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A Systematic Review of Passive Exposure to Cannabis

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Abstract

Passive exposure to cannabis smoke may induce effects on behavior and psychomotor skills, and have legal consequences, including the risk of being falsely considered as a cannabis user. This can become a concern, especially in occupational contexts or when driving vehicles. In order to enable a differentiation between a passive and an active exposure to cannabis and to limit the likeliness to be detected positive following passive exposure, this review identified specific biomarkers of passive exposure in urine, blood, oral fluid, hair, and sebum. Out of 958 papers identified on passive exposure to cannabis, 21 were selected. Although positive tests had been observed in all matrices following extremely high passive exposure, some distinctive features were observed in each matrix compared to cannabis active use. More specifically, in everyday life conditions, 11-nor-delta-9-THC-carboxylic acid (THC-COOH) urinary level should be detected below the positivity threshold used to confirm active smoking of cannabis, especially after normalization to creatinine level. Measuring delta-9-tetrahydrocannabinol (THC) and THC-COOH in blood is an appropriate alternative for appraising passive exposure as low and very low concentrations of THC and THC-COOH, respectively, should be measured. In hair, oral fluid (OF) and sweat/sebum emulsion, no THCCOOH should be detected. Its presence in hair argues for regular cannabis consumption and in OF or sweat for recent consumption. The experts should recommend to persons who have to demonstrate abstinence from cannabis to avoid heavily smoky and unventilated environments.

Keywords

Passive exposure, cannabis, urine, blood, oral fluid, hair

Introduction

Cannabis passive smoking referred to the inhalation of cannabis smoke, called secondhand smoke or environmental cannabis smoke, by persons other than intended "active" smokers. It occurs when cannabis smoke contaminates any environment and it is inhaled by people staying in that environment. Secondhand smoke is defined as the combination of the sidestream smoke released from a burning end of a marijuana cigarette and the mainstream smoke exhaled by a smoker [1]. Besides inhalation, unintentional cross-contamination could also occur by unintended direct contact with contaminated objects, as illustrated in Figure 1. Hence, cannabis smoke can be swallowed or deposited on hair, skin, clothes, and surrounding surfaces (e.g., furniture, doorknobs or water taps) [2]. This type of pollution is called thirdhand smoke [3]. However, the cross-contamination and exposure of non-smokers should happen less frequently than self-contamination, despite the fact that residual cannabinoids may build up on surfaces over time and resist normal cleaning and airing out [4]. Lastly, cannabis derivatives may be accidentally ingested with contaminated food.

Several studies evidenced detectable concentrations of cannabinoids in body fluids following exposure to secondhand cannabis smoke [5-23]. For instance, the recent studies by Herrmann et al. [10] and Cone et al. [8; 9] confirmed that passive exposure to cannabis smoke under extreme exposure conditions not only resulted in measurable cannabinoid concentrations in oral fluid, blood, and urine, but also in minor physiological (increased heart rate) and subjective drug effects, as well as minor impairments in a task requiring psychomotor ability and working memory. This exposure could be very common (e.g., one partner smoking marijuana, to sit in a car or stay at home with one or several smokers).

Passive exposure to cannabis is furthermore a significant legal issue, and it may be especially so in occupational contexts and when driving vehicles. In the workplace, passive exposure should not be mistaken for active use if it might lead to sanctions against employees. With regard to driving, active and regular cannabis consumption should not be mistaken for unintended frequent passive exposure. In cases of acute exposure and a zero-tolerance driving policy, a THC-positive blood specimen may well result in the same legal and administrative consequences, regardless of whether exposure was active or passive. In the forensic and medical contexts, differentiating passive, unintentional exposure to cannabis remains an issue of how to interpret the results of body fluid analyses.

Most experimental studies assessing the importance of passive contamination to environmental cannabis smoke were carried out with abstinent volunteers enclosed in an exposure chamber.

Many parameters were controlled as the smoke density, the cannabinoid concentrations, or the duration of exposure. From these studies, the present review summarizes findings obtained until December 2015, and discusses the relevance of the different biomarkers available for diagnosis of passive exposure *versus* active use. More specifically, it describes the current state of knowledge on the passive inhalation of cannabis, and the consequences of an external contamination of body surfaces on the results from tests of biological samples (urine, blood, oral fluid, hair, and sebum/sweat). The specific biomarkers and decision limits, or positivity thresholds, that can help differentiate between active consumption and passive exposure will particularly be discussed from a legal and forensic perspective. After a short presentation of the most important factors affecting the cannabis contamination, the selection strategy of the relevant scientific literature will be described. The paper will afterwards consider the important elements (i.e., analytical methods, concentration ranges, contamination, and interpretation) in result interpretation of each biological fluid and tissue following passive exposure to cannabis.

This review article is mainly intended for forensic experts who are confronted with statements of passive contamination or for persons frequently exposed and worried by passive cannabis smoke. This article should allay some of their concerns and facilitate the work of expertise of forensic experts.

Cannabinoids: metabolism in human

The plant precursor to THC is delta-9-tetrahydrocannabinolic acid A (THC-A) [24]. THC-A itself has no psychotropic effect and should be considered as a pro-drug. The main active cannabinoid responsible for the psychoactive properties of cannabis is THC [25]. The thermal decarboxylation of THC-A to THC is only partial when cannabis is smoked [26] or rarely complete when heated in an oven. Although it is mainly inhaled, cannabis can also be consumed in food and beverages. As medicine, cannabis is generally not smoked (but can be vaped); the risk of passive contamination is thus very low.

Cannabinoids can be absorbed by respiratory airways and to a lesser extent by oral route. The dermal route was reported to be minor; therefore, a passive contamination by this route seems unlikely [27]. After inhalation, THC is rapidly absorbed from the lungs into the bloodstream. It is metabolized by liver enzymes or distributed to adipose tissue, the lungs, and spleen due to its high lipophilicity [25]. In the liver, THC is oxidized mainly into 11-hydroxy-delta-9-THC (11-OH-THC) and then into 11-nor-delta-9-THC-carboxylic acid (THC-COOH) [28]. THC-COOH is

further rapidly conjugated to glucuronic acid, forming the ester-link glucuronide (THC-COOH-glucuronide). THC is slowly released from the body's lipid-storage compartments. THC's plasmatic terminal half-life is estimated at 1 to 6 h for infrequent users and 20 to 36 h for frequent users [29-31]. THC is eliminated slowly, mainly in the form of acid metabolites, and its main disposal route is via feces (60%–80%); the urine route is less important (20%–35%). In urine, the main metabolite excreted is THC-COOH-glucuronide. Only a small amount of free THC-COOH is excreted (< 4%), along with only traces of THC. The urinary excretion half-life of THC-COOH was estimated at 30 h by Musshoff and Madea [25] to 3 to 4 days by Huestis et al. [30], depending on cannabis conditions of use.

Cannabis smoke

Overall, it is the smoking of cannabis cigarette that raises a number of questions regarding the passive exposure to cannabinoids, and more specifically to THC. In an attempt to estimate inhaled THC doses and to determine an internal dose, some studies monitored THC levels in air [5-7; 14; 18; 19]. It is assumed that the smoking process itself degrades 23%–30% of the total THC content in cannabis by pyrolysis, and some 20%–37% is delivered to the active user in mainstream smoke. The remaining 40%–50% of THC is released to the environment in sidestream smoke [18; 25; 32; 33]. Consequently, despite the high influence of several factors on the rate of absorption, a notable amount of THC can still be inhaled by passive smokers and then be absorbed, metabolized, and excreted just like an active user.

Until recently, few investigations have been carried out to characterize the components of the smoke from marijuana cigarettes, and the majority of these concentrated on analyzing the cannabinoids in smoke, as they are the most biologically active constituents of cannabis [34]. Cannabis smoke is composed of gas and particulate phase substances. Cannabinoids are mainly found in the particulate phase [35]. This smoke is diluted in the environment, and low but notable concentrations of THC and other cannabinoids can be measured in several urban areas [36; 37].

Influence of experimental conditions

The studies on passive exposure to cannabis smoke clearly evidenced the importance of the different factors influencing the results and their interpretation. In 1983, Falck [38] highlighted the many factors influencing concentrations of urinary cannabinoids: amounts of water drunk

before urine collection, the rate of urine formation, metabolic rate, the quantity of urine voided, and the time of marijuana absorption or urine voiding. Similarly, Cone and Johnson [5] pointed out that plasma levels and the presence of urinary metabolites depended on a variety of factors, including duration and frequency of exposure to smoke, cannabinoid concentrations in the room's air, and individual sensitivity to marijuana. According to Moffat [31], the most important factors influencing body fluid concentrations were: smoking techniques (i.e., THC content, room size, ventilation, exposure time, the number of smokers in the room, the time between exposure to passive smoke and urine collection, and urine hydrolysis to obtain the free acid in order to increase the sensitivity of metabolite detection. Busuttil et al. [39] added dose (the amount of THC released in smoke), body weight, age, sex, renal and hepatic function, and the analytical techniques used as factors affecting the detection of THC and its metabolites in blood and urine. Furthermore, the studies by Niedbala et al. [17-19] confirmed that the detection of THC-COOH in urine (in free and conjugated forms) is affected by a multitude of pharmacological and physiological factors (i.e., THC content of marijuana, dose uptake, sampling time, individual renal and metabolic characteristics, body size). In addition, methods of cannabis inhalation can also modify exposure levels for non-smokers [40].

Biological markers and decision limits as criteria of passive exposure

Since 1977, several authors have studied passive exposure to cannabis smoke in order to better interpret analytical results and to validate the decision limit or positivity threshold fixed by different scholarly societies (see Table 1). However, as no standard definition of "passive inhalation" exists, concerns remain to diagnose active use or passive exposure based simply on levels in body fluids [39; 41]. From a forensic viewpoint, Busuttil et al. [39] defined passive exposure as "the presence of cannabinoids in the body fluids of non-users who have been passively exposed to marijuana smoke". The authors pointed out that any person who allows himself to be deliberately exposed to cannabis smoke—at high dosages, for long durations, and in a confined space, so as to absorb enough THC for metabolite levels to be measured at over 100 ng/mL in urine (total THC-COOH, without correction for creatinine) or 25 ng/mL in plasma (free THC-COOH)—must be a "willing participant" and knowingly aware of the potential effects [39]. Consequently, the concept of passive exposure involves unintended contamination. Moreover, THC in sidestream smoke is mainly released as aerosol particles and their concentration is rapidly and heavily diluted with the flow of surrounding air [19]. It remains that over the last few decades, the levels of THC in plants have raised substantially, mainly due to

the expansion of indoor cultivation and the selection of varieties that maximize THC yields [8; 29] (e.g., the average potency of all types of cannabis was 13.2% in 2012 vs 2.8% and 7.3% for marijuana and sinsemilla, respectively, in 1985 in the US [8], and remained unchanged for 10–20 years, consistently 2%–8%, to reach more than 10% in Europe [42]). Consequently, the higher the potency of the cannabis is, the greater the potential risk of positive body fluid test results after passive exposure.

Selection strategy of references

Several library databases were used to identify and select publications dealing with passive exposure to cannabis (i.e., PubMed, Medline Ovid SP, Embase, Cochrane Library Wiley, Cinahl, Web of Science and Google Scholar). Only papers published after 1970 and before August 2015 were considered. Different terms and research strategies were combined (see supplementary data for the combinations of search terms used). The selection was based on titles and abstracts, and papers in English, French, German, and Italian were considered. The initial investigation identified 958 papers; after removing duplicates and considering the suitability and appropriateness of titles, 98 abstracts were reviewed. Of these, 77 papers did not fulfill the criteria for eligibility. These criteria included only studies on exposure to passive cannabis smoke in controlled conditions, collecting biological matrices in non-users volunteers, and reporting results on matrix analysis. A final total of 21 studies on passive exposure to cannabis were selected. In agreement with Moffat [31], the authors of this review considered that the most important factors in each study were:

1. Volume of the exposure room and its ventilation characteristics (e.g., opening a door or window can reduce the concentration of THC in the air);
2. Number of non-smoker volunteers exposed to passive inhalation of cannabis;
3. Exposure time and exposure conditions for the non-smoker volunteers;
4. Magnitude of exposure (e.g., number of marijuana cigarettes smoked, dose of THC);
5. Analytical methods used to detect the cannabinoids and their metabolites in body fluids and tissues.

The 21 publications included in the present study are summarized in Supplementary Tables 1 and 2.

Biological samples: methods of analysis, concentration ranges after passive exposure compared to active use, result interpretation, and decision limits

Environmental exposure to cannabis smoke can be detected and analyzed in urine, blood, oral fluid, hair, and sebum/sweat. Each biological specimen provides different information regarding the drug's effects on health, performance, behavior, and on the individual's drug-exposure history. Likewise, each matrix has its specificities with regard to interpreting cannabis exposure, offering different advantages and disadvantages for drug testing. Figure 2 summarizes the main potential markers present in the different biological matrices, as well as their excretion routes following the involuntary exposure to cannabis.

Urine

Urine remains the matrix of choice for drug-testing programs to demonstrate past drug exposure in workers or drivers because of the long time detection of THC-COOH and its conjugated metabolite in urine. One of the major advantages of using urine as a matrix is the ease to collect spot samples at any time (determined collection time or ad libidum collection) from an analytical point of view. However, urine samples imply large variability in volume and, consequently, in chemical concentrations from void to void [43]. In addition, urine samples can be falsified by dilution, substitution, or adulteration using a wide array of substances.

Analysis

Urine is mainly analyzed using immunoassays and chromatography coupled to mass spectrometry methods. Regarding immunoassays, improvements in method sensitivity and specificity as well as more appropriate enzymes allowed selection of a lower cut-off to distinguish active from passive smoking and to develop a less invasive body fluid collection. As illustrated in Table 2, the enzyme multiplied immunoassay technique (EMIT) was first commonly used, but the labeling of antibodies was changed to decrease the limit of detection (LOD) value, and EMIT was replaced by 125I-radioimmunoassay (RIA, 2 ng/mL) or enzyme-linked immunosorbent assay (ELISA, 0.6 ng/mL). RIA had the advantage that no cross-reaction with other compounds than cannabinoids related to Δ8 or Δ9 was observed, reducing the risk of false positive results [13; 31]. Although immunoassays are considered as suitable methods for cannabinoids screening, some limits are recognized, such as cross-reaction with related and unrelated compounds (inducing false-positive results) or generation of artifacts in the presence

of adulterants affecting matrix pH, presence of detergents or surfactants (inducing false-negative results) [25; 29]. Therefore, immunoassays are commonly adopted as a preliminary test method while mass spectrometry based methods are currently used to confirm cannabinoid identity and assess cannabinoid levels [25; 31]. Nowadays, the single chromatography coupled to mass spectrometry (GC-MS) methods are replaced by two-dimensional gas-chromatography high resolution mass spectrometry methods or ultra high performance liquid chromatography interfaced with atmospheric pressure ionization coupled with tandem high resolution mass spectrometry (LC-MS/MS). This last method short-circuits the extraction step and allow the direct analysis of free THC-COOH and its glucuronide conjugates in urine [44]. In contrast, GC-based methods require the hydrolysis of conjugates and a derivatization step before analysis. Results are expressed as total THC-COOH (free plus conjugated).

