impairment in the workplace has been increasing over the past decades. OF for Tetrahydrocannabinol (THC), the active ingredient of cannabis is detected primarily from direct residues in the mouth, sometimes described as contamination [1]. There are typically two types of tests: an initial screening test at a lower cut-off with results within minutes and a confirmation laboratory test, (typically sent outside the employer) is used to address employee drug use. These tests are conducted in workplace settings by collecting saliva from the mouth with a swab. The screening tests for OF are highly variable in terms of sensitivity [2]. An issue of importance for either the purpose of detecting prior use or current impairment is the cut-off for THC concentrations. Higher cut-offs for OF are related to shorter detection periods [3] and critically important for the purpose of detecting impairment. While most employers are using a THC confirmation OF cut-off of 1 ng/mL, cut-offs as high as 10 ng/mL are known [4]. The Substance Abuse and Mental Health Service Administration (2024) recommends cutoffs of 3 ng/mL for screening of oral fluids and 1.5 ng/mL for confirmation, where the confirmation test is used for legal purposes, such as employment settings [5]. In this article, we focus only on OF confirmation tests for cannabis use.

An outstanding question is the accuracy of these tests for their intended purposes, either recent use in the USA or impairment in Canada. Among pharmacokinetic reviews of detection of THC in OF [3,6,7], all studies show OF THC concentrations decrease over time after cannabis administration. Also, all studies have found OF concentrations between individuals at the same time points are highly variable, especially shortly after use. Some studies have reported negative samples interspersed with positive ones for the same individuals at the subsequent time points [8]. Prior research shows some factors (i.e. confounders) may be related to positive tests, which can affect their validity. Desrosiers et al. (2014) noted that frequent users were substantially more likely than occasional users to test positiv e for THC [6]. Support of this claim also are findings of THC in OF after several days of abstinence among frequent users of cannabis [8,9]. Another issue of importance is the route of administration (either ingested or inhaled), which can affect the duration of THC in OF [10]. Milman et al. (2012) found that when ingested cannabis is swallowed in pill form, THC is **not** detectable in OF, thus raising the issue of possible false negatives. Other issues arise in research on OF testing of cannabis use [11]. For example, the device used for OF collection can have a significant impact on the resultant drug concentration [12]. These aforementioned variables and several others require more research for definitive findings.

Most research indicates that increased safety risk associated with impairment occurs within two or 3 h after smoking cannabis [13] and can persist between four [14–17] or 5 h [10]. Although some have claimed the impairing effects of cannabis can last 24 h or more [18], contrary research shows otherwise [19–22]. *Long-term cognitive* deficits of early onset cannabis use also are possible [15] but the cross-sectional nature of the observational research has not been able to properly address potential confounding variables [23]. Regardless of whether tests are designed to be a deterrent or to catch those under the influence on the job, reduction of impairment at work is the principal goal.

Several factors appear related to cannabis impairment, a Canadian objective of tests. The authors of one empirical meta-analysis noted substantial variation exists between individuals for intensity and duration of impairment and also concluded the magnitude and duration of impairment is dependent on dose, route of administration (i.e., inhaled or ingested) and frequency of use [10]. A recent study noted there is no clear relationship between oral fluid concentrations and impairment [24] among both blood and OF. Several studies have noted the challenges of interpretation of a positive OF test for THC. Tolerance has been demonstrated for cannabis use. Although proper epidemiological studies have been conducted assessing validity at 0.05 % and 0.08 % alcohol cut-offs for impairment [25], no comparable studies exist for cannabis and OF tests. In the material that follows, we review research on the factors related to OF THC concentrations and their relationship to impairment.

Dose. Research shows acute performance decrements are generally dose-related [14,26] although the claim is not universal. Therefore, in order to be valid, doses received should be positively related to OF THC concentrations. A challenge of past research is calibrating precise cannabis dosage when inhaled due to titration [16,27]. As well, although some researchers have administered various doses, they did not conduct tests of statistical significance to illustrate the importance of dose for OF THC concentrations.

Frequency of use. Most research has found increased tolerance to cannabis impairing effects with increased use [10]. One study found that heavy and chronic cannabis users showed no deficits in critical tracking or divided attention after being administered 54 mg THC cannabis cigarettes [28], yet studies with occasional users show more profound impairments [29]. Based on tolerance, more frequent cannabis use is related to better performance.

Therefore, for good validity of cannabis impairment, higher frequency of use should be inversely related to OF THC concentrations, since most research shows frequent cannabis users have better functioning after use [30]. A recent studies have found OF THC concentrations were significantly longer in frequent users than occasional users [6,31] and others found that chronic heavy use of cannabis can have prolonged OF detection times of days [8,9]. Another study found quantifiable THC in OF for 48 h after use in 4 of 28 chronic daily users [32]. Anizan et al. (2013) found detection times in OF extended beyond 30 h for chronic users and only 24 h for occasional users [33]. Newmeyer et al. (2014) and others found that THC in OF remained similar among occasional and frequent cannabis users for up to 30 h post-use, but beyond this timeframe, 67 % of frequent users tested positive compared to only 10 % of occasional users [34]. Although most research suggests that frequent users of cannabis have longer duration of THC than occasional users, definitive

findings based on statistics show more studies are still needed.

Route of administration. *Orally ingested* cannabis can cause longer impairment and more intense impairments than *smoked* cannabis, especially with higher doses [35]. Ideally a valid detection tool for recent use or impairment should yield longer detection times when ingested, taking into account the dose. Yet some research has shown that ingested cannabis swallowed in pill form is not detectable in OF [11]. Higher concentrations for OF THC are found when cannabis is chewed before ingestion.

