ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/7182630

Pharmacokinetics and Metabolism of the Plant Cannabinoids, Δ 9-Tetrahydrocannibinol, Cannabidiol and Cannabinol

Article *in* Handbook of Experimental Pharmacology · February 2005

DOI: 10.1007/3-540-26573-2_23 · Source: PubMed

CITATIONS
249

READS
2,013

1 author:

Marilyn A Huestis
Huestis & Smith Toxicology, LLC
626 PUBLICATIONS **31,523** CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:

ransactional relations between caregiving stress, executive functioning, and problem behavior from early childhood to early adolescence Article Prenatal Methamphetamine Exposure and Childhood Behavior Problems at 3 and 5 Years of Age View project

Synthetic cannobinoids Metabolite ID View project

All content following this page was uploaded by Marilyn A Huestis on 05 January 2016.

The user has requested enhancement of the downloaded file.

FM-011088

Handbook of Experimental Pharmacology

Volume 168

Editor-in-Chief

K. Starke, Freiburg i. Br.

Editorial Board

G.V.R. Born, London
M. Eichelbaum, Stuttgart
D. Ganten, Berlin
F. Hofmann, München
B. Kobilka, Stanford, CA
W. Rosenthal, Berlin
G. Rubanyi, Richmond, CA

Cannabinoids

Contributors

M.E. Abood, S. Bátkai, T. Bisogno, G.A. Cabral, M.J. Christie, A.A. Coutts, S.N. Davies, R. de Miguel, L. De Petrocellis, V. Di Marzo, M. Egertová, M.R. Elphick, J. Fernández-Ruiz, S.J. Gatley, S.T. Glaser, M. Gómez, S. Gonzáles, M. Guzmán, C.J. Hillard, W.-S.V. Ho, A.G. Hohmann, A.C. Howlett, M.A. Huestis, A.A. Izzo, M. Karsak, G. Kunos, C. Li, A.H. Lichtman, K.P. Lindsey, M. Maccarrone, K. Mackie, A. Makriyannis, B.R. Martin, S.P. Nikas, P. Pacher, R.G. Pertwee, J.A. Ramos, P.H. Reggio, G. Riedel, P. Robson, E. Schlicker, A. Staab, B. Szabo, G.A. Thakur, O. Valverde, C.W. Vaughan, J.M. Walker, T. Wenger, A. Zimmer

Editor

Roger G. Pertwee

Springer

HEP (2005) 168:657–690
© Springer-Verlag 2005

Pharmacokinetics and Metabolism of the Plant Cannabinoids, Δ^9-Tetrahydrocannabinol, Cannabidiol and Cannabinol

M.A. Huestis

Chemistry and Drug Metabolism, Intramural Research Program,
5500 Nathan Shock Drive, Baltimore MD, 21224, USA
mhuestis@intra.nida.nih.gov

Abstract Increasing interest in the biology, chemistry, pharmacology, and toxicology of cannabinoids and in the development of cannabinoid medications necessitates an understanding of cannabinoid pharmacokinetics and disposition into biological fluids and tissues. A drug's pharmacokinetics determines the onset, magnitude, and duration of its pharmacodynamic effects. This review of cannabinoid pharmacokinetics encompasses absorption following diverse routes of administration and from different drug formulations, distribution of analytes throughout the body, metabolism by different tissues and organs, elimination from the body in the feces, urine, sweat, oral fluid, and hair, and how these processes change over time. Cannabinoid pharmacokinetic research has been especially challenging due to low analyte concentrations, rapid and extensive metabolism, and physicochemical characteristics that hinder the separation of drugs of interest from biological matrices—and from each other—and lower drug recovery due to adsorption of compounds of interest to multiple surfaces. Δ^9-Tetrahydrocannabinol, the primary psychoactive component of *Cannabis sativa*, and its metabolites 11-hydroxy-Δ^9-tetrahydrocannabinol and 11-nor-9-carboxy-tetrahydrocannabinol are the focus of this chapter, although cannabidiol and cannabinol, two other cannabinoids with an interesting array of activities, will also be reviewed. Additional material will be presented on the interpretation of cannabinoid concentrations in human biological tissues and fluids following controlled drug administration.