The best means of reducing drug measurement variability is to normalize cannabinoid concentrations to the urinary creatinine level. The normalization also allows the monitoring of abstinence from cannabis use and reduces false-positive or false-negative drug tests, especially during the late elimination phase when concentrations are either just above or below threshold values [30; 45-47]. Consequently, it is recommended to take into account the creatinine concentration for urinary THC-COOH although the decision limits or positivity thresholds are fixed without creatinine correction. In serial urine specimens, creatinine-normalized THC-COOH concentrations are also considered as better indicators to predict reuse of marijuana than without creatinine normalization [48].

Concentration ranges

The detection of cannabinoids in urine indicates a past exposure to cannabis. However, urine gives no information related to the exposure route, the duration of exposure, or the amount of cannabis absorbed because of the long excretion half-life and the wide inter-individual variability [17; 30; 49]. Figure 3 summarizes the concentrations adjusted for creatinine of THC-COOH time profile in urine of different studies during and following a passive exposure to cannabis. Only studies analyzing urine by GC-MS and adjusting by creatinine were considered in Figure 3. Hence, in passive exposure studies, THC-COOH can be detected in urine around 1 h after exposure, and peak THC-COOH concentrations are observed at 6 to 8 h after exposure. Nevertheless, according to Westin and Slordal [49], any measurement of THC and THC-A, or of cannabinoids above the limit of quantification (15 ng/mL for THC-COOH, without correction for creatinine) in the urine of passive smokers must be related to such an extremely high exposure

that the person concerned could not be unaware that smokers in the immediate vicinity were smoking cannabis. Figure 3 supports a limit value of 15 ng/mg of creatinine for THC-COOH; higher values were obtained in extremely high exposure conditions. As no mandated creatinine-normalized thresholds are available, Schwilke et al [48] have developed empirically derived statistical models using limit concentration values of 15 and 6 ng/mg creatinine as cutoffs to distinguish abstinence from new cannabis use in chronic smokers. These cutoffs are similar to the limit value observed in Figure 3.

Interpretation

The interpretation of urinary results is complex, and several factors may influence urinary concentrations of the main metabolite, THC-COOH-glucuronide. In addition to creatinine normalization, individual variability, and exposure conditions (cannabis dose and number of smokers, design of the room), the exposure room's ventilation appears to be a relevant factor to consider. According to the study of Cone et al. [8], for the same inhaled dose of cannabis, total THC-COOH concentrations in the urine of passive non-smokers was two-thirds lower when the room was ventilated (median maximum concentration, or C_{max}, of 24.9 and 8.5 ng/mL THC-COOH (30.8 and 9.1 ng THC-COOH/mg creatinine, respectively) without and with ventilation, respectively). Cone et al. [8] also noticed similar differences for THC-COOH levels in the last collected urine specimen (4 ng/mL (6.7 ng THC-COOH /mg creatinine) versus 1.2 ng/mL (2.4 ng THC-COOH /mg creatinine) in a ventilated room, 31 h after exposure). In studies with ventilation, C_{max} was found to be slightly delayed to 6 h, compared to the 4 h observed in studies with poor or no ventilation (see Figure 3). Besides ventilation effects, the range of THC concentrations has been correlated with the potency of marijuana cigarettes. Elimination time profiles shifted to greater concentrations when potency or dose was increased, but their time-appearance remained very similar across the whole experiment. Consequently, urinary concentrations are mainly dose-dependent [12]. Further, the choice of the positive threshold value and the screening test characteristics will greatly influence the rate of positive sample detection. Hence, Cone et al. [8] found that increasing the immunoassay cut-off from 20 ng/mL to 50 ng/mL significantly decreased the rate of positive presumptive urine tests in non-smokers. At a 50 ng/mL cut-off, all but one of the immunoassays included in the experiment provided negative results. In summary, urine is an appropriate matrix to monitor abstinence from cannabis after creatinine normalization, even after moderate second-hand smoke exposure. In extreme conditions, THC-COOH may be detected in urine after passive exposure to cannabis

smoke. However, ventilation strongly attenuates the likelihood of being tested positive, and urinary concentrations of cannabinoids are greatly influenced by the potency of the marijuana and the dose.

Blood

Blood analyses are necessary for the detection of recent exposure to cannabis or for the evaluation of its effects on behavior and performance [9; 10]. In general, as THC is extensively bound to lipoproteins, the preferred specimens for blood analyses are plasma or serum. The two main metabolites considered as detectable in blood specimens after passive exposure are THC-COOH and its glucuronide ester conjugate [39].

Analysis

The majority of passive exposure experiments involving THC measurements in plasma were performed in the 1980s. At that time, blood analyses were carried out using a radioimmunoassay or, less frequently, single-quadrupole gas chromatography–mass spectrometry (GC-MS). RIA was the main radioimmunoassay method for plasmatic THC determination (cutoff of 3 ng/mL). However, due to cross-reactions of antibodies with metabolites in a radioimmunoassay, it is difficult to compare these estimates with the results obtained using modern mass spectrometry techniques. As for urine, immunoassays are considered as a preliminary test method and results have to be confirmed using mass spectrometry based methods. However, highly sensitive and accurate methods are required to detect and quantify the low blood concentrations of THC observed during the late time course of drug effects due to THC's rapid distribution to bodily tissues and to the time delay between exposure and sample collection [30; 50; 51]. Hence, more recently, Röhrich et al. [22] and Cone et al. [9] used more sophisticated mass spectrometry assays (e.g., liquid chromatography interfaced with tandem MS) either with serum or whole blood, and managed to extend the time since exposure in which cannabinoids can be measured accurately (Table 2).

To accurately compare concentrations detected in blood specimens, the distribution ratio of cannabinoids between plasma or serum and whole blood should also be considered. A mean plasma to whole blood ratio of 1.6 has been suggested for both THC and THC-COOH [52]. Nonetheless, contrary to urine with creatinine, normalization with hematocrit is hardly ever done for blood, serum, or plasma. Hematocrit values are systematically ignored, although they vary substantially between whole blood specimens. Likewise, the small fraction of free cannabinoids

315 ables to bind to brain receptors and to induce the typical effects of cannabis is never evaluated
316 either. Nevertheless, with the recent development of deuterated homologs and specific
317 quantification methods, it is now possible to analyze free and conjugated cannabinoids
318 separately. These two values should therefore be quantified to give a better interpretation of
319 results.

320

321 *Concentration ranges*

322 Cannabinoid kinetics in blood are complex and difficult to interpret. Figure 4 summarizes the
323 concentrations of THC (a) and THC-COOH (b) time profile in blood of different studies during
324 and following a passive exposure to cannabis. The results of Morland et al. [15] showed that the
325 highest levels of plasmatic THC were measurable immediately after the three volunteers had
326 been exposed to 30 min of secondhand smoke generated by two smokers in a small car.
327 Despite only two sampling times in this study, it can be assumed that the levels of plasmatic
328 THC measured in blood just after leaving the car were close to the maximum values, as it has
329 been observed in more recent studies (Figure 4a). At 2 h, THC levels had decreased to
330 insignificant values. However, the use of low-potency marijuana cigarettes (1.5% THC) highly
331 limits the relevance of this study today. Currently, cannabis is far more potent, and the
332 composition of the different cannabinoids in cannabis plants has diversified. For instance, some
333 plant strains may be characterized by a high proportion of THC and cannabidiol (CBD) (e.g.,
334 10% THC and 15 % CBD), whereas others have a high content of tetrahydrocannabivarin
335 (THCV). THCV is a THC variant with short C3 lateral chain reported to have psychoactive
336 properties at high doses (e.g., Perplex Feminized Seeds marketed by Seed Supreme) [53]. For
337 the recent studies by Röhrich et al. [22] and Cone et al. [9], comparing Figures 4a and 4b
338 reveals similar ranges of THC and THC-COOH concentrations, as well as similar C_{max} (at T_{max}
339 between 20 to 60 min) for both compounds. Concurrent measurements of THC and THC-COOH
340 in whole blood after passive exposure indicated a rapid absorption and metabolism of THC.
341 However, Röhrich et al. [22] detected very low concentrations of THC and THC-COOH in
342 passive smokers at the end of exposure. Indeed, they were so close to the analytical cut-off that
343 calculation of their relative levels was irrelevant. The maximum THC concentration was
344 observed at 90 min after the beginning of the exposure, and undetected 180 min after exposure
345 to cannabis smoke. The exposure scenario conditions selected for non-smoker volunteers in
346 this study seemed closer to real passive smoking conditions than the 1980s studies (e.g., large
347 room, efficient ventilation, quite a long exposure time (3 h), and between 8 and 25 cannabis

users). In the study by Cone et al. [9], the range of reported C_{max} levels over the three sessions was 0.5–3.1 ng/mL for THC and 0.2–2.5 ng/mL for THC-COOH at 0.25 h following the 1 h exposure session. As expected, higher C_{max} were observed in unventilated conditions. It was estimated that active smokers delivered 6%–18% of the dose to passive smokers in an unventilated room, and this decreased with ventilation. At these estimated cannabis doses, volunteers reported some of the typical psychoactive effects of cannabis. However, the effects due to THC exposure remain difficult to interpret in the absence of a placebo session.

Contamination

In order to avoid direct contamination, it is recommended that blood specimens should be collected outside the contaminated place or room and that butterfly catheters are protected from cannabis smoke in serial blood sample collection. In the earliest studies, the elimination profiles in the plasma from the studies by Perez-Reyes et al. [21] and Mason et al. [54] were not considered in Figure 4a, due to possible contamination and the absence of controls or placebos. In these studies blood sampling only restricted the exposure period and collection occurred inside the exposure room so as to reach a steady-state THC level in volunteers (Supplementary Table 2). Unlike these two studies, Morland et al. [15] collected blood specimens after the exposure period and outside the exposure area in order to reduce the risk of contamination during blood sampling.

Interpretation

When interpreting blood results, it is important to consider certain factors other than the complete description of exposure parameters. Goullé et al. [29] interpreted the blood kinetics following inhalation by using a multiphase profile. High plasmatic concentrations of THC are reached within the first minutes of the inhalation phase. This is followed by an initially rapid decrease (distribution phase) and then a slower elimination, implying the use of a multi-compartment pharmacokinetic (PK) model or alternative complex models. The multiphase absorption and elimination time-profile can be inferred from the broad range of early passive smoking studies presented by Cone et al. [5-7]. Volunteers stayed in a closed, unventilated room for six consecutive days and were exposed to 4 or 16 marijuana cigarettes (2.8% THC) for 60 min each morning (Supplementary Table 2). Despite the daily repetition of exposure sessions, proof of THC accumulation in plasma remained inconclusive [7]. Nevertheless, the highest mean plasma levels (2.4 and 7.4 ng/mL for 4 and 16 cigarettes, respectively) were

indeed observed on the last day of exposure. The exposure conditions of this study were extreme and are unlikely to occur in daily practice (i.e., an unventilated room and 16 marijuana cigarettes smoked for 1 h each day for 6 consecutive days): volunteers had to wear goggles to tolerate the noxious smoky environment.

Researchers have been trying to identify the criteria and potential markers able to distinguish active consumption from passive exposure from the very earliest studies on passive cannabis exposure [15; 21; 54]. In this perspective, Mason et al. [54] suggested comparing the concentrations of THC and THC-COOH in plasma; after active smoking, THC is present in low concentrations in the latter part of the elimination curve and THC-COOH levels always exceed those of THC: after passive exposure, THC-COOH concentrations are always lower than THC concentrations. This scenario can be observed by comparing Figures 4a and 4b. Consequently, threshold values for THC-COOH have been proposed for differentiating regular cannabis use from occasional smoking. Blood levels above 40 ng/mL of free THC-COOH strongly suggest regular consumption of cannabis [55; 56]. After passive exposure, Toennes et al. [51] and Röhrich et al. [22] reported THC-COOH concentrations in serum of 2 ng/mL at 1 h after exposure; it was lower than 1 ng/mL for THC. They thus suggested that THC and THC-COOH serum levels higher than 2 ng/mL would imply deliberate consumption. However, it remains unclear whether regular passive exposure over a long period can lead to higher cannabinoid levels.

Overall, blood is an appropriate matrix to detect recent exposure and evaluate the effects of cannabis on behavior and performance. After passive exposure in extreme conditions, low and very low concentrations of THC and THC-COOH, respectively, should be observed (values should be insignificant 2 h after exposure). To avoid direct contamination of the matrix, sampling must be performed outside of the smoking area.

Oral fluid

Oral fluid (OF) is considered a suitable matrix for monitoring recent cannabinoid use or unintentional passive exposure [57]. It is commonly accepted that the presence of THC and THC-A (the plant precursor of THC) in OF is evidence of recent exposure to cannabis [17; 18]. The presence of THC-COOH molecules (free and conjugated) is generally considered as the best biomarker to detect active cannabis use as THC-COOH in OF is related to plasmatic concentrations and it is not present in smoke [58]. However, contrary to THC, THC-COOH

metabolite can be detected in a glucuronidated form and in very low concentration ranges (pg/mL), requesting more sensitive and up-to-date methods; consequently, most investigations are limited to THC as it is present in very high levels [14; 30; 57; 59; 60]. To increase the sensitivity of THC-COOH detection in OF, recent analytical methods have been developed either for including a preliminary step to hydrolyze THC-COOH-glucuronide or for determining THC-COOH and THC-COOH-glucuronide separately [59; 61; 62]. However, the presence of beta-glucuronidase enzymes in the OF could hydrolyze THC-COOH glucuronide and hamper the detection of glucuronide conjugates [57; 61]. Until now no study has demonstrated the presence of THC-COOH in OF following passive exposure to cannabis smoke [58], THC-COOH alone or in the free and conjugated forms should be monitored in OF to identify active cannabis smoking or in suspicion of active cannabis use.

Analysis

OF samples were analyzed by very sensitive, selective and specific two-dimensional gas-chromatography high resolution mass spectrometry methods or by high resolution liquid chromatography interfaced with atmospheric pressure ionization coupled with tandem high resolution mass spectrometry (Table 2). These methods allow a direct analysis of OF without performing extraction previously [63]. Notwithstanding, a GC- or a target LC-MSMS method can be as sensitive as a high-resolution mass spectrometry (HR-MS); however, direct analysis of untreated oral fluid is not really recommended.

Concentration ranges

Five studies on the passive inhalation of cannabis smoke monitored THC concentrations in OF specimens. The Figure 5 represents the concentrations of THC time profile in OF of different studies during and following a passive exposure to cannabis. As illustrated in Figure 5, THC C_{max} was observed until 20 min after exposure to cannabis smoke. THC concentrations were then seen to decrease rapidly until 60 min. Niedbala et al. [18] explained the high concentrations observed shortly after passive exposure to cannabis smoke by the fact that up to 50% of the total THC content in a cannabis cigarette is released in sidestream smoke. Determining a reliable, accurate C_{max} for cannabinoids using OF specimens is very difficult considering the sampling device's potential for contamination and the rapid decrease in concentrations after passive exposure to cannabis smoke. Actually, the higher THC

concentrations observed in volunteers by Niedbala et al. [19] in their study I compared to their study II was probably due to device contamination (Supplementary Table 2). To limit contamination, Moore et al. [14] collected OF outside coffee shops in the Netherlands. However, variations in the number of smokers present inside the coffee shops during the 3-hour exposure period make the results difficult to interpret. This study only highlighted positive test results following passive exposure to cannabis smoke, but no conclusions could be made regarding kinetics or elimination after 3 h of exposure (Figure 5).