OF collection device. Although the type of collection device appears to be related to concentrations of THC [12,36], there is little research on this issue. Dobri et al. (2019) [37] in a systematic review indicated there is a lack of device consistency making it difficult to draw conclusions. Crouch et al. (2005) [38] noted the average collection volume of varied considerably among collection devices. Some studies have found stimulated salivary flow culminates in lower drug concentrations than direct measures of [12,39]. Expectorant (i.e. saliva) appears to culminate in higher OF THC concentrations than other types of collection devices based on some research, yet statistical tests of significance are still needed. This conclusion is drawn most persuasively from comparisons between OF THC concentrations in two studies [40] assumed to have used the same data set due common features [40].[1] A critical difference of the two studies was that Milman et al. (2012) [11] collected expectorant whereas Lee et al. (2012) [40] used the Quantisal device. The average THC concentrations were substantially higher for expectorant but statistical tests of significance are not publicly available. Overall, research shows substantial differences between the OF collection devices [41], although some devices are comparable [6].

Other variables of age, sex, race and BMI. Several variables have been postulated as related to degree of impairment, but research remains inconsistent and it is largely unknown how these factors may be related to OF. Some research shows females get more intoxicated than males by cannabis [42]. Possibly people with lower BMI get more acutely impaired from cannabis than those with higher BMI, but the research base, unlike for alcohol, is very limited. Demographic variables may also be related to OF THC detection times; but the research evidence needs to be better understood. In one study, the authors noted that women had higher maximum OF THC concentrations at a 50 mg oral dose compared with men but not for other doses [43]. The authors suggest that BMI may be related to OF THC concentrations based on differences between males and females. Although the importance of both body weight and sex has been suggested to be related to concentrations for OF tests, these conclusions have not been statistically proven. Also, if these variables are confounders for OF concentrations, OF validity may be reduced. The degree to which OF for THC are related to these variables is unknown.

In the **U.S.A.**, detection of prior cannabis use is the purpose for OF THC drug tests with the assumption that that a positive test is related to recent cannabis use or abuse [44] and deters use [15], with an ultimate aim to reduce accidents [45,46]. A 24-h detection window for OF tests is often justified for the use of, instead of urine that has a much longer detection window [1,47]. If the time interval of a positive test is consistent across people, then OF tests of THC are a good measure of recent use. However, if OF tests durations are highly variable among people and related to several external factors (i.e. confounders), the validity of the tests for this purpose should be reconsidered.

In most **Canadian** provinces, drug testing is appropriate only if employers can demonstrate a bona fide occupational requirement. Based on the principle of a bona fide occupational requirement, drug testing is acceptable if it can be shown that the tests are valid for identifying those who are impaired and therefore represent a meaningful safety risk [48]. This principle of detecting impairment rather than prior use also applies to driving under the influence of cannabis in Canada [49]. Although research has convincingly shown the acute effects of cannabis cause impairment [13,50], a question of importance is whether OF drug tests for THC alone are sufficiently accurate to identify those who have used cannabis and/or those who are impaired. Regardless of the intended purposes between jurisdictions described above, drug testing is intended as a prevention to reduce the likelihood of job accidents. In this article, we address both the U.S. and Canadian purposes of drug tests.

Since **blood** tests detect THC circulating in the body, it is often described as a superior biological sample for impairment than OF. Studies have suggested that blood THC concentrations of 2–5 ng/mL are associated with substantial impairment [26]. Some reviews of the pharmacokinetics of THC in OF with comparisons to other biological tests have been published [7,39,51,52]. Recent evidence shows good accuracy when *detecting* THC in OF compared to blood but poorer accuracy for OF at commonly used cut-off values for predicting common blood per se limits [52]. Some have suggested the use of additional biomarkers to aid interpretation of concentrations, such as the metabolite of 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol (i.e. THCCOOH), which has a longer detection window than THC, is needed [45,53]. Comparisons between OF and blood test ratios are highly variable, depending on the time after use [1,54–58]. Divergent interpretations on the degree of accuracy needed for OF tests is likely based on different purposes for which drug tests are envisioned.

2. Objectives

1. To describe the summary statistics for OF THC concentrations at different time points after cannabis administration.
2. To describe the relationship between the variables of dose of THC, frequency of using cannabis, route of administration (i.e., inhaled or ingested), OF collection device and sex, (upon availability of sufficient data) with THC concentrations in OF
3. To describe the independent contribution of each of the variables in Objective 2, based on a multivariate analysis of THC concentrations.

[1] Common features were a total of 10 subjects in each study of the same sex, race, and body mass, the same criteria for frequency of use, administration of smoked 6.8 % cannabis and collected OF at the same time points.

3. Methods

3.1. Inclusion and exclusion criteria

Our inclusion criteria included published empirical articles that administered natural cannabis to subjects in a controlled setting and the exact THC concentrations in OF for each subject (i.e., raw data) for at least two time points after cannabis administration were provided using LC-MS-MS tests or comparable confirmatory tests. For inclusion in our manuscript as a controlled study, studies must have: the frequency of cannabis use by the subjects in general, the time after use, whether cannabis was inhaled or ingested, dose or calculation of the median, and the raw data published. We excluded studies focused only on passive use (i.e., second hand smoke), synthetic cannabis, such as Sativex and those focused exclusively on cannabinoid metabolites other than THC. Since our study was aimed at publicly available data, authors of studies that appeared relevant without data were not contacted. This article represents the amalgamated data that is currently available to the public. All the selected articles were from peer reviewed journals at the University of Victoria library and not necessarily open access. We used automation tools from the University of Victoria to determine studies that were reviews of the literature.