Keywords Cannabinoids · Pharmacokinetics · Tetrahydrocannabinol · Cannabidiol · Absorption · Distribution · Metabolism · Excretion · Interpretation · Oral fluid · Sweat · Hair · Plasma · Urine · Alternate matrix · Marijuana

1 Introduction

Currently, there is a growing interest in the biology, chemistry, pharmacology, and toxicology of cannabinoids and in the development of potential cannabinoid medications. It is clear that the endogenous cannabinoid system plays a critical role in physiological and behavioral processes. Endogenous cannabinoid neurotransmitters, receptors, and transporters, synthetic cannabinoid agonists and antagonists, and cannabis-based extracts are the subject of extensive research. It is hoped that these agents might provide novel approaches to treat human diseases and disorders. The therapeutic usefulness of oral cannabinoids is being investigated for medicinal applications, including analgesia, treatment of acquired immunodeficiency syndrome (AIDS)-wasting disease, counteracting spasticity of motor diseases, and the prevention of emesis following chemotherapy, among others. Cannabis, also, is one of the oldest and most commonly abused drugs in the world, and its use may have consequences in terms of pathological and behavioral toxicity. For these reasons, it is important to understand cannabinoid pharmacokinetics and the disposition of cannabinoids into biological fluids and tissues. Understanding a drug's pharmacokinetics is essential to understanding the onset, magnitude, and duration of its pharmacodynamic effects.

Pharmacokinetics encompasses the absorption of cannabinoids following diverse routes of administration and from different drug formulations, the distribution of analytes throughout the body, the metabolism of cannabinoids by different tissues and organs, the elimination of cannabinoids from the body in the feces, urine, sweat, oral fluid, and hair, and how these processes change over time. In this chapter, we will review the many contributions to our understanding of cannabinoid pharmacokinetics from the 1970s and 1980s and the more recent research that expands upon this knowledge. Cannabinoid pharmacokinetic research has been especially challenging due to low analyte concentrations, rapid and extensive metabolism, and physicochemical characteristics that (1) hinder the separation of drugs of interest from biological matrices and from each other and (2) lower drug recovery due to adsorption of compounds of interest to multiple surfaces. Much of the earlier data utilized radio-labeled cannabinoids yielding highly sensitive but less specific measurement of individual cannabinoid analytes. Mass spectrometric developments now permit highly sensitive and specific measurement of cannabinoids in a wide variety of biological matrices.

Cannabis sativa contains over 421 different chemical compounds, including over 60 cannabinoids (Claussen and Korte 1968; ElSohly et al. 1984; Turner et al. 1980). Cannabinoid plant chemistry is far more complex than pure Δ^9-tetrahydrocannabinol (THC), and different effects may be expected due to the presence of additional cannabinoids and other chemicals. In all, 18 different classes of chemicals, including nitrogenous compounds, amino acids, hydrocarbons, sugars, terpenes, and simple and fatty acids, contribute to cannabis' known pharmacological and toxicological properties. THC is usually present in cannabis plant material as a mixture of monocarboxylic acids that readily and efficiently decarboxylate upon heating. THC decomposes when exposed to air, heat, or light; exposure to acid can oxidize the compound to cannabinol, a much less potent cannabinoid. In addition, cannabis plants dried in the sun release variable amounts of THC through decarboxylation. During smoking, more than 2,000 compounds may be produced by pyrolysis. The focus of this chapter will be THC, the primary psychoactive component of cannabis, its metabolites, 11-hydroxy-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-tetrahydrocannabinol (THCCOOH), and two other cannabinoids present in high concentrations, cannabidiol (CBD), a non-psychoactive agent with an interesting array of other activities, and cannabinol, which is approximately 10% as psychoactive as THC (Perez-Reyes et al. 1982). Mechoulam et al. elucidated the structure of THC after years of effort in 1964, opening the way for studies of the drug's pharmacokinetics (Mechoulam 1970). THC, containing no nitrogen but with two chiral centers in the *trans*-configuration, is described by two different numbering systems, the dibenzopyran or Δ^9, and the monoterpene or Δ^1 system; the dibenzopyran system is used throughout this chapter.