Contamination

As for blood sampling, to avoid direct contamination, OF specimens must be collected outside the contaminated place or room and sampling devices should be protected from cannabis smoke. Another element to consider as potential contamination is THC accumulation in the mucosa of the upper respiratory tract following active or passive smoking, even though cannabinoids are very poorly excreted in saliva [19; 30]. This contamination may last for 6 to 9 h and can be detected using an adequately sensitive test; however, positive tests are very rarely obtained more than 2 h after the last use [30; 64]. Furthermore, exposure to cannabis inhibits the formation of saliva, resulting in a dry mouth [24] and hampering the collection of OF just after cannabis exposure or smoking.

Interpretation

Reliable testing for THC in OF faces some analytical concerns and requires an efficient test system (i.e., collection device, screening procedure, or confirmation assay). Among the most important issues are: i) the potential environmental contamination of the collection devices, ii) the stability of THC and its absorption to the polystyrene surfaces of collection devices, iii) the variability in the design of collection devices, and iv) the potential for false-positive test results following passive exposure if low THC concentrations are measured [14; 17; 30; 57; 64].

To bypass these issues, other possible markers have been suggested for detecting active smoking and differentiating it from passive exposure: THC-COOH, THC-A, and other minor cannabinoids. Whether it is possible to detect THC-COOH in OF after long-term passive exposure to cannabis smoke has not yet been evaluated. Consequently, Cone et al. [9] suggested measuring THC-COOH in OF in order to differentiate active cannabis use from passive exposure as no THC-COOH concentrations were detected in non-smoker OF

specimens under their three session conditions. Moreover, THC-COOH has never been detected in either cannabis plants or the smoke from cannabis joints. Therefore, THC-COOH is the best-known marker of active cannabis consumption in OF, although the concentration cut-off selected (50 pg/mL) has a significant influence on how frequently it is detected compared to THC [65]. THC-A was also suggested as a marker because most THC/ cannabidiol-based medicines do not contain it. Its presence in OF is therefore probably due to its incomplete decarboxylation [66]. It could also be the result of direct contact between the plant material in the cannabis cigarette and the mouth. It should not be detectable in passive smokers. Lastly, Anizan et al. [67] proposed some minor cannabinoids, the cannabidiol (CBD), and the cannabinol (CBN) as markers of recent cannabis consumption. However, they were only detected when a single brand of cannabis cigarettes was tested, containing no tobacco and a specified proportion of THC and CBD. In addition, the presence of CBD could also be related to the therapeutic administration of a variety of medicinal cannabis [68]. THC, THC-COOH, and THC-A thus remain the main compounds that should be monitored in OF in order to distinguish active exposure from passive exposure to cannabis. A particular carefulness is nonetheless required if blood is present in OF (e.g., in case of bleeding gums) as it can noticeably increase cannabinoid concentrations [69; 70]. Consequently, determination of several cannabinoids may help to interpret concentration results in OF.

The advantage of OF testing over urine testing is that the presence of THC in OF suggests recent exposure. A fraction of the THC retained in the oral cavity may be passively absorbed into the bloodstream through the mucosa, enhancing THC concentrations in blood [17]. Consequently, OF is probably not the most appropriate matrix to demonstrate or evaluate the extent of passive exposure to cannabis smoke.

Hair

Hair samples offer some advantages over other matrices: collection is non-invasive and less intrusive than urine or blood, and can be stored at room temperature. Sampling limitations include baldness or short hair [25]. The presence of cannabinoids in hair, especially THC, provides information on repeated or chronic exposure [25; 64].

Analysis

To quantify cannabinoids in hair, analytical methods require to detect femto- to picogram residue ranges per milligram of hair [30]. From the end of 1990's, the main analytical methods used to analyze THC in hair was via GC-MS. Recently, THC-A can also be measured in hair, and as for THC-COOH a negative ion chemical ionization mass spectrometry, GC-NCI–MS or GC-NCI–MS/MS is needed [4]. A new approach has also been developed by Duvivier et al. [71] and consists of a longitudinal scanning of THC in hair using direct analysis in real time (DART) ambient ionization orbitrap MS. This method allows to perform a pre-screening test of THC in hair without sample preparation.

Concentration ranges

THC is the most common compound measured in hair, followed by CBD and CBN, and THC-COOH [4; 30]. THC and THC-COOH have very low incorporation rates into hair [72]. THC's presence may be explained by its weak bond to melanin, whereas THC-COOH's absence may be due to the acidic nature of hair [4; 25].

In the study by Moosmann et al. [73], the highest concentrations in hair for THC, THC-A, and CBN were observed at the end of the passive exposure period, i.e., after an exposure of one joint every weekday for three weeks (17.3 pg/mg for THC-A, 803 pg/mg for THC, and 307 pg/mg for CBN; Table 2). THC-COOH in urine was measured twice a week during the exposure period in order to control abstinence in volunteers. Hair analyses for THC-A and THC-COOH could be considered as useful complementary procedures for monitoring active and passive exposure using other matrices. The only exposure to cannabis that the detection of plant cannabinoids in hair (THC-A, CBD, THC-V) excludes is a single oral administration of a therapeutic dose of synthetic THC (dronabinol). THCV (in hair) and its metabolite THCV-COOH (in urine) could be useful markers to differentiate dronabinol intake from exposure to cannabis smoke [74].

Contamination

With regard to exposure to passive smoke, environmental contamination may cause misinterpretations and false-positive test results [75]. Contamination is mainly due to cannabis smoke, to direct contact with contaminated surfaces, without ruling out the possibility of an exposure to urine aerosols present in contaminated public lavatories and public areas (Figure 1). To reduce this potential for contamination and prevent false-positive results, it is advisable to

perform extensive hair washing procedures before analyses, measure both THC and THC-COOH, select appropriate cut-offs, and analyze the wash-off residue [25; 76; 77]. Because marijuana smoke does not contain THC-COOH but THC, the detection of even trace concentrations of THC-COOH might well indicate active use, whereas its absence does not preclude cannabis consumption at all [4; 25; 77]. Some recent studies have also recommended measuring THC-A in hair, in order to distinguish passive exposure from active cannabis use [4; 73; 78]. THC-A in hair originates exclusively from external contamination, mainly by direct transfer after manipulation of cannabis plant material, or through smoke condensing on the hair shaft. In cannabis smoke, only small amounts of THC-A are present resulting from incomplete decarboxylation; this suggests a more important source of contamination than the deposition of sidestream smoke. Consequently, THC-A is monitored as a biomarker of environmental contamination.

Interpretation

Interpreting an analysis of the hair matrix is also quite complex. At least six mechanisms are thought to be involved in the incorporation of cannabinoids into the hair's shaft and root. For the hair shaft, cannabinoids may be incorporated from a) environmental exposure to cannabis smoke, b) direct contact with a contaminated object or body part, c) exposure to sweat or d) sebum, or e) diffusion from the skin. For the hair's root, cannabinoids could be incorporated from the bloodstream during hair development [25; 30; 64]. Mechanisms a) and b) are related to external contamination, whereas the other mechanisms require active biological processes. If one supposes that cannabinoids are almost exclusively incorporated through the bloodstream, a sequential analysis of hair segments would allow assessing past periods of drug consumption or abstinence. However, it is currently assumed that the THC (like all the other plant cannabinoids and CBN) measured in hair is almost exclusively the result of external contamination and not from incorporation through the bloodstream. This has been evidenced by the distribution of THC along the entire hair shaft after passive exposure to marijuana smoke, despite intensive hair washing. Therefore, to retrospectively assess cannabis use, a segmental hair analysis is not scientifically founded. Washing procedures are equally ineffective for removing other hair contaminants, and similar observations have been noticed for THC metabolites. Because THC-COOH concentrations decreased from the proximal to the distal segments of the hair shaft, Auwärter et al. [4] suggested that metabolites are transferred to it via sebum by diffusion along and inside the shaft. Moreover, results from segmental analyses evidenced barely any

correlation between self-reported past periods of consumption and changes in THC-COOH levels in correspondingly aged hair segments [79].

Other important elements to consider in the interpretation of results are hair sampling sites and the hair's condition. In their study involving the chronic marijuana smoke exposure of three volunteers using a breathing apparatus to avoid smoke inhalation, Moosmann et al. [73] observed that the degree of contamination depended on hair length and on the sampling site on the skull. The posterior vertex (the back of the top) was the most contaminated area of the head. This is also the sampling site that several scientific societies recommend for routine forensic investigations. The study also noted that short hairs were less contaminated than long hairs due to the more effective removal of hair sebum from the skin surface in daily washing; hair sebum stores and transfers cannabinoids along the hair shaft [73]. Another explanation could be that short hair is "younger" and its external cuticle is less porous and more impervious than longer, older distal hair. The diffusion of external contamination into the cortex and medulla of young hair is far less important. Likewise, physically or chemically damaged hairs are more affected by external contamination than healthy hairs. They thus present a higher risk of testing positive, even after a single exposure to cannabis smoke. The detection of damaged hair, as suggested by Hill et al. [80], is thus an opportunity to avoid a cosmetic bias.

In summary, cannabinoid measurements in hair remain useful as a complementary matrix. A lack of cannabinoid detection at the recommended cut-off levels suggests abstinence or very occasional consumption. If THC is detected in hair, then it undoubtedly originates from contamination, however, that does not mean that this contamination was not initiated by the individual tested when smoking cannabis or preparing marijuana cigarettes. Contamination by nearby smokers is also possible, especially in a heavily contaminated environment. To confirm an external contamination, THC-A may be quantified. An extensive washing procedure should also be performed before hair analysis and wash residues should be analyzed when necessary.

Sweat and sebum

As with OF and hair, sweat is a non-invasive means of collecting biological specimens. Based on drug pharmacokinetics, sweat has been reported to be a suitable alternative matrix for monitoring recent drug use or external contamination. Its fat properties also allows the transfer of cannabinoids to the hair shaft [30].

Analysis

Sweat can be sampled by dedicated sweat patches (e.g., Pharmchek® absorption pads, Fort Worth, Texas, USA); however, depending on the sampling site, sweat is generally mixed with sebum, forming an emulsion [81]. This emulsion is sampled using special cotton swabs; sebum is more easily collected using special lipid-sensitive tapes (e.g., Sebutape®, Cuderm Corp, Dallas, USA or Sebufix@, C+K Electronic, Cologne, Germany). However, only the drug fraction not bonded to proteins can diffuse from plasma to sweat through lipid membranes [81]. Nonetheless, the drug fraction excreted in sweat by passive diffusion is sufficient to be analyzed using standard mass spectrometry methods. It remains that patch analysis requires sensitive analytical methods (in the ng/patch range).

Concentration ranges, contamination, and interpretation

It appears that only THC can be measured in sweat; THC-COOH being never detected, or in extremely low concentrations [82]. Because of its neutral properties, THC diffusion is suspected to be slow [81]. Therefore, THC is monitored by using a patch sampling method from a specific time point in order to detect recent cannabis use. The interpretation of results is complicated by a potential re-absorption of THC by the skin, the adsorption of THC onto the patch-collection device, and environmental contamination [30; 81]. No THC should be detected in sweat in cases of passive exposure, as no THC was measured in recreational cannabis users, who should have similar or higher exposure levels to cannabis than passive smokers [81]. Sebum, however, could be a vector of THC-COOH by transferring it from bodily stores and fluids to hair shafts [83].

Analytical limitations

In addition to a potential contamination, analytical issues may also be influential, and some analytical methods produce artifacts. Typical examples are the hydrolysis of conjugates, the conversion of THC-A into THC (under alkaline conditions or upon heating), the isomerization of delta-9-THC into delta-8-THC (under acid conditions), or the possible conversion of CBD into THC (under acid conditions). A further problem is that results are not always reported as levels of free cannabinoids or as total cannabinoids (the sum of free and conjugated molecules), nor are levels normalized to the creatinine concentration for urine samples. All these issues complicate the interpretation of results and make comparisons impossible.

Conclusion

From the studies identified on passive exposure to cannabis of non-user subjects in controlled conditions, specific biomarkers of passive cannabis exposure were identified in urine, blood, oral fluid, hair, and sebum. It results that urine is an appropriate matrix to monitor passive exposure, especially after normalization to creatinine levels. Important concentrations of THC-COOH can be measured; however, concentrations exceeding the usual thresholds of positivity require very extreme environmental conditions that cannot be ignored. Likewise, low blood concentrations of THC and THC-COOH could be determined for a few hours following acute exposure to heavy cannabis smoke. Measuring THC-COOH in blood is also a good alternative for appraising passive exposure as it is detectable for a much longer time than THC and it accumulates to high levels during chronic use. THC is detected in oral fluid after active consumption or passive exposure. However, THC-COOH which is found only after voluntary consumption can be considered as a reliable marker of active use. If the skin and the sebum are easily contaminated by cannabis smoke, the skin layer limits the passage of cannabinoids into the bloodstream. However, cannabinoids can be incorporated from sebum into the hair shaft by diffusion. The presence of THC and THC-A in hair indicates that the subjects live or work in an environment contaminated with cannabis. The detection of THC-COOH argues for regular active use of cannabis. In contrast, a long period of abstinence can be strongly suspected if no cannabinoids are detected in the hair shaft.

From a forensic outlook, in order to demonstrate conclusively that the cannabinoids measured from different parts of the body are the result of active consumption, the expert should be able to positively exclude different sources of potential contamination, such as:

- Self and cross-contamination from cannabis users: heavily contaminated hands and fingers, contaminated surfaces or cannabis smoke can contaminate a non-smoker's body as a result of poor personal hygiene and their environment;
- Extreme exposure to cannabis smoke: this may result in subjective and pharmacological effects on physiology, behavior, cognitive capabilities, and psychomotor performances, and these effects may sometimes be similar to those experienced by active smokers, especially when the potency of cannabis is high;

- Secondhand smoke contamination: this should also be considered, especially in cases of extreme exposure conditions. Thirdhand and secondhand contaminations are usually difficult to discern and may be combined and cumulated.

As a concluding remark, the experts should clearly inform persons who have to demonstrate prolonged abstinence from cannabis to avoid heavily smoky and unventilated areas. Moreover, such persons must not handle or come into contact with objects and surfaces containing or contaminated with cannabis material.

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Conflict of interest

All authors declare no conflict of interest.

Research involving Human Participants and/or Animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

As this review does not contain any studies with human participants performed by any of the authors, no informed consent was needed.