Based on our review of studies, we excluded three studies without published primary data [40,59,60] that used the same data sets as a selected study, and the selected studies had all the required information. Another study [9] provided raw data for each subject after use but was excluded because doses were unknown. Key characteristics from the 7 articles that met our inclusion/exclusion criteria are provided in Table 1 and the data can be accessed [61].

Nine studies otherwise eligible were excluded because the raw data of THC concentrations was not provided [1,27,33,34,36, 62–65]. We excluded data of special trials within the selected studies that addressed objectives other than those listed above (e.g., some trials were excluded because the focus was the influence of mouthwashes [66], blood analyses [67,68], and multiple cannabinoids). Eligibility for inclusion/exclusion was determined by SM and JZ.

3.2. Identification of studies

We conducted our search on PubMed and Scopus in October 2023 with the keywords (((cannabis) or (marijuana) or (hash))) and (oral fluid). We selected studies from 303 articles from PubMed and 385 articles from Scopus. We electronically excluded grey literature reports, review articles and articles not in English (n = 116). We also removed duplicate references in both databases. Fig. 1 shows the Flow diagram for search of the databases [69].

Both the included and excluded studies had very different features: different number of subjects, different past experience of subjects with cannabis, different routes of administration (i.e., smoked, vaporized, and ingested), different cannabis doses, different OF collection devices, and different time points of collection. Some authors allocated the same subjects to multiple conditions, such as different doses [67,68].

3.2.1. Measures

Two investigators (SM and JZ) reviewed eligible papers to extract and code data independently from all studies fulfilling the inclusion criteria, and any disagreements were resolved by discussion. The measures were coded into more parsimonious categories for analysis. We coded the variables of dose, frequency of use, and route of administration as follows, based on the most common approaches employed by the original study's authors.

Dose was assessed in milligrams of THC, which was provided in most studies. One author [11] reported the dosage as 6.8 % THC, which we were able to convert into 53.7 mg of THC, as reported in another study using the same data set [40]. Although de Castro et al. (2014) administered doses based on the usual use by subjects [66], actual doses are used in our study. We used a mid-point dose of 22.5 mg THC (range = 20–25 mg of THC) for each subject in one study [70] and a median dose of 33 mg (range = 22.5–47.5 mg of THC) for each subject for another study [68] because the exact doses were not provided. Inactive doses or passive doses (e.g. second-hand smoke)[2] were excluded for the results. Data when OF was taken at maximum levels rather than OF collected at specific time points were excluded in one study [68].

For frequency of use, each subject was classified as either an occasional or a frequent user using the following criteria: occasional = weekly use or less in the prior month, and frequent = more than weekly. However, all studies reported the frequent group used at least 4 times a week or more or over 3 cannabis cigarettes per week.

Route of administration was grouped for every subject in two categories of inhaled (i.e., smoked or vaporized) or ingested. OF THC concentrations from smoked and vaporized cannabis were treated as equivalent, based on findings from research showing no differences [68].

For OF collection device, only one study used the Quantisal device [66], which was excluded from our analyses of THC, based on our exclusion criteria. Therefore, we only compared the Intercept DOA collection device with expectorant. For demographic variables of age, sex, race and BMI, we only included studies that provided the exact information for each participant.

[2] All passive doses resulted in zero OF THC at all time points.

Table 1
Key features of studies included in the meta-analysis.