2 Pharmacokinetics of THC

2.1 Absorption

2.1.1 Smoked Administration

Route of drug administration and drug formulation determine the rate of drug absorption. Smoking, the principal route of cannabis administration, provides a rapid and efficient method of drug delivery from the lungs to the brain, contributing to its abuse potential. Intense pleasurable and strongly reinforcing effects may be produced due to almost immediate drug exposure to the central nervous system. Slightly lower peak THC concentrations are achieved after smoking compared to intravenous administration (Ohlsson et al. 1980). Bioavailability following the smoking route was reported as 2% to 56%, due in part to the intra- and inter-subject variability in smoking dynamics that contribute to uncertainty in dose delivery (Agurell et al. 1986; Agurell and Leander 1971; Ohlsson et al. 1982, 1985). The number, duration, and spacing of puffs, hold time and inhalation volume, or smoking topography, greatly influences the degree of drug exposure (Azorlosa et al. 1992; Heishman et al. 1989; Perez-Reyes 1990). Expectation of drug reward also may affect smoking dynamics. Cami et al. noted that subjects were able to change their method of smoking hashish cigarettes to obtain higher plasma concentrations of THC when they expected to receive active drug in comparison to placebo cigarettes (Cami et al. 1991).

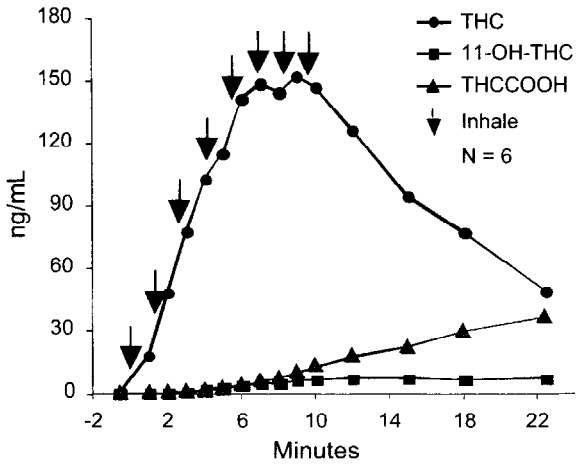

Fig. 1. Mean ($n = 6$) plasma concentrations of Δ^9-tetrahydrocannabinol (*THC*), 11-hydroxy-Δ^9-tetrahydrocannabinol (*11-OH-THC*), and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (*THCCOOH*) during smoking of a single 3.55% THC cigarette. *Each arrow* represents one inhalation or puff on the cannabis cigarette (M.A. Huestis, unpublished data)

Fig. 2. Indivi
a single 3.55%
Publications,

A conti
sorption o
smoking (
followed a
Plasma co
try (GC/M
puff (Fig. 1
1992d). M
observed f
16 mg) or
(Huestis e
of 84.3 ng
high-dose
initiation
procedure
and time b
concentrat
their THC
20% of pea
plasma TH
THC (GC/
6 to 27 h a
Similar
immediate
tions after
and 155.1
concentrat
proximatel

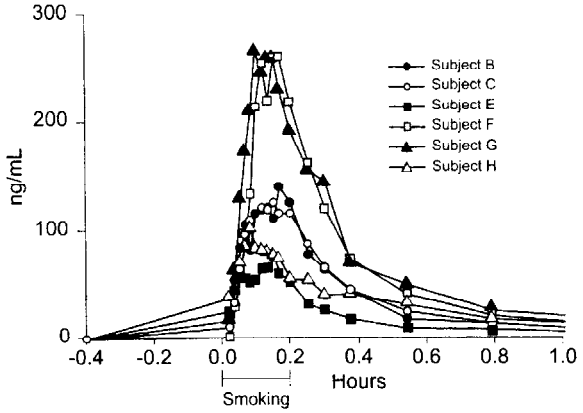

Fig. 2. Individual plasma Δ^9-tetrahydrocannabinol (THC) time course for six subjects following smoking of a single 3.55% THC cigarette. (Reproduced from the *Journal of Analytical Toxicology* by permission of Preston Publications, a division of Preston Industries; Huestis et al. 1992b, Fig. 1d therein)