Fig 1. Creative Commons License Deed

Figure 1 is adapted from a figure in the Moosmann et al. [84] article entitled “Finding cannabinoids in hair does not prove cannabis consumption”. The original version is licensed under a Creative Commons Attribution 4.0 International License, a copy of which can be found at http://creativecommons.org/licenses/by/4.0/. The figure was modified as follows, after discussion with the original authors. An additional arrow indicates possible contamination of the hair by urinary THC-COOH. The transfer of THC is described differently, with references to secondhand and thirdhand smoke, and to mainstream and sidestream smoke. Secondhand cannabis smoke is a mixture of the smoke from a smoldering marijuana cigarette (sidestream smoke) and the smoke exhaled by a smoker (mainstream smoke). The cannabis smoke condensate left on a variety of indoor surfaces, which is also a potential source of environmental contamination, is known as thirdhand smoke.

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Table 1 Cut-offs proposed by different scholarly societies according to biological matrices and analytes

Society	Biological matrix	Initial test analyte (immunoassay)	Initial test cut-off concentration	Confirmatory test analyte	Confirmatory test cut-off concentration
SAMHSA 2008[a,b]	urine	Marijuana metabolites	50 ng/mL	THC-COOH total	15 ng/mL
GTFCh[c]	urine			THC-COOH total	10 ng/mL
EWDTS 2015[d]	urine	Marijuana metabolites	50 ng/mL	THC-COOH	15 ng/mL
GTFCh[c]	serum/plasma			THC free	1 ng/mL
GTFCh[c]	serum/plasma			THC-COOH free	10 ng/mL
SFTA[e]	whole blood			THC	0.5 ng/mL
SFTA[e]	whole blood			THC-COOH	2.0 ng/mL
GTFCh[c]	hair			THC	0.02 ng/mg
SoHT[f]	hair	THC	0.1 ng/mg	THC	0.1 ng/mg
SoHT[f]	hair			THC-COOH	0.2 pg/mg
EWDTS 2015[d]	hair	THC	0.05 ng/mg	THC	0.05 ng/mg
EWDTS 2015[d]	hair			THC-COOH	0.2 pg/mg
SAMHSA 2004[g]	hair	Marijuana metabolites	1 pg/mg	THC-COOH	0.05 pg/mg
SAMHSA 2004[g]	oral fluid/saliva	THC	4 ng/mL	THC	2 ng/mL
SAMHSA 2015 (proposal)[h]	oral fluid/saliva	THC	2-3 ng/mL	THC	1 ng/mL
SAMHSA 2015 (proposal)[h]	oral fluid/saliva			THC-COOH	50 pg/mL
EWDTS 2015[d]	oral fluid/saliva	THC	10 ng/mL	THC	2 ng/mL
SAMHSA 2004[g]	sweat patch	Marijuana metabolites	4 ng/patch	THC	1 ng/patch

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Table 2 **Summary of the analytical methods used, the cut-offs, and the maximum cannabinoid body fluid concentrations reported in studies on the passive exposure to cannabis**

Reference	Matrix	Analytes	Analytical method[a]	LOD of analytical method (ng/mL)	Cut-off (ng/mL)	Exposure time (min)	THC dose (mg)	C_{max} (ng/mL) (time after exposure)[b]
[21] Study I	Urine	Cannabinoids	EMIT	n.a.	20	60	46	< cut-off
Study II	Urine	Cannabinoids	EMIT	n.a.	20		52	< cut-off
Study III	Urine	Cannabinoids	EMIT	n.a.	20		105	< cut-off
[13]	Plasma	THC	RIA	n.a.	3	60	105	2.2 (5 min)
		THC	GC/MS	0.2	n.a.			4 (5 min)
		11-OH-THC	GC/MS	0.5	n.a.			Negative
		THC-COOH	GC/MS	0.1	n.a.			< 0.1
[11]	Urine	THC-COOH + its ester glucuronide	RIA	0.32 ± 0.23 (mean ± SD)	2	180	103	4.7 (90 min)
	Plasma	THC-COOH + its ester glucuronide	RIA	1.8 ± 2.5 (mean ± SD)	2			0
[15] Study I	Urine	Cannabinoids	EMIT	n.a.	20	30	90	Negative
		Cannabinoids	RIA	n.a.	13			NA
	Blood	Cannabinoids	RIA	n.a.	13			< cut-off
		THC	GC/MS	0.5	0.5			1.3 – 6.3 (immediately)
[15] Study II	Urine	Cannabinoids	EMIT	n.a.	20	30	90	< cut-off
		Cannabinoids	RIA	n.a.	13			21 (immediately)
	Blood	Cannabinoids	RIA	n.a.	13			20 (immediately)
		THC	GC/MS	0.5	0.5			1.3 – 6.3 (immediately
[5-7]	Urine	Cannabinoids	EMIT	n.a.	20	60 (6 consecutive days)	393.4 (average weight of cigarettes: 877±20 mg)	Positive urines after 1st exposure session for 6 subjects (n = 16 cigs)
		Cannabinoids	RIA	5	10			≈75 days 2–6 (n = 16 cigs)
								≈14.1 days 2–6 (n = 4 cigs)
		THC-COOH	GC/MS	2	5			30 at day 4 (n = 16 cigs)
								almost 0 (n = 4 cigs)
	Plasma	THC	RIA	1.5	2.5			7.3 at day8 (n = 16 cigs)
								2.5 at day6 (n = 4 cigs)

Reference	Matrix	Analytes	Analytical method[a]	LOD of analytical method (ng/mL)	Cut-off (ng/mL)	Exposure time (min)	THC dose (mg)	C_{max} (ng/mL) (time after exposure)[b]
[16]	Urine	Cannabinoids	RIA	n.a.	12	60	108	< 6
[20] Study I	Urine	THC	EMIT	n.a.	20	60	45	8.5 (120 min)
		THC	ADx	n.a.	25			5.7 (44 h)
Study II	Urine	THC	EMIT	n.a.	20	30	30	9.6 (7h)
		THC	ADx	n.a.	25			21.3 (7 h)
[17]	Urine	THC-COOH	EIA	3	50	240	n.a.	3.2 (24 h)
		THC-COOH	GC/MS/MS	5	15			Negative
	Oral fluid	THC	EIA	0.5	1			Positive (60 min)
		THC	GC/MS/MS	0.2l	0.5			Negative
[18]	Urine	THC-COOH	EIA	n.a.	50	240	n.a.	Negative
		THC-COOH	GC/MS/MS	1	1			0.9 (5 min)
	Oral fluid	THC	EIA	n.a.	3			Positive (20 min after start of exposure)
		THC	GC/MS/MS	0.3	0.75			13.4 (20 min after start of exposure)
[19] Study I	Urine	THC-COOH	EIA	n.a.	50	60	158	Negative
		THC-COOH	GC/MS/MS	1	1			8.4 (6h)
	Oral fluid	THC	EIA	n.a.	3			Positive (15 min)
		THC	GC/MS/MS	0.3	0.75			5.3 (immediately)
Study II	Urine	THC-COOH	EIA	n.a.	50	60	333	Negative
		THC-COOH	GC/MS/MS	1	1			8.9 (6h)
	Oral fluid	THC	EIA	n.a.	3			Negative
		THC	GC/MS/MS	0.3	0.75			1 (90 min)
[22]	Urine	THC-COOH	ELISA	n.a.	0.6	180	n.a.	0.8 (30 min)
		Cannabinoids	EIA	1.3	25			9.8 (3h)
		THC-COOH	GC/MS	0.4	0.6			2.3 (11h)
	Hydrolyzed urine	THC-COOH	GC/MS	0.7	1			3.8 (11h)
	Serum	Cannabinoids	ELISA	1	3			3 (30 min)
		THC	GC/MS	0.1	0.5			0.5 (1.5 h after the start of exposure)
[23]	Urine	Cannabinoids	EIA	n.a	25	180	8 g of hashish and marijuana were burnt	Negative
		THC-COOH	GC/MS	1	8			3.6 (3h)
	Serum	Cannabinoids	EIA	n.a	3			2/8 volunteers positive (30 min)
		THC	GC/MS	0.1	1			Negative

Reference	Matrix	Analytes	Analytical method[a]	LOD of analytical method (ng/mL)	Cut-off (ng/mL)	Exposure time (min)	THC dose (mg)	C_{max} (ng/mL) (time after exposure)[b]
[14] Location 1	Oral fluid	11-OH-THC	GC/MS	0.1	1	180	n.a.	Negative
		THC-COOH	GC/MS	1	8			≈ LOD (0.5-3 h)
		THC	ELISA	2	4			Positive over the 20 min to 3h exposure
		THC	GC/MS	0.5	0.5			4.3 (2h after the start of exposure)
		Cannabinol	GC/MS	0.5	0.5			0.7 (2h after the start of exposure)
		Cannabidiol	GC/MS	1	1			Negative
		THC-COOH	Two-dimensional GC-GC/MS	0.002	> 0.002			Negative
Location 2	Oral fluid	THC	ELISA	2	4	180	n.a.	Positive (immediately)
		THC	GC/MS	0.5	0.5			7.5 (immediately)
		Cannabinol	GC/MS	0.5	0.5			0.9 (immediately)
		Cannabidiol	GC/MS	1	1			Negative
		THC-COOH	Two-dimensional GC-GC/MS	0.002	> 0.002			Negative
[8; 9] Session I	Urine	Cannabinoids	EMIT	n.a.	50	60	5.3%	Negative
		THC	EMIT	n.a.	20			85.6 (4-6h)
		THC-COOH	GC/MS	0.75	15			22.4 (4-6h)
	Whole blood	THC	LC/MS/MS	0.1	0.5			1.4 (15 min)
		THC-COOH (free)	LC/MS/MS	0.1	0.5			1.2 (15 min)
		11-OH-THC	LC/MS/MS	0.1	0.5			Negative
	Oral Fluid	Cannabinoids	ELISA	2	4			Positive (15 min)
		THC	LC/MS/MS	0.1	1			34 (15 min)
		THC-COOH (total)	LC/MS/MS	0.02	0.02			Negative
Session II	Urine	Cannabinoids	EMIT	n.a.	50	60	11.3%	Negative
		THC	EMIT	n.a.	20			140 (4h)
		THC-COOH	GC/MS	0.75	15			33.3 (4h)
	Whole blood	THC	LC/MS/MS	0.1	0.5			3.1 (15 min)
		THC-COOH (free)	LC/MS/MS	0.1	0.5			2.5 (15 min)
		11-OH-THC	LC/MS/MS	0.1	0.5			Negative
	Oral Fluid	Cannabinoids	ELISA	2	4			Positive (15 min)

Reference		Matrix	Analytes	Analytical method[a]	LOD of analytical method (ng/mL)	Cut-off (ng/mL)	Exposure time (min)	THC dose (mg)	C_{max} (ng/mL) (time after exposure)[b]
			THC	LC/MS/MS	0.1	1			81.5 (15 min)
			THC-COOH (total)	LC/MS/MS	0.02	0.02			Negative
	Session III	Urine	Cannabinoids	EMIT	n.a.	50	60	11.3%	Negative
			THC	EMIT	n.a.	20			55.2 (4-6h)
			THC-COOH	GC/MS	0.75	15			8.61 (4h)
		Whole blood	THC	LC/MS/MS	0.1	0.5			0.5 (15 min)
			THC-COOH (free)	LC/MS/MS	0.1	0.5			0.2 (15 min)
			11-OH-THC	LC/MS/MS	0.1	0.5			Negative
		Oral Fluid	Cannabinoids	ELISA	2	4			Positive (15 min)
			THC	LC/MS/MS	0.1	1			16.9 (15 min)
			THC-COOH (total)	LC/MS/MS	0.02	0.02			Negative
[73]		Urine	THC-COOH	EMIT	n.a.	10		500 mg of marijuana containing 9.2% THC	Negative
		Hair	THC-A	LC/MS/MS	2.5 pg/mg	2.5 pg/mg	15-20 min (one joint) every weekday for 3 weeks		17.3 pg/mg (end of exposure period)
			THC	LC/MS/MS	20 pg/mg	20 pg/mg			803 pg/mg (end of exposure period)
			Cannabinol	LC/MS/MS	20 pg/mg	20 pg/mg			307 pg/mg (end of exposure period)

EIA: Cannabinoids Intercept MICRO-PLATE Enzyme Immunoassay; ELISA: Enzyme linked immunosorbent assay; EMIT: Enzyme multiplied immunoassay technique; GC/MS: Gas chromatography–mass spectrometry; GC/MS/MS: Gas chromatography–tandem mass spectrometry; LC/MS/MS: liquid chromatography coupled with tandem mass spectrometry; n.a.: non available; RIA: Radioimmunoassay;

[a] Analytical methods reported to be used in the referent study on passive exposure to cannabis.
[b] The maximal concentration obtained in calculating a mean between the non-smoker values at a specific time.

Figure captions

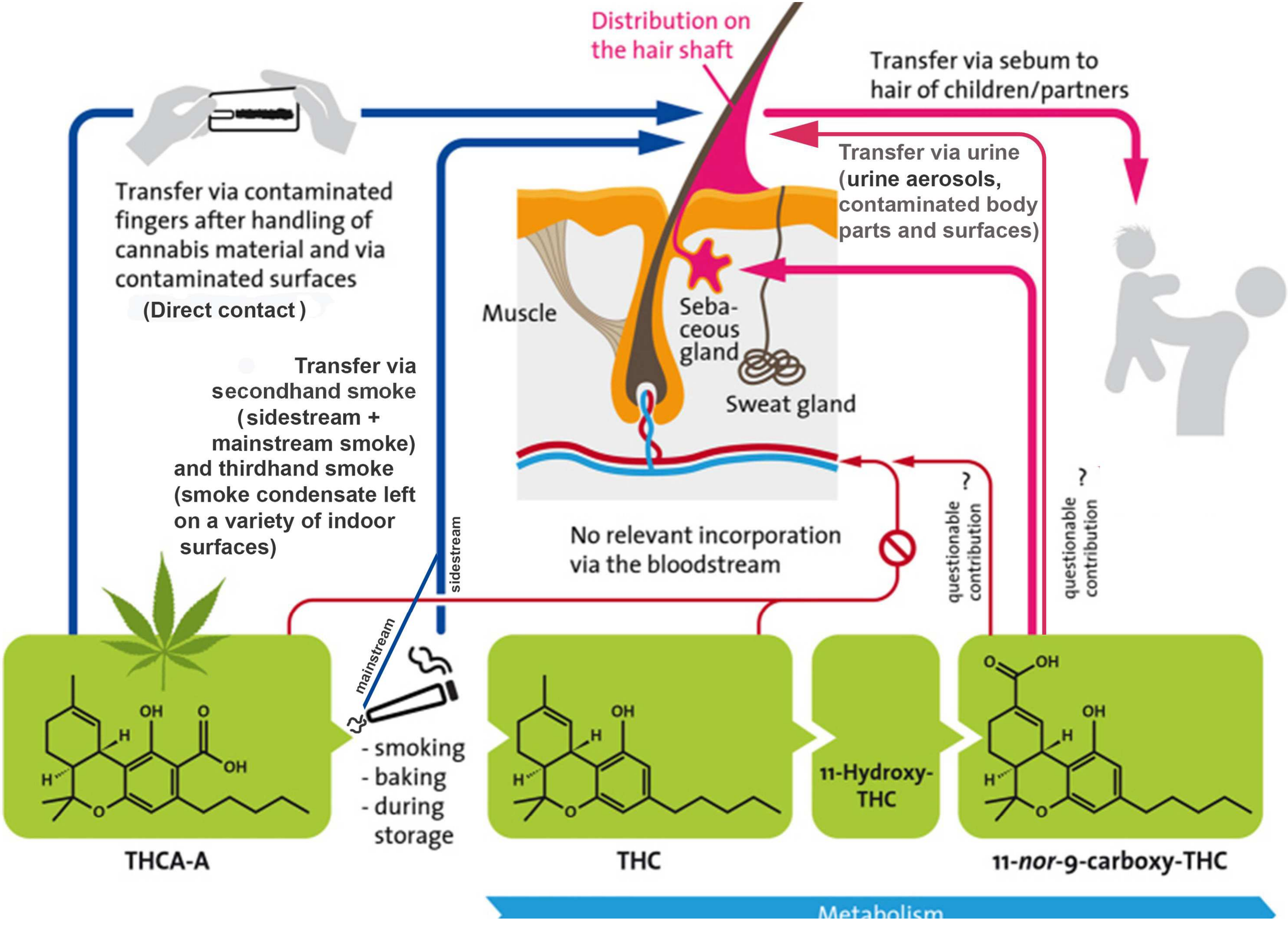
Fig. 1 Potential external cross-contamination from cannabis use and incorporation pathways of cannabinoids into human hair. Incorporation of Δ9-tetrahydrocannabinolic acid A (THCA-A), Δ9-tetrahydrocannabinol (THC), and its metabolite, 11-nor-9-carboxy-THC (THC-COOH), into human hair can occur in the hair's root via the bloodstream, by diffusion from sweat or sebum into the hair shaft, or by external contamination (e.g., contaminated fingers or sidestream smoke). The main metabolic pathway for THC and the molecular structures of its analytes are also given. Reprinted and adapted with the permission by "Nature Publishing Group" and "Creative Commons", "Finding cannabinoids in hair does not prove cannabis consumption, 2015, p. 2, Figure 1" [84].