First author, publication year	Study objectives	Study Design	Inclusion criteria and group/s based on cannabis usage	Number of subject	Dose of THC	Route of use	Time points of tests for THC	Oral fluid collection device	Demographic Variables available
Niebala et al., 2001	Multiple objectives with three sub-studies - THC *detection* time in OF following smoked and oral administration	Repeated measures design of three groups.	Three sub- studies: Study 1: 5 daily users and 5 occasional users over a period of at least a month; Study 2: 5 occasional users; Study 3: 3 occasional users.	18	20–25 mg THC in Cigarettes or brownies. Smoked cannabis consumed between 20 and 30 min	Either smoked or ingested	1, 2, 4, 8, 16, 24, 48, and 72 h	Intercept DOA Oral Specimen collection device – treated absorbent-cotton fiber pad affixed to nylon stick, a preservative solution in plastic container	Age – no Sex – yes, for sub-study 1 only, Race – no BMI – no
Toennes et al., 2010	Comparison of oral fluid and serum THC concentrations in chronic and occasional users	double-blind, placebo-controlled, two-way, mixed-model design	Group 1: Chronic users of 4 times per week or more in last year, Group 2: occasional users of weekly use or less	24	500 ng THC per kg of body weight.	Smoked	5 min, 1 and 8 h	Intercept DOA - a treated absorbent cotton fiber pad affixed to nylon stick, a preservative solution in plastic container	Age – no Sex- no Race – no BMI – no
Milman et al., 2012	To quantify THC and metabolites in expectorated OF following controlled smoked cannabis	One group repeated measure design	Minimum use of at least 2 times per month for 3 months prior to the study who reported using cannabis within 1–4 days prior to use and had a positive urine test	10	THC 6.8 % cigarette *0.79 g ad libitum for 10 min use = 53.7 mg THC	Smoked	0.25, 0.5, 1, 2, 3, 4, 6, and 22 h No 8 h	Expectoration into polypropylene tubes	Age -yes Sex - yes Race – Yes, reported by Lee et al. (2012), BMI - no
de Castro et al., 2014	The effects of mouth washes on oral fluid detection	Before and after within group design	A minimum of 3 cannabis cigarettes per week	11	2.1 mg–12.2 mg THC based on usual dose	Smoked	0.25, 0.5, 1, 3, 6, 12, and 24 h	Quantisal	Age – no Sex- yes Race – no BMI- yes
Vandrey et al., 2017	To observe pharmacokinetics and pharmacodynamics from oral cannabis administration (edibles) of three doses	Random double-blind assignment between-subjects.	History of lifetime use but no use in the prior 3 months	18	10, 25 and 50 mg of THC.	Ingested	0.17, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 22, 26, 30, 34, 46, 50, 54, 58, 70, 74, 78, 82, 94, 98, 102, 106, 118, 122, 126 and 130 h	Expectoration into 8 mL glass screw culture tubes - Thermo Fisher Scientific	Age – no sex- no Race – no BMI- no
Spindle et al., 2019b	To compare whole blood and OF cannabinoids concentrations after smoked and vaporized administration in infrequent users	random double-blind assignment within-subjects design	Infrequent users with no use in the past month.	9 males and 8 females	Doses of 0, 10 and 25 mg THC smoked ad libitum within 10 min	Smoked and vaporized	0.17, 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 8 h	Expectoration into 8 mL glass screw culture tubes - Thermo Fisher Scientific	Age – no Sex - yes Race - no BMI - no
Spindle et al., 2020a	To conduct a controlled pharmacokinetic evaluation of subjects administered cannabis brownies.	random double-blind assignment within-subjects design	Infrequent users with no use in the past 30 days.	8 males and 9 females	Doses 0, 10, 25, 50 mg THC	Brownies ingested	0.17, 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 8 h	Expectoration into glass culture tubes with a 4 ng/mL cut-off	Age – no Sex - yes Race - no BMI- yes

Figure 1: Flow diagram for search of relevant articles

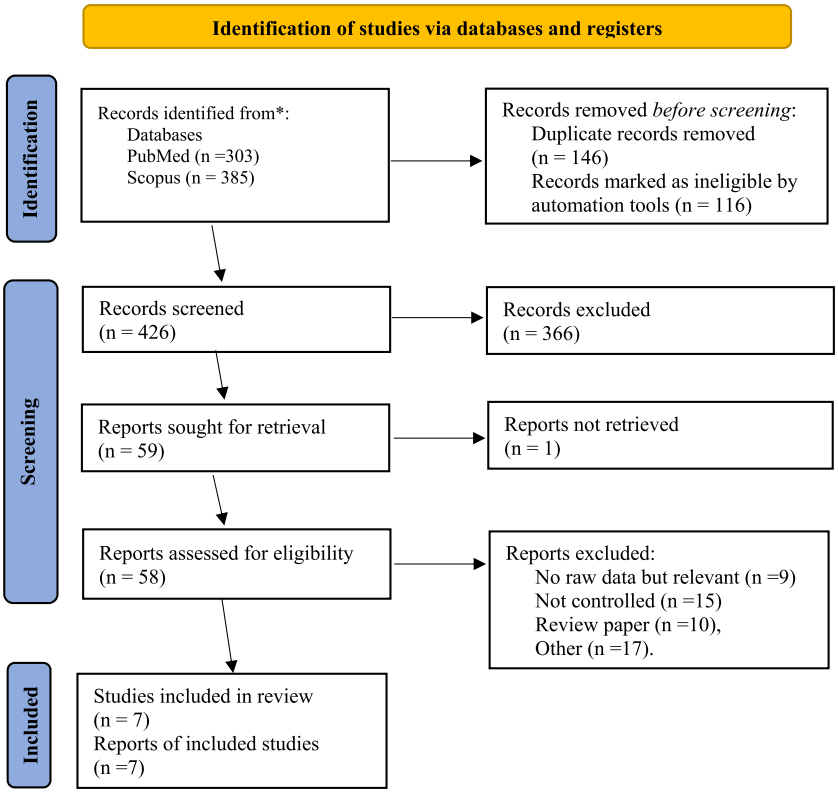

Fig. 1. Flow diagram for search of relevant articles.

3.3. Bias assessments

We used PRISMA guidelines to assess the validity of this data [69]. The sample sizes in every study were small with less than 25 subjects per study. The variability between subjects was very large reducing the likelihood of finding statistical significance. Extreme between study differences also exist – for example, OF THC concentrations in one study [68] were substantially higher than other studies.

Every study was limited in terms of generalizability, as all studies were restricted to particular groups of cannabis users. Although such research designs were informative within the parameters of the study, the findings of each study may not be representative of general use. We do not have a good idea of the degree to which the subjects are representative of persons who use cannabis.

Although the selected studies had common elements, they had different features, creating heterogeneity. The study designs and categorization of cannabis usage varied among studies. The OF collection devices varied considerably too, with 4 of 7 studies using expectorant in tubes, and several OF collection devices commonly used in practice were not represented in these studies. However; frequency of using cannabis, route of administration (i.e., inhaled or ingested) were reported in each study, and dose was either exact or estimated, which allowed for an in-depth analysis of these variables.

Each of the selected studies was assessed for risk of bias on several dimensions: selection, performance, detection, and attrition. Only three studies reported randomization, important for selection. Although, lack of randomization is typically considered high risk in terms of certain variables, it is not considered a severe limitation for this meta-analysis since the groups in all studies were homogeneous and individual characteristics of subjects were not viewed as affecting the outcomes. Lack of randomization for doses appears to be a possible limitation in one study [66] as subjects were given three different doses of THC over three days. Four studies specifically mentioned blinding of both the subjects and experimenters [43,67,68,71], important for performance and detection. Attrition bias was assessed for each study, where we found 1934 valid measures and 80 time points with missing OF (see Table 2), a missing data rate of 3.97 %. One study had the most observations, 748 from 17 subjects [67] and another study had 561 from 17 subjects. Three studies assessed as the most rigorous methodologically [43,67,71] had a missing data rate between 2.32 % and 4.17 %. A common reason reported for missing OF readings was a dry mouth, which mostly occurred within the first 2 h after cannabis administration and subsequent OF tests were valid [11]. Also, one study had 5 missing observations at 24 h [66], suggestive that some subjects may have gone home before the final test. With repeated measures, valid data could be used for the observations before or after the missing data and therefore missing data was not considered a severe limitation. We did not observe any selective reporting or other possible biases among the studies to alter our interpretations. Overall, we did not assess the results to be biased substantially

Table 2
Missing data analysis for the 7 included studies.

Study author and publication year	Number of Subjects	Number of time points	Number of observations with complete OF measures	Number of observations with missing OF	Percent with missing OF measures
Niedbala et al., 2001	19	Variable	153	1	0.65
Toennes et al., 2010	24	2	46	2	4.17
Milman et al., 2012	10	9	80	10	11.11
de_Castro et al., 2014	11	7	69	8	10.39
Vandrey et al., 2017	18	Variable	322	14	4.17
Spindle et al., 2019b	17	11	716	49	4.28
Spindle et al., 2020a	17	11	548	13	2.32
Total	**115**		**1934**	**80**	**3.97**

enough to affect our conclusions.

For two studies in the meta-analysis, different doses of THC were administered to subjects, using repeated measures [43,67]. A possible disadvantage of repeated measures is ordering effects, when doses are not randomized and the time lapse between administrations is very short; however, both these studies had randomization.

Atypical findings were reported for some subjects in some studies. For example, in Milman et al. (2012) [11], one subject had a THC concentration 43.6 ng/mL before cannabis administration, indicating prior use. Another subject with highly elevated cannabinoid concentrations at all time points had visible bleeding from the gums. Also, at 0.5 h, four of 10 subjects were unable to provide a sufficient OF sample due to a dry mouth [11].

The dose that subjects used is subject to error in relation to inhaled cannabis. Subjects in some studies had rigid smoking schedules where as in other studies subjects inhaled ad libitum, which may have influenced the amount administered and affected the generalizability of the results. As well, in some studies, we cannot be 100 % certain that some subjects did not use cannabis against guidelines [11,66,70]. Nonetheless, our final sample size was sufficiently large so that possible random errors in dose were not viewed as a major shortcoming.

3.4. Ethics

Ethical approval was not necessary for a secondary analysis of publicly available data.

3.5. Analyses

In one study with OF tests, diluted samples were used, and therefore multiplication of THC concentrations by a factor of 3 was used for comparability to other studies, as recommended by the authors [70]. Also, since an objective of this study was to compare THC concentrations from the left and right cheeks and no significant difference was found, we used the average of the two samples to improve reliability [70].

Pairwise deletion was used throughout which allowed us to utilize all valid data. We decided that at least 30 cases for each known category were needed for comparisons between OF THC concentrations and OF collection device, age group, sex, race or BMI group for sufficiently valid conclusions [72]. These criteria restricted our analyses to only OF collection device and sex and the variables of age, race and BMI were not analyzed. We first produced summary statistics of concentrations at selected time points, which included data from seven studies (note: one article [70] had three sub-studies).

Our final approach was a mixed regression analysis with OF THC concentrations as the dependent variable. We conducted both bivariate and multivariate models. Bivariate models, refer to direct relationships between each independent variable and THC concentrations, whereas for multivariate models, each variable is controlled with all other variables. Thus, the multivariate probability values represent the *unique* variation explained by each independent variable.

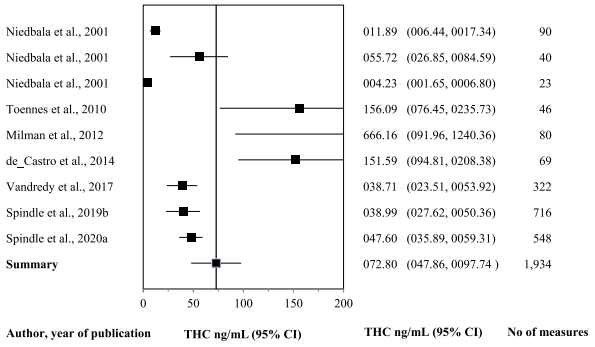

Fig. 2. Heterogeneity of mean THC concentrations in nine studies and sub-studies.