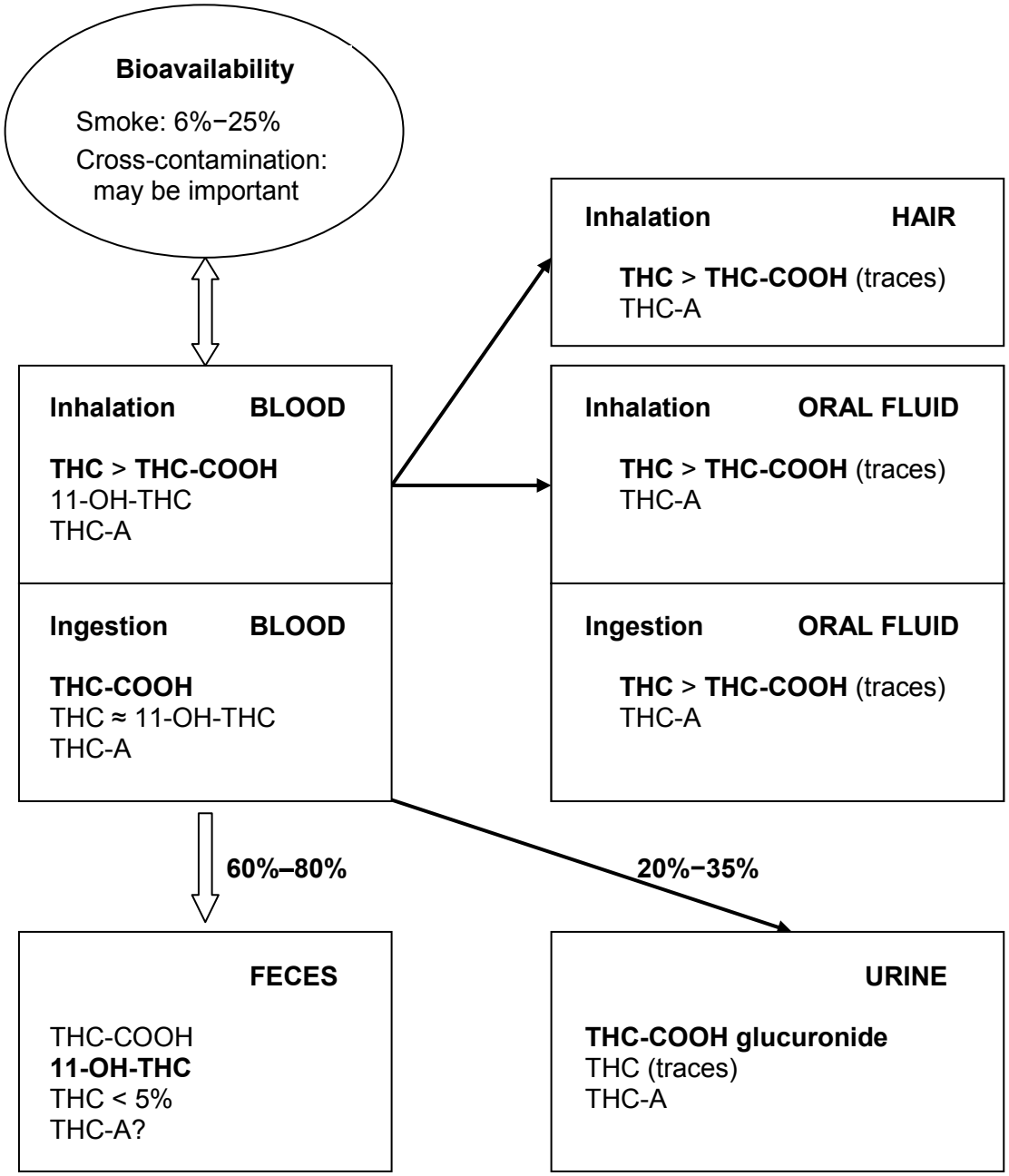
Fig. 2 Bioavailability and elimination of cannabinoids in different matrices following passive exposure to cannabis smoke. Cannabinoids in bold type denote markers considered suitable for differentiating passive from active exposure. Reprinted and adapted with permission by "Science Direct" and "Elsevier Science", "Mise en evidence des cannabinoïdes : quel milieu biologique ? [Which biological matrix for cannabis testing?], 2006, p. 186, Figure 5" [64].

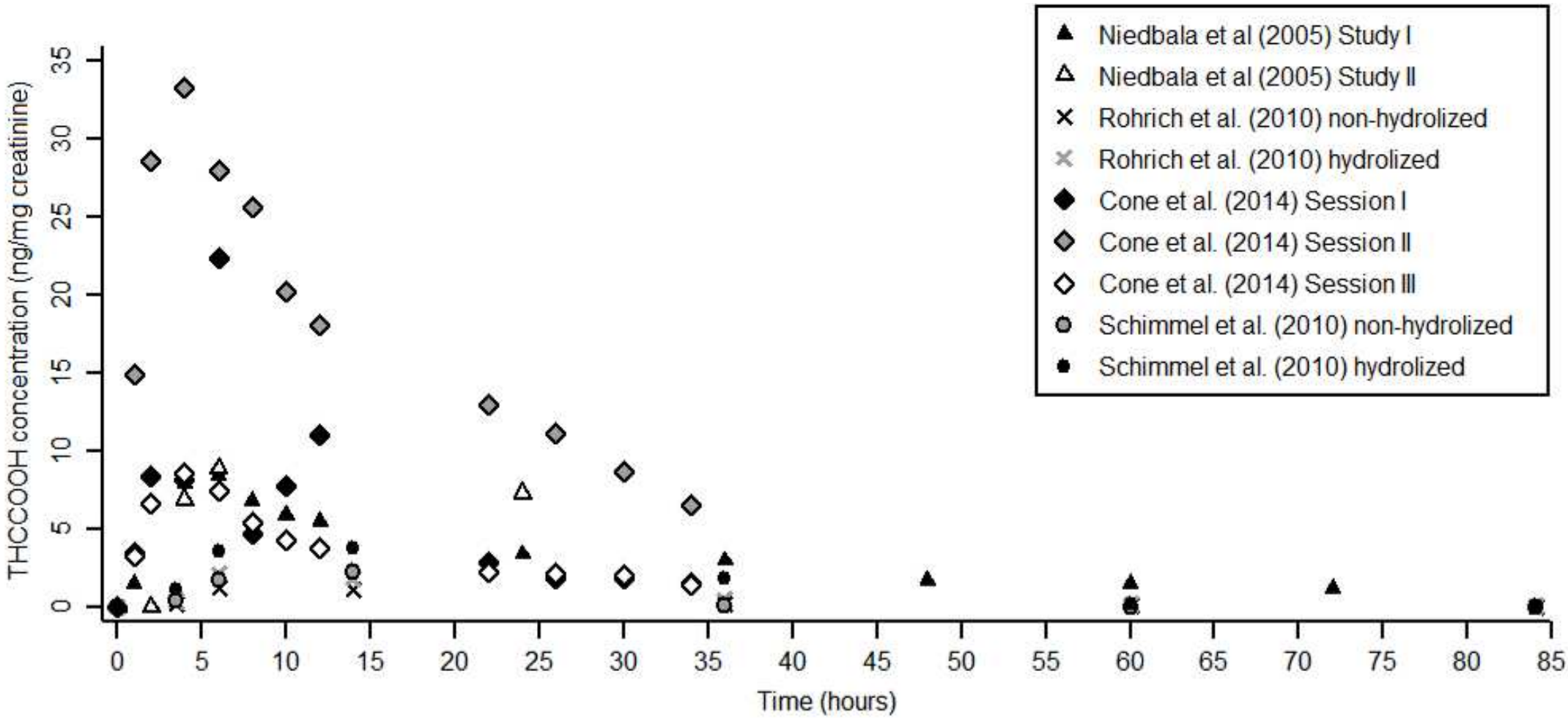
Fig. 3 THC-COOH concentration time profiles in urine reported in several studies on passive exposure to cannabis smoke. Profiles are adjusted for creatinine concentrations. Each study is identified by a differently-shaped dot, with different colors denoting different sessions.

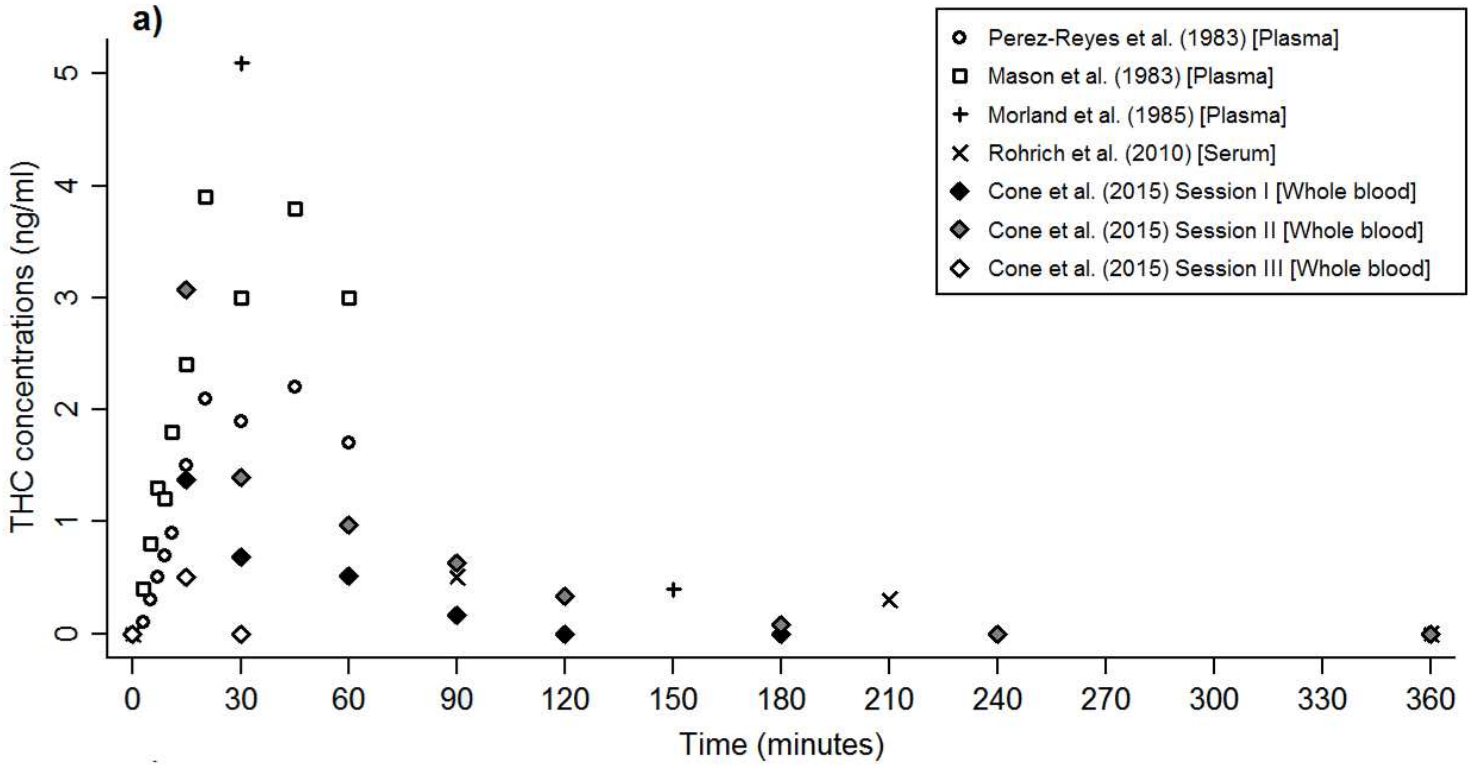
Fig. 4 Concentration time profiles of a) THC in plasma or b) THC-COOH in serum and whole blood reported in several studies on passive exposure to cannabis smoke. Each study is identified by a differently-shaped dot, with different colors denoting different sessions.