In order to conduct the mixed regression analysis, we met various assumptions of this statistical test as follows. To identify between-study heterogeneity of our samples, we visually presented on a forest graph of the mean THC levels in each of the studies and sub-studies and corresponding 95 % confidence interval (CI) [72]. Fig. 2 shows substantial heterogeneity between studies. Accordingly, we calculated the I^2 statistic [73] to statistically assess the degree of heterogeneity among the studies for the OF concentrations. Since the heterogeneity exceeded a value of 0.75 and a P-value of $I^2 < 0.05$, the multivariate procedure was treated as a random effect. We also specified the repeated effect variable for measures of for subjects within each study in the mixed regression analysis to control for the repeated measures when the covariance parameter estimate for subjects was significant at the 0.05 level [74]. In order to meet the assumptions of mixed effects models for skewed distributions of the dependent variable, OF THC concentrations was transformed to the natural log, based on recommendations [72]. Multicollinearity was examined by exploring the correlation matrix [75,76]. If two or more covariates were highly correlated (i.e., coefficient >0.80), the variable with the lowest P–value from the bivariate test would be included in the multivariate regression analyses. However, multicollinearity was not present and therefore all covariates were included in models to adjust for their potential confounding effects [77]. We used two–tailed tests and present actual P-values. P-values equal to or less than 0.05 were considered significant. All statistical analyses were performed using SAS 9.4 [78] and the SAS PROC MIXED procedure [79].

4. Results

Objective 1: To describe the summary statistics of THC concentrations at different time points after cannabis administration.

The final list of studies and their objectives can be found on Table 1. Summary statistics of the THC concentrations from this merged data set are shown in Table 3. As expected, mean THC concentration decreased over time. THC concentrations, decreased dramatically, from 28.73 ng/mL at 2 h to 5.71 ng/mL at 4 h, and then gradually declined thereafter. However, the standard deviation was very large at all time points. At every time point someone had zero THC concentrations, indicating poor sensitivity and over 6 h, at least one person had at least 23.00 ng/mL suggesting possibly poor specificity. The most common THC concentration across all time points of 2 or more hours is zero. However, the variability between subjects at any time point is extremely large, illustrated by the standard deviations and the range. At each time point, THC concentrations are distributed very widely around the mean, often double the size of the mean. At all-time points up to 24 h at least one subject had a THC concentration level above 20 ng/mL. The distributions at every time point are highly positively skewed, illustrated by the mean exceeding the median, and the standard deviation exceeding the mean at every time point. Also, of note in every study, instances were found with higher THC concentrations for the same subject at longer time points than shorter ones. Every study except for one [68] reported a pre-test of THC before controlled administration to ensure no usage outside of the study.

Surprisingly, few studies had measures taken at 24 h (n = 19). Only two studies collected OF tests after 24 h [70,71]. One study found four of 13 (30.8 %) tests were positive at a THC cut-off of 1.0 ng/mL [70] at this time point. Interestingly in this study, an increase in positive tests at a cut-off of 1.0 ng/mL from 48 to 72 h also occurred [70]. The other study [71] found no positive tests at this cut-off beyond 24 h.

Objective 2: To describe the relationship between the variables of dose of THC, frequency of using cannabis, route of administration (i.e., inhaled or ingested), OF collection device and sex, with THC concentrations in OF, based on bivariate analyses.

Table 4 presents unadjusted mean concentrations (ng/mL) of THC in OF for several variables. The unadjusted analysis, based only on combinations of two variables, shows significant contrasts of THC concentrations for every variable, including OF collection device and sex. Specifically, as expected THC concentrations decreased at every time point and higher doses were significantly related to concentration levels. Unfortunately, increased frequency of use, inhaling cannabis versus ingestion, the OF collection device and being male (versus female) were all significantly related to OF THC concentrations.

Objective 3: To describe the independent contribution of each of the variables in Objective 2, based on a multivariate analysis of THC concentrations.

For objective 3, Table 4 shows the adjusted (multivariate) analyses of concentrations by time after cannabis administration for all variables. The adjusted analyses show the concentrations of THC in OF were significantly associated with hours after cannabis administration, with increased THC dose, increased frequency of use and inhaled route of cannabis administration versus ingested (t-tests, $P < .001$). The only inconsistency found between significance for a variable in the bivariate and multivariate model was for OF collection device and sex, which both became non-significant in the multivariate models.

Table 3
Summary Statistics of THC ng/mL concentrations in OF at different times after THC use, based on all included studies.

Statistics	1 h	2 h	4 h	6 h	8 h	12 h	24 h
# Subjects	115	75	75	73	86	29	24
# THC measures	190	155	155	156	167	27	19
# Missing THC	8	5	5	2	4	2	5
Mean	91.24	28.73	5.71	3.42	2.64	4.06	3.61
Median	38.50	6.00	1.00	0.00	0.00	0.00	1.35
Mode	3.00	0.00	0.00	0.00	0.00	0.00	0.00
Std. Deviation	171.31	123.39	20.67	9.49	6.22	6.69	6.25
Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	1435.90	1310.00	245.00	90.40	38.80	26.00	23.10

Table 4
Mean concentration (ng/mL) of THC in oral fluid by main variables.

Variable	N/n1/n2[a]	Unadjusted log transformed mean THC concentration[b]				Adjusted log transformed mean THC concentration[c]			
		Mean	95 %	CI	*t*-test P	Mean	95 %	CI	*t*-test P
Hours after cannabis administration									
0 (-1 – 0)	7/80/164	0.015	0.010	0.022	ref	0.035	0.022	0.055	ref
1 (0.05–1)	8/103/465	57.081	45.663	71.353	0.0001	132.795	93.168	189.276	0.0001
2 (1.17–2)	7/79/298	4.771	3.610	6.305	0.0001	12.074	8.113	17.971	0.0001
4 (3–4)	6/74/298	0.694	0.525	0.917	0.0001	1.469	0.986	2.187	0.0001
6 (5–6)	4/62/278	0.137	0.102	0.182	0.0001	0.296	0.196	0.447	0.0001
8 (8–126)	7/93/362	0.056	0.043	0.072	0.0001	0.119	0.084	0.170	0.0001
THC dose									
1.2–10 mg	3/40/641	0.398	0.298	0.531	ref	0.300	0.209	0.431	ref
12.2–25 mg	7/82/846	1.398	1.088	1.796	0.0001	1.091	0.788	1.511	0.0001
33–53.7 mg	3/33/378	1.973	1.356	2.871	0.0001	4.959	3.410	7.212	0.0001
Frequency of use									
Weekly or less	7/77/1717	0.780	0.554	0.929	ref	0.782	0.585	1.043	ref
2–4 times/week/more	3/27/148	12.724	7.006	23.111	0.0001	1.766	1.032	3.023	0.0079
Route of cannabis administration									
inhaled	5/66/972	2.542	2.021	3.194	ref	2.904	2.154	3.971	0.0001
Ingested	3/38/893	0.342	0.269	0.435	0.0001	0.475	0.298	0.759	ref
Collection device									
DOA oral	4/42/199	3.492	2.073	5.883	ref	1.671	1.030	2.711	ref
Expectorant	4/62/1666	0.835	0.698	1.001	0.0001	0.826	0.601	1.136	0.0102
Sex [d]									
Male	7/54/948	2.195	1.745	2.760	ref	1.611	0.788	3.293	ref
Female	4/21/618	1.005	0.757	1.336	0.0001	1.462	0.663	3.222	0.6786

Note.
[a] N= Number of studies, n1 = Number of subjects and n2 = Number of THC estimates.
[b] Natural log-THC in oral fluid was modeled to reduce the effect of skewed distribution.
[c] mean THC estimates for hours after cannabis administration, THC-dose, experience of users, routes of cannabis administration and types of collection device, further adjusted for potential confounding effects of one another as well as between-study variation and between-subject variation.
[d] The adjusted THC estimates for sexes were based on five studies [11,43,66,67,70].

4.1. Limitations and discussion

This study has several limitations. Overall, the studies in this meta-analysis had many more males (n = 79) than females (n = 36), thus reducing generalizability of findings for females. Sex was not statistically related to OF THC concentrations in the multivariate analyses, consistent with the mechanism that OF tests detect residuals of THC in the mouth. Therefore, no difference between sexes were expected. Since some research has suggested greater cannabis impairment for females than males [42], if correct, the similarity of males and females for OF in our multivariate analysis may be contrary to the validity of the tests for impairment. In any case, our research does not support the hypothesis that men and women have different OF THC concentrations while controlling for other variables. More types of collection devices in the selected studies is desirable since many devices are presently used.

More research is needed on time frames of 24 h or more. Only two of the studies in our meta-analysis took OF readings beyond 24 h [70,71]. Niedbala et al. (2001) [70] found positive readings at 72 h and others in our review observed extended THC readings beyond 24 h [8,9,32]. Overall, results from our study and others that claim positive tests only occur up to 24 h is a myth. Generally, OF THC tests were 24 h or less in most studies. However, research has shown that with chronic use of cannabis, THC concentrations can remain in OF for days. More information is needed on OF concentrations beyond 24 h.

We only analyzed two saliva collection devices (see Table 4) and there are numerous other devices currently being used. Others have claimed the OF collection device can have a significant impact of drug concentration [12,37]. As well, prior research comparing findings of the *same data set* [40] shows THC concentrations from expectorant was higher than the Quantisal device. Examination of statistical differences in the same data set is more valid than between different data sets. More research is needed on the role of collection devices and other factors for OF concentrations.

This meta-analysis is limited based on the keywords used. All selected studies known to the first author as an expert witness, except the most recent one, were included in this review, giving credence that the keywords were adequate for the purpose. Our study is very focused on specific issues, culminating in fewer articles (n = 688) than many other reviews. Also, we only used two databases, which is a possible limitation.

Our meta-analysis is limited to studies with published raw data for OF THC concentrations after cannabis administration. We examined the excluded studies and found one study with the largest sample consisting of 43 subjects [27]. The penultimate sample size of our meta-analysis, if every study was included, is limited. Overall, the excluded studies due to lack of published data were highly diverse in their objectives, samples and time frames of follow-up. More studies would allow for more precise analysis how third variables influence OF THC concentrations.

For smoking cannabis, a possible error for dose occurred from titration or an ad libitum approach in some studies [11,67,71].

Another limitation was that some subjects could not provide an adequate volume of fluids due to a dry mouth [11].