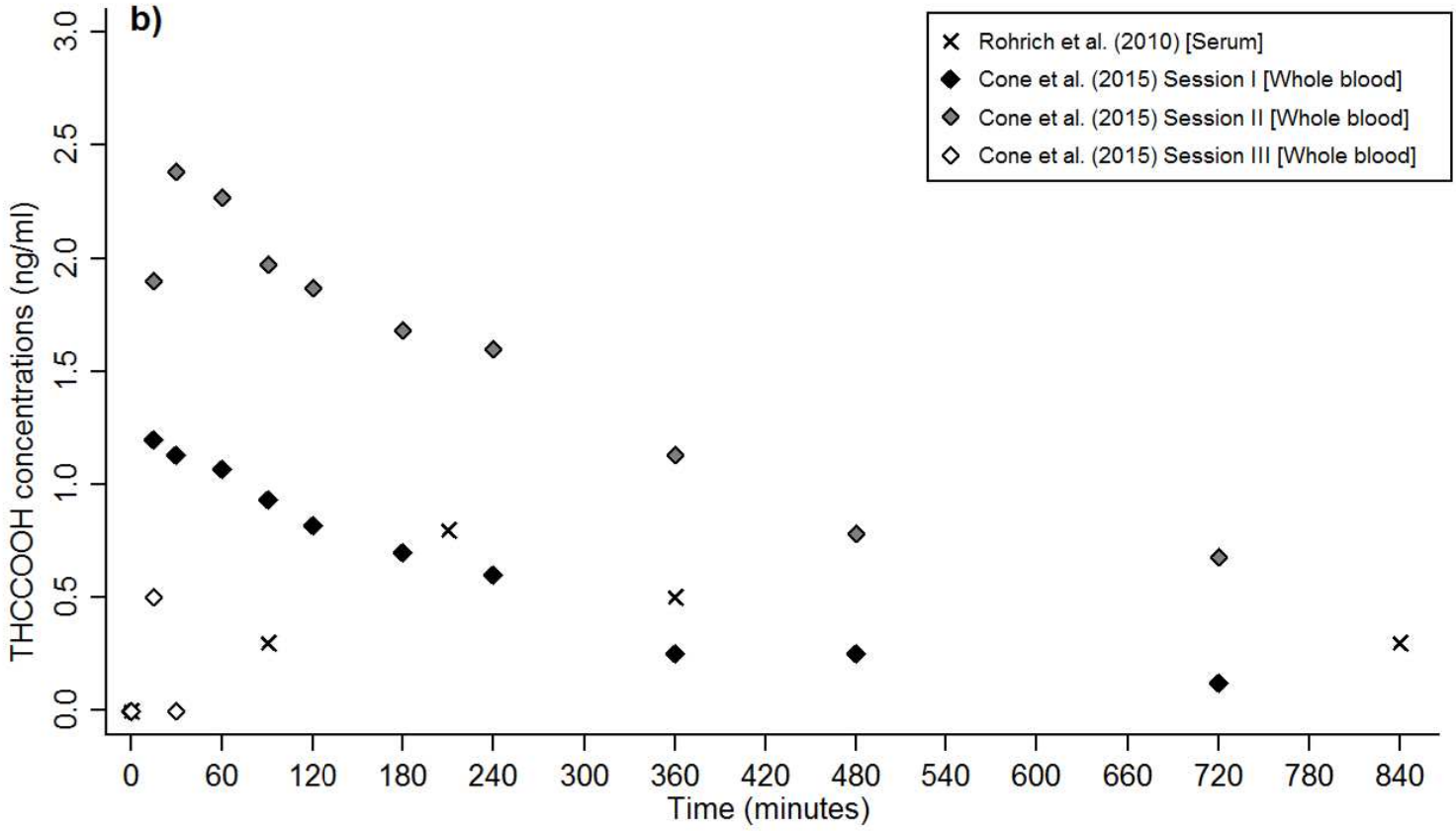
Fig. 5 THC concentration time profiles in oral fluid reported in several studies on passive exposure to cannabis smoke. Each study is identified by a differently-shaped dot, with different colors denoting different sessions.

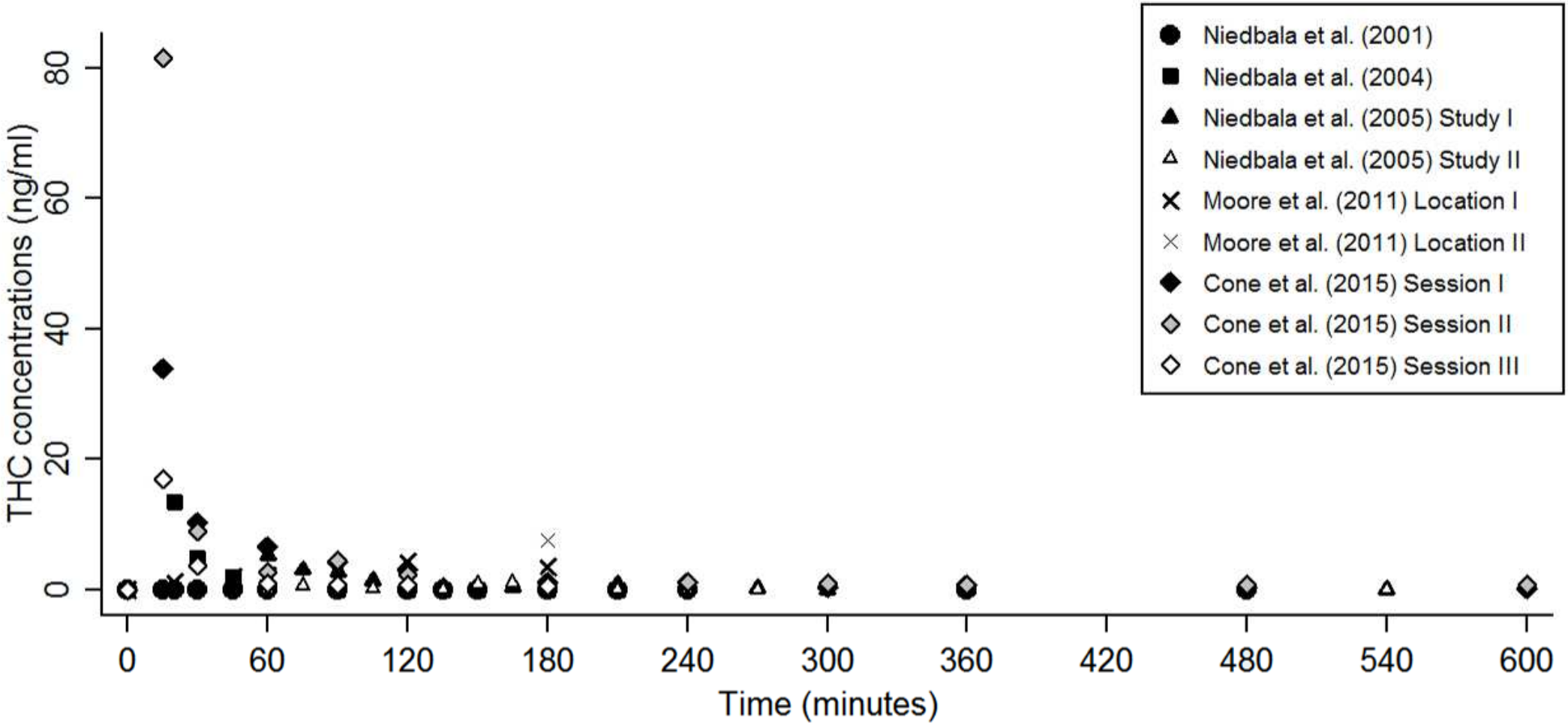

Distribution on the hair shaft
Transfer via sebum to hair of children/partners
Transfer via urine (urine aerosols, contaminated body parts and surfaces)
Transfer via contaminated fingers after handling of cannabis material and via contaminated surfaces (Direct contact)
Transfer via secondhand smoke (sidestream + mainstream smoke) and thirdhand smoke (smoke condensate left on a variety of indoor surfaces)
Muscle
Seba-ceous gland
Sweat gland
sidestream
mainstream
No relevant incorporation via the bloodstream
questionable contribution
questionable contribution
- smoking
- baking
- during storage
THCA-A
THC
11-Hydroxy-THC
11-nor-9-carboxy-THC
Metabolism

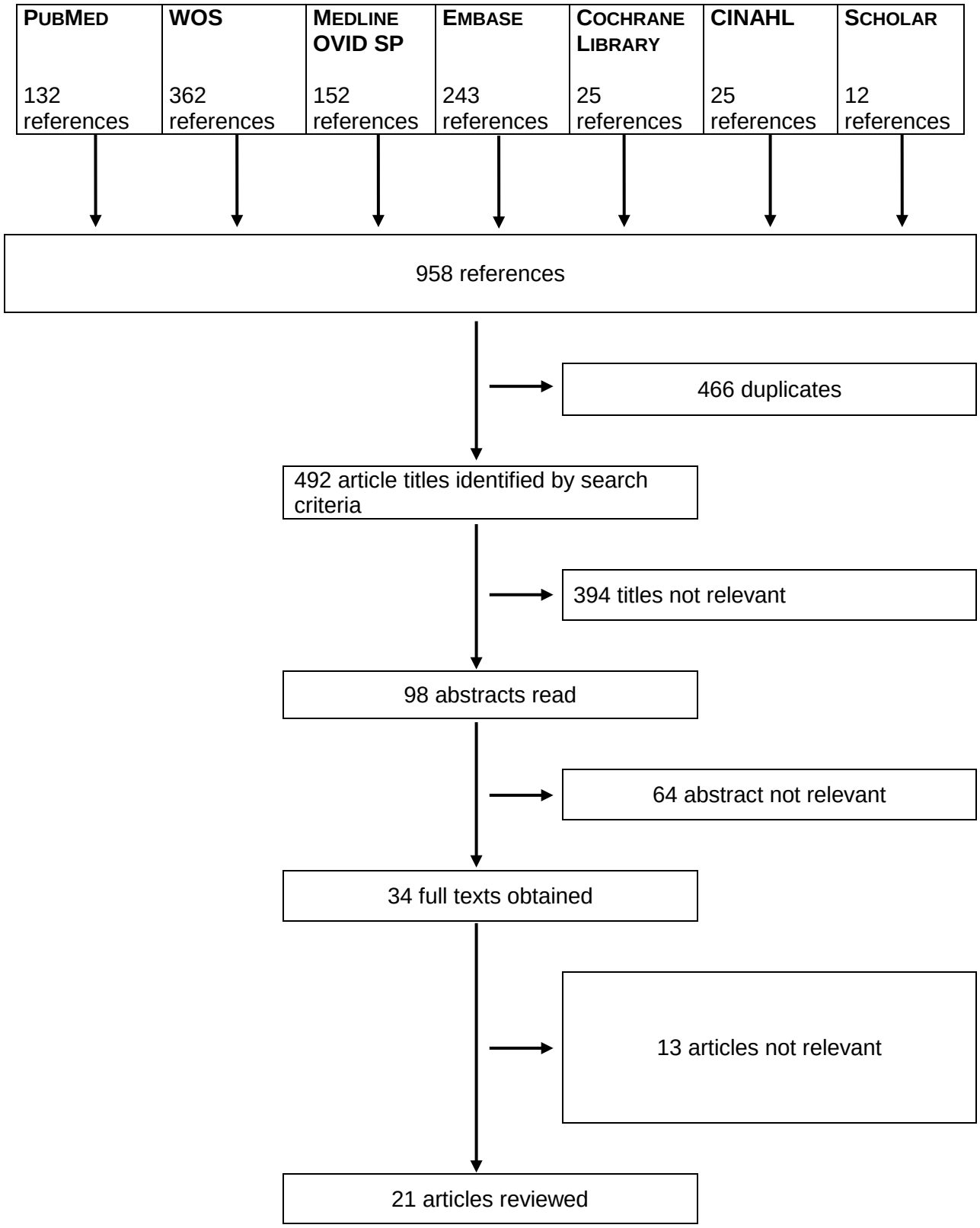

Bioavailability
Smoke: 6%−25%
Cross-contamination: may be important
Inhalation BLOOD
THC > THC-COOH
11-OH-THC
THC-A
Ingestion BLOOD
THC-COOH
THC ≈ 11-OH-THC
THC-A
Inhalation HAIR
THC > THC-COOH (traces)
THC-A
Inhalation ORAL FLUID
THC > THC-COOH (traces)
THC-A
Ingestion ORAL FLUID
THC > THC-COOH (traces)
THC-A
60%–80%
20%−35%
FECES
THC-COOH
11-OH-THC
THC < 5%
THC-A?
URINE
THC-COOH glucuronide
THC (traces)
THC-A


THCCOOH concentration (ng/mg creatinine)
0
5
10
15
20
25
30
35
Time (hours)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
Niedbala et al (2005) Study I
Niedbala et al (2005) Study II
Rohrich et al. (2010) non-hydrolized
Rohrich et al. (2010) hydrolized
Cone et al. (2014) Session I
Cone et al. (2014) Session II
Cone et al. (2014) Session III
Schimmel et al. (2010) non-hydrolized
Schimmel et al. (2010) hydrolized


a)
Perez-Reyes et al. (1983) [Plasma]
Mason et al. (1983) [Plasma]
Morland et al. (1985) [Plasma]
Rohrich et al. (2010) [Serum]
Cone et al. (2015) Session I [Whole blood]
Cone et al. (2015) Session II [Whole blood]
Cone et al. (2015) Session III [Whole blood]
THC concentrations (ng/ml)
0
1
2
3
4
5
0
30
60
90
120
150
180
210
240
270
300
330
360
Time (minutes)


b)
Rohrich et al. (2010) [Serum]
Cone et al. (2015) Session I [Whole blood]
Cone et al. (2015) Session II [Whole blood]
Cone et al. (2015) Session III [Whole blood]
THCCOOH concentrations (ng/ml)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0
60
120
180
240
300
360
420
480
540
600
660
720
780
840
Time (minutes)


THC concentrations (ng/ml)
0
20
40
60
80
0
60
120
180
240
300
360
420
480
540
600
Time (minutes)
Niedbala et al. (2001)
Niedbala et al. (2004)
Niedbala et al. (2005) Study I
Niedbala et al. (2005) Study II
Moore et al. (2011) Location I
Moore et al. (2011) Location II
Cone et al. (2015) Session I
Cone et al. (2015) Session II
Cone et al. (2015) Session III


PUBMED
132 references
WOS
362 references
MEDLINE OVID SP
152 references
EMBASE
243 references
COCHRANE LIBRARY
25 references
CINAHL
25 references
SCHOLAR
12 references
958 references
466 duplicates
492 article titles identified by search criteria
394 titles not relevant
98 abstracts read
64 abstract not relevant
34 full texts obtained
13 articles not relevant
21 articles reviewed

Non-relevant articles by title:

Articles or studies on animals, relative to infertility, preconception, pregnancy, infants, children, teen-agers, nicotine dependence, effects of cannabis use, health effects, polymorphism, human milk.

Non-relevant articles by abstract:

No human biomonitoring sampling, quantification methods only, no passive volunteers or participants, opinion.

Non-relevant articles by full texts:

No data on passive exposure (human biological matrices), no placebo volunteers (only smokers), no relevant data.

Table 1 **Summary of the analytical methods used and the cannabinoid body fluid concentrations reported in studies on the passive inhalation of cannabis**

Body fluid	Analytical method	Cut-off (ng/ml)	Substances analyzed	Sampling scenario	Total number of samples	Last sample collection	Value of last collected samples	Maximum concentration obtained after exposure[a]
Perez-Reyes et al. (1983)								
Urine (Study I)	EMIT	20	Cannabinoids	All urines collected separately for 24 h after exposure	26 urine samples	24 h after exposure		Urinary drug levels were below the cut-off
Urine (Study II)	EMIT	20	Cannabinoids	All urines collected separately for 24 h after exposure	23 urine samples	24 h after exposure		One urine was above the cut-off at 6 h after exposure
Urine (Study III)	EMIT	20	Cannabinoids	All urines collected separately for 3 consecutive days	27 urine samples	72 h after exposure		One urine slightly above the cut-off at 5 h after 3rd exposure day
Plasma (Study III)	RIA	NA	THC	Blood collected from one subject at different intervals for 1 h after exposure	11 blood samples	1 h after the 2nd exposure day	1.9 ng/ml	2.2 ng/ml at 5 min after exposure
Mason et al. (1983)								
Plasma	RIA	3	THC		24 blood samples		1.9 ng/ml	2–2.2 ng/ml at 5 min after exposure
	GC/MS	NA	THC	Blood samples obtained at frequent intervals from beginning of exposure to 1 h after exposure	24 blood samples	1 h after exposure	3 ng/ml	4 ng/ml at 5 min after exposure
			11-OH-THC				NA	Not detected
			THC-COOH				0.5 ng/ml	< 0.5 ng/ml
Law et al. (1984)								
Urine	RIA	2	11-OH-THC- and its ester glucuronide	At 0, 1, 2, 3, 6 h	20 urine samples	6 h after start of exposure	4.2 ng/ml at 6 h after start of exposure	4.7 ng/ml at 4.5 h after start of exposure
Plasma	RIA	NA		At 0, 0.5, 1, 2 and 4 h	20 blood samples	4 h after start of exposure	NA	0 ng/ml
Morland et al. (1985)								
Urine (Study I)[b]	EMIT	20	Cannabinoids	Before exposure, 0 to 4h, 4 to 24 h, and days 2, 3, 4, and 5	11 urine samples	Day 5 morning	Negative	Negative
	RIA	13	Cannabinoids				NA	NA
Blood (Study I)[b]	RIA	13	Cannabinoids	Before exposure, immediately after exposure (0.5 h) and 2 h later (2.5 h)	6 blood samples	2.5 h after start of exposure	0 ng/ml	One sample was at the cut-off at 30 min.

Body fluid	Analytical method	Cut-off (ng/ml)	Substances analyzed	Sampling scenario	Total number of samples	Last sample collection	Value of last collected samples	Maximum concentration obtained after exposure[a]
	GC/MS	0.5	THC				0 ng/ml	1.2 ng/ml at 30 min after start of exposure
Urine (Study II)[c]	EMIT	20	Cannabinoids	Before exposure, 0 to 4h, 4 to 24h, and days 2, 3, 4, and 5	20 urine samples	Day 5 morning	Negative	One sample positive at 4–24 h
	RIA	13	Cannabinoids				< cut-off	22 ng/ml at Day 2 morning
Blood (Study II)[c]	RIA	13	Cannabinoids	Before exposure, immediately after exposure (0.5 h) and 2 h later (2.5 h)	9 blood samples	2.5 h after start of exposure	18 ng/ml	26 ng/ml at 30 min after start of exposure
	GC/MS	0.5	THC				0 ng/ml	5.2 ng/ml at 30 min after start of exposure
Cone and Johnson (1986); Cone et al. (1987a); Cone et al. (1987b)								
Urine	EMIT	20 and 75	Cannabinoids	*Ad libidum* + daily at 8:00, 16:00 and 24:00 to complete the collection period.	n = 882 (682 + 200)	14 days for 16-cig exposure study (n = 16 cigs); 10 days for 4-cig exposure study (n = 4 cigs)	< cut-off (n = 4 or 16 cigs)	Positive urines after 1st exposure session for 6 subjects (n = 16 cigs) and 4/5 subjects over the 6-day exposure (n = 4 cigs)
	RIA	10	Cannabinoids				0 ng/ml (n = 4 or 16 cigs)	≈75 ng/ml days 2–6 (n = 16 cigs) ≈14.1 ng/ml days 2–6 (n = 4 cigs)
	GC/MS	5	THC-COOH				0 ng/ml (n = 4 or 16 cigs)	30 ng/ml at day 4 (n = 16 cigs) almost 0 ng/ml (n = 4 cigs)
Plasma (venous blood)	RIA	2.5	THC	30 min prior and 20–30 min following each exposure session with 16 cigs (only 1 subject donated blood samples during the 4-cig exposure study)	55 blood samples (n = 16 cigs) and 10 blood samples (n = 4 cigs)	10 days (n = 16 cigs) and 9 days (n =4 cigs)	0 ng/ml (n = 4 or 16 cigs)	7.3 ng/ml at day8 (n = 16 cigs) 2.5 ng/ml at day6 (n = 4 cigs)
Mule et al. (1988)								
Urine	RIA	12	Cannabinoids	20–24 h after exposure	3	24 h	< 6 ng/ml	NA
Palmieri et al. (1995)								
Urine (Study I)	EMIT	20	THC	Before exposure, 2, 12, and 20 h and for next 6 mornings (44, 68, 92, 116, 140, and 164h)	27 urine samples	164 h after exposure	NA	8.5 ng/ml at 2 h
	ADx	25	THC				0 ng/ml	5.7 ng/ml at 44 h

Body fluid	Analytical method	Cut-off (ng/ml)	Substances analyzed	Sampling scenario	Total number of samples	Last sample collection	Value of last collected samples	Maximum concentration obtained after exposure[a]
Urine (Study II)	EMIT	20	THC	Before exposure, 3, 7, and 16h and for next 4 mornings (40, 64, 88, and 112h)	21 urine samples	112 h after exposure	0 ng/ml	9.6 ng/ml at 7 h
	ADx	25	THC				0 ng/ml	21.3 ng/ml at 7 h
Niedbala et al. (2001)								
Oral fluid (OF)	EIA	1	THC	Prior to exposure and at 1, 2, 4, 8, 16, 24, 48, and 72 h after marijuana administration	18 OF samples	72 h following start of exposure	Negative	Positive at 1h
	GC/MS/MS	0.5	THC				0 ng/ml	0 ng/ml
Urine	EIA	50	THC-COOH		18 urine samples		9.7 ng/ml[d]	3.2 ng/ml at 24 h[d]
	GC/MS	15	THC-COOH				0 ng/ml	0 ng/ml
Niedbala et al. (2004)								
Oral fluid (OF)	EIA	3	THC	Before exposure and at 20, 35, 50, 65, 95, 125, 155, 185, 215, and 245 min after start of exposure	44 OF samples	245 min	Negative	Positive at 20 min
	GC/MS/MS	0.75	THC				0 ng/ml	13.4 ng/ml at 20 min after start of exposure
Urine	EIA	50	THC-COOH	Before exposure and at 20 and 245 min after start of exposure.	12 urine samples	245 min	Negative	Negative
	GC/MS/MS	1	THC-COOH				0.9 ng/ml	0.9 ng/ml at 245 min after start of exposure
Niedbala et al. (2005)								
Oral fluid (OF) (Study I)	EIA	3	THC	Before exposure and at 0 (immediately at end of smoking), 15, 30, and 45 min (inside the van) and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 h (outside of the van)	184 OF samples	72 h	Negative	Positive at 0 and 15 min after exposure
	GC/MS/MS	0.75	THC				≈ 0 ng/ml	5.3 ng/ml immediately after exposure
Urine (Study I)	EIA (EMIT)	50	THC	Before exposure and at 1, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 h after start of exposure	48 urine samples	72 h	Negative	Negative
	GC/MS/MS	1	THC-COOH				1.2 ng/ml[d]	8.4 ng/ml at 6 h after exposure[d]
Oral fluid (OF) (Study II)	EIA	3	THC	Before exposure and at 0 (immediately at end of smoking),15, 30, 45 min, 1,	184 OF samples	72 h	Negative	Negative
	GC/MS/MS	0.75	THC				0 ng/ml	1 ng/ml at 1.5 h after exposure

Body fluid	Analytical method	Cut-off (ng/ml)	Substances analyzed	Sampling scenario	Total number of samples	Last sample collection	Value of last collected samples	Maximum concentration obtained after exposure[a]
				1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 h (outside the van)				
Urine (Study II)	EIA (EMIT)	50	THC	Before exposure and at 1, 2, 4, 6, and 8 h.	24 urine samples	8 h	Negative	Negative
	GC/MS/MS	1	THC-COOH				7.3 ng/ml[d]	8.9 ng/ml at 6 h after exposure[d]
Rohrich et al. (2010)								
Serum	ELISA	3	Cannabinoids	Before exposure and at 1.5, 3.5, 6, and 14 h after start of exposure	25 blood samples	14 h	2 ng/ml	3 ng/ml at 3.5 h after start of exposure
	GC/MS	0.5	THC				0 ng/ml	0.5 ng/ml at 1.5 h after start of exposure
Urine	ELISA	0.6	THC-COOH	Before exposure and at 3.5, 6, 14, 36, 60, and 84 h after start of exposure.	40 urine samples	84 h	0.3 ng/ml	0.8 ng/ml at 3.5 h after start of exposure
	EIA	25	Cannabinoids				1.4 ng/ml[d]	9.8 ng/ml at 6 h after start of exposure[d]
	GC/MS	0.6	THC-COOH				0 ng/ml	2.3 ng/ml at 14 h after start of exposure
		1	THC-COOH (hydrolyzed urine)				0.4 ng/ml	3.8 ng/ml at 14 h after start of exposure
Schimmel et al. (2010)								
Blood (Serum)	EIA	3	Cannabinoids	Before exposure and at 1.5, 3.5, 6, and 14 h after start of exposure	16	14 h	Negative	Positive for 2 volunteers at 1.5 and 3.5 h
	GC/MS	1	THC				0 ng/ml	0 ng/ml
		1	11-OH-THC				0 ng/ml	0 ng/ml
		8	THC-COOH				<LOD	4 samples were > LOD (1 to 2 ng/ml at 3.5–6 h)
Urine	EIA	25	Cannabinoids	Before exposure and at 3.5, 6, 14, 36, 60 and 84 h after	24	84 h	Negative	Negative

Body fluid	Analytical method	Cut-off (ng/ml)	Substances analyzed	Sampling scenario	Total number of samples	Last sample collection	Value of last collected samples	Maximum concentration obtained after exposure[a]
	GC/MS	8	THC-COOH	start of exposure			0 ng/ml	3.6 ng/ml at 6h and 3.7 ng/ml at 14 h
Moore et al. (2011)								
Oral fluid (OF) (Location 1)	ELISA	4	THC	Before exposure, at 20, 40, 60, 120, and 180 min during passive exposure to marijuana (outside coffee shop), and between 12 and 22 h (average 14.6 h) after leaving the coffee shop	70 OF samples	180 min	> 4 ng/ml for 3 subjects	Positive over the 20 min to 3 h period
	GC/MS	0.5	THC			12–22 h	0.4 ng/ml	4.3 ng/ml at 2 h
		0.5	Cannabinol				0 ng/ml	0.7 ng/ml at 2 h
		1 (CBD)	Cannabidiol				0 ng/ml	0 ng/ml
	Two-dimensional GC-GC/MS	0.002	THC-COOH				0 ng/ml	0 ng/ml
Oral fluid (OF) (Location 2)	ELISA	4	THC	Before exposure, at 20, 40, 60, 120, and 180 min during passive exposure to marijuana (outside the coffee shop), and between 12 and 22 h (average 14.6 h) after leaving the coffee shop	70 OF samples	180 min	THC: > 4 ng/ml for 3 subjects	Positive at the 3 h period
	GC/MS	0.5	THC			12–22 h	0 ng/ml	7.5 ng/ml at 3 h
		0.5	Cannabinol				0 ng/ml	0.9 ng/ml at 3 h
		1 (CBD)	Cannabidiol				0 ng/ml	0 ng/ml
	Two-dimensional GC-GC/MS	0.002	THC-COOH				0 ng/ml	0 ng/ml
Cone et al. (2014); Cone et al. (2015)								
Urine (Session I)	GC/MS	15	THC-COOH	Before session, at end of exposure period, and at 0.25, 1, 2, 3, 4 h, then for the following time intervals: 4–6, 6–8, 8–10, 10–12, 12–22, 22–26, 26–30, and 30–34 h (urine pooled for each subject)	84	30–34 h	1.5 ng/ml[d]	22.4 ng/ml at 4–6 h after exposure[d]
	EMIT	20	THC				29.7 ng/ml	86.5 ng/ml at 4–6h after exposure
		50	Cannabinoids				Negative	Negative

Body fluid	Analytical method	Cut-off (ng/ml)	Substances analyzed	Sampling scenario	Total number of samples	Last sample collection	Value of last collected samples	Maximum concentration obtained after exposure[a]
Oral Fluid (OF) (Session I)	ELISA	4	Cannabinoids	Immediately prior to each session and following 1-h exposure session at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 22, 26, 30, and 34 h after end of exposure	102	34 h	Negative	Positive at 15 min (all subjects); mean (range) 1.25 (0.25–3) h after exposure
	LC/MS/MS	2	THC				0 ng/ml	34 ng/ml at 0.25h
		0.02	THC-COOH (total)				0 ng/ml	0 ng/ml
Whole blood (Session I)	LC/MS/MS	0.5	THC	Before session, at end of 1-h exposure session, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 22, 26, 30, and 34 h after end of each exposure session	96 h	34 h	0 ng/ml	1.4 ng/ml at 0.25h
			THC-COOH (free)				0 ng/ml	1.2 ng/ml at 0.25h
			11-OH-THC				0 ng/ml	Negative
Urine (Session II)	GC/MS	15	THC-COOH	Before session, at end of exposure period, at 0.25, 1, 2, 3, 4 h, and then for following time intervals: 4–6, 6–8, 8–10, 10–12, 12–22, 22–26, 26–30, and 30–34 h (urine pooled for each subject)	84	30-34 h	6.5 ng/ml[d]	33.3 ng/ml at 4 h after exposure[d]
	EMIT	20	THC				44.8 ng/ml	140 ng/ml at 4 h after exposure
		50	Cannabinoids				Negative	A single presumptive positive result at 4 h after exposure
Oral Fluid (OF) (Session II)	ELISA	4	Cannabinoids	Immediately prior to each session and following 1-h exposure session at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 22, 26, 30, and 34 h	102	34 h	Negative	Positive at 15 min (all subjects); mean (range) 1.38 (0.25-3) h after exposure
	LC/MS/MS	2	THC				0 ng/ml	81.5 ng/ml at 0.25h
		0.02	THC-COOH (total)				0 ng/ml	0 ng/ml
Whole blood (Session II)	LC/MS/MS	0.5	THC	Before session and following 1-h exposure session at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 22, 26, 30, and 34 h	96	34 h	0 ng/ml	3.1 ng/ml at 0.25h
			THC-COOH (free)				0 ng/ml	2.5 ng/ml at 0.25h