We confirmed findings by others that THC levels are very high within 1 h after use, decline rapidly over time and are positively skewed. The high average levels are sometimes used to support the use of tests; however, a major shortcoming of tests is that OF THC samples are highly dispersed at every time point after cannabis administration and ingestion of cannabis may result in negative tests. Prior research also shows a high degree of variability in THC concentrations for subjects given the same amount of cannabis [12]. This variability produced some very high outliers in terms of THC concentrations and detracts from OF tests as a valid tool. For example, in our data, at least one subject tested positive at over 20 mg/mL THC from 6 to 24 h after cannabis administration, a level much higher than any workplace cut-off. Given prior research that acute impairment may last 4–5 h [10,14–17] from smoking cannabis, if detection of impairment is the goal, these results suggest punitive interventions may be unfair. Although this study is limited without any measures of impairment, the data suggest the validity of tests for this purpose does not appear optimal. Additional research does not show the variability for OF concentrations is related to variability in impairment [24]. Our research shows that some subjects transition from negative to positive at longer time points, consistent with findings reported elsewhere [8]. There is not a good empirical foundation that people transition between states of non-impairment to impairment from cannabis at different time points, consistent with the variability in consecutive OF tests. Dobri et al. (2019) [37] noted there is a lack of standardized test protocols for concentration cut-offs. Another shortcoming of tests for cannabis is research (identified above) shows those who inhale cannabis are significantly more likely to test positive that those who ingest cannabis. This finding is despite research that shows ingested cannabis can be more impairing than inhaled cannabis. These observations suggest that for the purpose of detecting cannabis users, false negatives could result. If the purpose of the test is to detect impairment, both false positives and false negatives could result. Since OF tests detect direct residuals of THC rather than how cannabis is influencing the individuals, and we do not have good research knowledge on the validity of concentrations for impairment at any cut-off, use of tests appear premature for this purpose.

Frequent users of cannabis, route of administration through smoking, and increased dose were statistically related to higher OF THC concentrations. Although dose should be related to increased likelihood of positive tests for validity, frequent use and route of administration should not. For frequency of use, prior research also found some very heavy cannabis users had positive OF THC readings days after use [8,9,32]. Ideally for fairness, regardless of the purpose, OF tests should accurately distinguish two groups and not be influenced by outside factors. For impairment, proper epidemiological studies have been conducted assessing validity at 0.05 % and 0.08 % alcohol cut-offs [25] but equivalent studies are **not** available for THC drug concentrations in OF at any level and impairment. As well, the detection period was significantly shorter for ingested than inhaled cannabis, likely contrary to validity of fluids. Prior research has shown that THC taken in pill form is undetectable [80]. Both occasional users and those who ingest cannabis are potentially at higher safety risk due to longer and more intense impairments, yet these groups are less likely to be detected by OF tests of THC. These above results on factors related to impairment are consistent with conclusions by other authors [10]. Finally, we found THC from expectorant was significantly lower than the DOA collection device only in the bivariate model. Overall, our findings suggest there are confounders that detract from objective assessments.

In the U.S., where detection of prior use of cannabis is the goal, several authors have noted that OF tests detect more recent cannabis use than urine tests and some have suggested a 24-h window for use. However, our meta-analysis only included two studies where tests OF tests were conducted after 24 h [70,71] highlighting the dearth of evidence on the prevalence of THC in oral fluid at longer times after use. Overall, our results are indicative that the 24-h window for positive tests is false. Furthermore, other studies have found extended OF detection times of days [8,9,32]. Of note, one study that supports a 24-h window, excluded chronic users from their analysis [1]. Although OF THC testing for THC is now commonplace, the research base from our meta-analysis of published OF THC concentrations does not support claims about detection times of up to 24 h. However, the detection time for OF is shorter than urine tests where the cannabis metabolite (i.e., THCCOOH) is the focus of testing.

We conclude from our meta-analysis that validity is not ideal for either detection of prior use or impairment at a commonly used THC cut-off of 1 ng/mL. Although OF does identify prior use of cannabis, the possibility of false negatives exists. This observation raises the issue of the fairness of the tests. For identification of impairment, a preferable epidemiological approach for validity involves calculation of sensitivity and specificity for OF test cut-offs against a "gold standard" of impairment. No commonly accepted gold standard exists of cannabis impairment, making this goal illusive and research challenging. Nonetheless, more studies are needed with direct comparisons of psychomotor impairment and OF THC concentrations tests. At present, all studies demonstrated a great deal of variability in OF THC concentrations between people at the same time points after cannabis administration. We also know from prior research that there are substantial variations in impairment between people administered the same doses of cannabis. We do not have a good idea for the degree of accuracy of any THC OF cut-off for impairment. Our meta-analysis of controlled cannabis administration studies shows that in the absence of optimal assessment of validity, OF tests should *not* be considered a valid indicator of impairment.

Based on our analyses from published controlled administration studies of cannabis and OF tests, several issues should be addressed before oral tests are adopted. Although OF tests are less invasive than blood and urine tests [13], justification for their general use should be based on validity of the test for the intended purpose. In this respect, OF THC drug tests are typically used to detect drug users or to detect current impairment. This research has shown that OF tests for THC have greater validity for detecting cannabis users (i.e. only false negatives) than those impaired by cannabis (i.e. both false positives and false negatives). Proponents for OF tests acknowledge some limitations, but appear to justify its use since all biological tests have imperfections and some enforcement system is needed. More research is needed on the possible roles of confounding variables for OF THC concentrations before OF is accepted as a valid test for cannabis. The research is quite diverse, which means findings from individual studies may not be generalizable. Rather, contradictions among findings may be due to differences in cannabis administration, characteristics of the user, and collection approach: most importantly, ingested vs inhaled, the experience of the user or collection device.

CRediT authorship contribution statement

Scott Macdonald: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Jinhui Zhao:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis.

Declaration of interest and ethics

Manuscript contents are derived partially from prior paid expert report testimony for the International Longshore and Warehouse Union, conducted in November 2020, by Scott Macdonald and statistical assistance by Jinhui Zhao. Since this study was a secondary analysis of existing data in peer reviewed Journals, no ethical clearance was needed.

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Declaration of competing interest

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Appendix A. Supplementary data

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