Body fluid	Analytical method	Cut-off (ng/ml)	Substances analyzed	Sampling scenario	Total number of samples	Last sample collection	Value of last collected samples	Maximum concentration obtained after exposure[a]
			11-OH-THC				0 ng/ml	Negative
Urine (Session III)	GC/MS	15	THC-COOH	Before session, at end of exposure period, and at 0.25, 1, 2, 3, 4 h, then for the following time intervals: 4–6, 6–8, 8–10, 10–12, 12–22, 22–26, 26–30, and 30–34 h (urine pooled for each subject)	84	30-34 h	1.4 ng/ml[d]	8.61 ng/ml at 4 h after exposure[d]
	EMIT	20	THC				26.3 ng/ml	55.2 ng/ml at 4–6 h after exposure
		50	Cannabinoids				Negative	Negative
Oral Fluid (OF) (Session III)	ELISA	4	Cannabinoids	Immediately prior to each session and following the 1-h exposure session at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 22, 26, 30 and 34 h	102	34 h	Negative	Mean (range) 0.38 (0.25–1.5) h after exposure
	LC/MS/MS	2	THC				0 ng/ml	16.9 ng/ml at 0.25h
		0.02	THC-COOH (total)				0 ng/ml	0 ng/ml
Whole blood (Session III)	LC/MS/MS	0.5	THC	Before session and following the 1-h exposure session at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 22, 26, 30, and 34 h	96	34 h	0 ng/ml	0.5 ng/ml at 0.25 h
			THC-COOH (free)				0 ng/ml	0.2 ng/ml at 0.25 h
			11-OH-THC				0 ng/ml	Negative
Moosmann et al. (2014)								
Hair	LC/MS/MS	NA	THC-A	Before exposure period, 2 strands every week after the weekend (shortly before exposure to joint), and 2 strands 4 weeks after the exposure period. One participant gave 4 strands for seven weeks after the exposure period	30 strands of hair from various regions of the head	4 weeks after exposure for two participants and 7 weeks after exposure for one participant	0 pg/mg	17.3 pg/mg at the end of exposure period
		20 pg/mg	THC				50 pg/mg	803 pg/mg at the end of exposure period
		20 pg/mg	Cannabinol				36.7 pg/mg	307 pg/mg at the end of exposure period
Urine	EMIT	10	THC-COOH	Before exposure period, and	NA	NA	0 ng/ml	0 ng/ml

Body fluid	Analytical method	Cut-off (ng/ml)	Substances analyzed	Sampling scenario	Total number of samples	Last sample collection	Value of last collected samples	Maximum concentration obtained after exposure[a]
				twice a week				

ADx, Abbott automated method; Cigs, cigarettes; EIA, Enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; EMIT, enzyme multiplied immunoassay technique; GC/MS: Gas chromatography–mass spectrometry; LC/MS/MS, liquid chromatography–tandem mass spectrometry; NA, Information not available; RIA, Radioimmunoassay; THC, Δ^9-tetrahydrocannabinol; THC-A, Δ^9-tetrahydrocannabinolic acid A; THC-COOH, 11-nor-delta-9-THC-carboxylic acid; 11-OH-THC,11-hydroy-delta-9-THC.

[a] The maximal concentration obtained in calculating a mean between the non-smoker values at a specific time.
[b] In study I, volunteers were passively exposed to hashish smoke.
[c] In study II, volunteers were passively exposed to marijuana smoke.
[d] Urine values were adjusted for creatinine.

Table 2 Summary of the exposure scenarios of studies on the passive inhalation of cannabis smoke

Exposure area's volume (L)	Room type	Room ventilation	Substance	Smoking mode	Exposure smoke type	Protective equipment used	Specific exposure conditions	Placebo exposure	Non-smoking subject exposed	Gender	Age (years)	Exposure time (min)	Total exposure number	Exposure time period	No. of cannabis cigarettes smoked	THC dose (mg)
Perez-Reyes et al. (1983)																
15,500[a]	Small room	Unventilated	Marijuana	Smokers (n = 4)[b]	Sidestream	None	None	None	2	3 F / 3 M	NA	60	1	NA	8[b]	46
15,500[a]	Small room	Unventilated	Marijuana	Smokers (n = 4)[c]	Sidestream	None	None	None	2	3 F / 3 M	NA	60	1	NA	8[c]	52
3,500	Station wagon	Unventilated	Marijuana	Smokers (n = 4)[c]	Sidestream	None	None	None	2	3 F / 3 M	NA	60	1	NA	8[c]	52
15,500	Small room	Unventilated	Marijuana	Smokers (n = 4)[d]	Sidestream	None	None	None	2	3 F / 3 M	NA	60	3	NA	4[d]	105
Mason et al.(1983)																
15,500	Small room	unventilated	Marijuana	Smokers (n = 4)[e]	Sidestream	None	All analyses were performed blind	None	3[f]	Males	NA	60	1	NA	4[e]	105
Law et al. (1984)																
27,950	small office	Unventilated[g]	Cannabis resin	Smokers (n = 6)[h]	Sidestream	None	None	None	4	Males	NA	180	1	NA	6[h]	103
Morland et al.(1985)																
1,650	Small car	NA	Hashish	Smokers (n = 3)	Sidestream	None	None	None	2	3 F / 7 M[i]	35–50	30	1	NA	6	90
1,650	Small car	NA	Marijuana	Smokers (n = 2)	Sidestream	None	None	None	3	3 F / 7 M[i]	35–50	30	1	NA	12	90
Cone and Johnson (1986); Cone et al. (1987a); Cone et al. (1987b)																
≈12,226[j]	Closed ward under close surveillance	Small unventilated room	Marijuana	Machine	Only sidestream smoke (mainstream was removed)	Goggles[k] Not allowed to drink or eat during exposure sessions.	At rest. Double-blind conditions to the smoke	Yes[l]	5 (healthy drug-free with a history of Marijuana use)	Males	22, 26, 33, 40 and 54	60	12 (6 consecutive days per exposure)	Morning (8:30 to 9:30 am)	16[m]	393.98[n]
≈12,226[j]	Closed ward under close surveillance	Small unventilated room	Marijuana	Machine	Only sidestream smoke (mainstream was removed)	Goggles[k] Not allowed to drink or eat during exposure sessions.	At rest Without blind conditions	None	2 (healthy drug-free with no history of Marijuana use, from staff)	Males	37 and 42	60	6 (6 consecutive days)	Morning (8:30 to 9:30 am)	16	2.8% Δ-9-THC

Exposure area's volume (L)	Room type	Room ventilation	Substance	Smoking mode	Exposure smoke type	Protective equipment used	Specific exposure conditions	Placebo exposure	Non-smoking subject exposed	Gender	Age (years)	Exposure time (min)	Total exposure number	Exposure time period	No. of cannabis cigarettes smoked	THC dose (mg)
Mule et al (1988)																
21,600	room	Windowless	Marijuana	Smokers (n = 8)	Sidestream	None	None	None	3	Males	NA	60	1	NA	4	108
Palmeri et al. (1995)																
30,780	room	unventilated	Hashish	machine	Sidestream	None	None	None	3	2 F / 2 M	30–50	60	1	NA	3	45
3,000	Car	Car windows closed	Hashish	machine	Sidestream	None	None	None	3	2 F / 2 M	30–50	30	1	NA	2	30
Niedbala et al. (2001)																
≈133,960	Room	No central ventilation system, but windows were opened occasionally to relieve the smoky atmosphere	Marijuana	Smokers (n = 10)[p]	Sidestream	None	Drinking beer or soda during exposure was allowed. Food (pizza) was available after first 2 h of specimen collection[q]	None	2 (control subjects)	Males	32 and 39	240	1	NA	10[p]	NA
Niedbala et al. (2004)																
36,000	Room	A closed room with all door and window openings sealed	Marijuana	Smokers (n = 5)[r]	Sidestream	None No drinking allowed for first 60 min.	Located approx.. 1.5 m from smokers	None	4	Males	37–49	240 (4h)	1	NA	5[r]	NA
Niedbala et al. (2005)																
Study 1 15,300	Motor vehicle (8 passengers)	Unventilated (doors and windows closed, and engine turned off)	Marijuana	Smokers (n = 4)[s]	Sidestream	None	Seat[t]	None	4	Males	34–50	60	1	NA	4[s]	158[s]
Study 2 15,300	Motor vehicle (8 passengers)	Unventilated (doors and windows closed, and engine turned off)	Marijuana	Smokers (n = 4)[u]	Sidestream	None	Seat[t]	None	4	Males	25–50	60	1	NA	4[u]	333[u]

Exposure area's volume (L)	Room type	Room ventilation	Substance	Smoking mode	Exposure smoke type	Protective equipment used	Specific exposure conditions	Placebo exposure	Non-smoking subject exposed	Gender	Age (years)	Exposure time (min)	Total exposure number	Exposure time period	No. of cannabis cigarettes smoked	THC dose (mg)
Rohrich et al. (2010)																
200,000	Coffee shop (large room)	No windows but relatively efficient ventilation; not very smoky during the exposure period.	Cannabis cigarettes Additional 8 g hashish and marijuana was burned down by the volunteers in an ashtray about 1.5 m away from them.	Smokers (n = 8 to 25) stayed around 15 min, but some up to 1h. Not less than 1 m from passive smokers, mostly 5 to 6 m away.	Sidestream	None	Volunteers sat together at a table almost in middle of room. Each volunteer consumed 2 to 3 cans (0.33 L) of soft drinks (no food)	None	8	4 F / 4 M	28–49	180	1	NA	8–25 smoking guests[v]	[v]
Schimmel et al. (2010)																
200,000	Coffee shop	Yes (no window)	Hashish and marijuana	Smokers (n = 8 to 25)	Sidestream	NA	NA	None	8	4 F / 4 M	27–59	180	1	NA	NA	8 g of hashish and marijuana were burnt
Moore et al. (2011)																
Place 1: 122,500	Coffee shop (large room)	NA	Marijuana	Smokers (n = 4 to 16; mean: 8)	Sidestream	None	NA	None	10	3 F / 2 M	22.5–23	180	1	NA	4–16 active smokers	NA
Place 2: 42,000	Coffee shop (small room)	NA	Marijuana	Smokers (n = 0 to 6; mean: 2.5)	Sidestream	None	NA	None	10	3 F / 2 M	23–25	180	1	NA	0–6 active smokers	NA
Cone et al. (2014, 2015)																
≈ 25,726	Exposure chamber[w]	Unventilated	Cannabis	Smokers[x]	Sidestream	Goggles	Non-smokers remained in their assigned	None	6	9 F / 9 M in total	Av. age 28 (7x 20–45)	60	1	NA	*Ad libitum*	5,3%[x]
≈ 25,726	Exposure chamber[w]	Unventilated (the door was opened briefly	Cannabis	Smokers[y]	Sidestream	Goggles		None	6			60	1	NA	*Ad libitum*	11,3%[y]

Exposure area's volume (L)	Room type	Room ventilation	Substance	Smoking mode	Exposure smoke type	Protective equipment used	Specific exposure conditions	Placebo exposure	Non-smoking subject exposed	Gender	Age (years)	Exposure time (min)	Total exposure number	Exposure time period	No. of cannabis cigarettes smoked	THC dose (mg)
		for exit and entry)					seats.									
≈ 25,726	Exposure chamber[w]	Ventilated (comparable to home air-conditioning (11.2 air changes per hour)	Cannabis		Sidestream	Goggles	Not allowed to eat or drink during or after session until after first oral fluid specimen collected.	None	6			60	1	NA	*Ad libitum*	11,3%[y]
Moosmann et al. (2014)																
12,500	Room	NA	Marijuana	Water-jet vacuum pump	Sidestream	Smoke inhalation excluded by breathing compressed air through SCUBA regulators	Non-smokers sat in a circle facing each other. Joint held in front participant's mouth for 10–15 s, then connected to vacuum for one puff, then passed on to next participant	None	3	NA	NA	15–20 minutes (one joint) every weekday for 3 weeks	15	Morning	1 every weekday for 3 weeks	500 mg of marijuana flowers containing 9.2% THC[z]

F, female; M, males; NA, information not available.

[a] The volume of solid furniture present in the room was subtracted from the total room volume.
[b] Each smoker smoked 2 marijuana cigarettes containing 2.5% of THC.
[c] Each smoker smoked 2 marijuana cigarettes containing 2.8% of THC. 2.8% is the highest potency marijuana cigarette available from NIDA (National Institute on Drug Abuse).
[d] Each smoker smoked 4 marijuana cigarettes containing 2.8% of THC daily for 3 consecutive days. 2.8% is the highest potency marijuana cigarette available from NIDA.
[e] Each cigarette contained 26.2 mg of THC.
[f] Two non-smokers participated at the beginning of exposure; on the second day of study, a third passive smoker participated.
[g] The single door was opened and closed approximately 18 times during the experiment to allow access to the subjects.
[h] Cigarettes contained an average of 175 mg resin, equivalent to 17.1 mg THC per cigarette. The smoking period lasted 10–34 min.
[i] No information about the gender repartition between studies.
[j] Volume adjusted for contents and the presence of 5 volunteers.
[k] To minimize eye irritation and to prevent color discrimination between placebo and active cigarettes.
[l] Before and after marijuana exposure, exposure to 16 placebo cigarettes in the same conditions for 2 days (1st exposure) and 1 day (2nd exposure) to 4 placebo cigarettes.
[m] 8 cigarettes burnt from 8:30 to 8:45 am; and from 9:00 to 9:15 am 8 others for the 1st exposure; 4 cigarettes (and not 8) burnt for the 2nd exposure using the same exposure pattern.
[n] Cigarettes had an average weight of 877±20 mg.
[o] There were in total 4 volunteers including 2 females and 2 males, and 3 of them have participated in each study.
[p] Cigarettes contained an average of 20–25 mg THC. The smoking period was 20–30 min.

[q] Collection of oral fluid specimens was preceded by a 10-min "time-out" period (no eating or drinking).
[r] Joints contained an average of 1.75% THC per cigarette (≈ 12.75 mg of THC). The smoking period was 20 min.
[s] Joints contained an average of 5.4% THC per cigarette (≈ 39.5 mg of THC mixed with tobacco). The smoking period was 20 min.
[t] One cannabis smoker sat on each row alongside one passive subject.
[u] Joints contained an average of 10.9% THC per cigarette (≈ 83.2 mg pure THC). The smoking period was 20 min.
[v] The exact number of joints smoked during the 3 h period and the average THC content of the cannabis cigarettes is unknown. Additionally, 8 g of both hashish and marijuana was burned by the volunteers in an ashtray about 1.5 m away from them.
[w] A specially designed smoking chamber made of Plexiglas walls and aluminum supports was built for this experiment.
[x] The lower potency cannabis cigarettes were machine rolled to 85 mm in length, 25 mm in circumference, and weighed a mean 0.92 g/cigarette (SD = 0.06); the cigarettes had an assayed mean content of cannabinoids as follows: 5.3% (0.48%) total THC, 0.01% (0.0%) CBD, and 0.35% (0.04%) CBN.
[y] The higher potency cigarettes were hand-rolled to 70 mm in length (24.5 mm) and had a mean weight of 1.0 g/cigarette (SD = 0.04); the cigarettes had an assayed mean content (n = 12 for THC; n = 4 for other cannabinoids) of cannabinoids as follows: 11.3% (0.29%) total THC, 0.08% (0.12%) CBD, and 0.76% (0.06%) CBN.
[z] Each day, one joint was prepared using 500 mg marijuana flowers with a total THC content of 9.2% and 500 mg tobacco.

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