A continuous blood withdrawal pump was utilized to capture the rapid absorption of THC and formation of 11-OH-THC and THCCOOH during cannabis smoking (Huestis et al. 1992b). The disposition of THC and its metabolites were followed after smoking a single placebo, 1.75%, or 3.55% THC cigarette over 7 days. Plasma concentrations were determined by gas-chromatography mass spectrometry (GC/MS). THC was detected in the plasma immediately after the first cigarette puff (Fig. 1) and was accompanied by the onset of cannabinoid effects (Huestis et al. 1992d). Mean±SD THC concentrations of 7.0±8.1 ng/ml and 18.1±12.0 ng/ml were observed following the first inhalation of a low-dose (1.75% THC, approximately 16 mg) or high-dose (3.55% THC, approximately 30 mg) cigarette, respectively (Huestis et al. 1992b). Concentrations increased rapidly, reaching mean peaks of 84.3 ng/ml (range 50–129) and 162.2 ng/ml (range 76–267) for the low- and high-dose cigarette, respectively. Peak concentrations occurred at 9.0 min, prior to initiation of the last puff sequence at 9.8 min. Despite a computer-paced smoking procedure that controlled the number of puffs, length of inhalation, hold time, and time between puffs, there were large inter-subject differences in plasma THC concentrations due to differences in the depth of inhalation as participants titrated their THC dose (Fig. 2). Mean THC concentrations were approximately 60% and 20% of peak concentrations 15 and 30 min post smoking, respectively. Within 2 h, plasma THC concentrations were at or below 5 ng/ml. The time of detection of THC (GC/MS LOQ = 0.5 ng/ml) varied from 3 to 12 h after the low-dose and from 6 to 27 h after the high-dose cannabis cigarette.

Similar mean THC C_{max} concentrations were reported in specimens collected immediately after cannabis smoking was completed. Mean peak THC concentrations after smoking a single 1.32%, 1.97%, or 2.54% THC cigarette were 94.3, 107.4, and 155.1 ng/ml, respectively (Perez-Reyes et al. 1982). Other reported peak THC concentrations ranged between 45.6 and 187.8 ng/ml following smoking of an approximately 1% THC cigarette (Perez-Reyes et al. 1981) and 33 to 118 ng/ml 3 min

after ad lib smoking of an approximate 2% THC cigarette (Ohlsson et al. 1980). Many individuals prefer the smoked route, not only for its rapid drug delivery, but also because it allows them to titrate their dose.

2.1.2 Oral Administration

There are fewer studies on the disposition of THC and metabolites after oral as compared to the smoked route of cannabis administration. THC is readily absorbed due to its high octanol/water coefficient, estimated to be between 6,000 and over 9 million by different technologies (Harder and Rietbrock 1997). The advantages of cannabinoid smoking are offset by the harmful effects of cannabinoid smoke; hence, smoking is generally not recommended for therapeutic applications. Synthetic THC preparations such as dronabinol (Marinol) are usually taken orally but may also be administered rectally. In addition, abuse of cannabis by the oral route also is common. Absorption is slower when cannabinoids are ingested with lower, more delayed peak THC concentrations (Law et al. 1984; Ohlsson et al. 1981). Dose, route of administration, vehicle, and physiological factors such as absorption and rates of metabolism and excretion can influence drug concentrations in the circulation. Perez-Reyes et al. described the efficacy of five different vehicles used in the oral administration of THC in gelatin capsules (Perez-Reyes et al. 1973a). Glycocholate and sesame oil improved the bioavailability of oral THC; however, there was considerable variability in peak concentrations and rates of absorption, even when the drug was administered in the same vehicle. Oral THC bioavailability was reported to be 10% to 20% by Wall et al. (1983). In their study, participants were dosed with either 15 (women) or 20 mg (men) THC dissolved in sesame oil and contained in gelatin capsules. THC plasma concentrations peaked approximately 4 to 6 h after ingestion of 15 to 20 mg of THC in sesame oil. A percentage of the THC was radio-labeled; however, investigators were unable to differentiate labeled THC from its labeled metabolites. Thus, THC concentrations were overestimated.

Possibly a more accurate assessment of oral bioavailability that utilized GC/MS to quantify THC in plasma samples was reported by Ohlsson et al. (1980). Peak THC concentrations ranged from 4.4 to 11 ng/ml and occurred 1 to 5 h following ingestion of 20 mg of THC in a chocolate cookie. Oral bioavailability was estimated to be 6%. Slow rates of absorption and low THC concentrations occur after oral administration of THC or cannabis. Several factors may account for the low oral bioavailability of 4% to 20% (as compared to intravenous drug administration) including variable absorption, degradation of drug in the stomach and significant first-pass metabolism to active 11-OH-THC and inactive metabolites in the liver.

Recently, there has been renewed interest in oral THC pharmacokinetics due to the therapeutic value of orally administered THC. In a study of THC, 11OH-THC, and THCCOOH concentrations in 17 volunteers after a single 10 mg Marinol capsule, mean peak plasma THC concentrations of 3.8 ng/ml (range 1.1–12.7), 11-

OH-THC 3.4 ng/ml (range 1.2–5.6), and THCCOOH 26 ng/ml (range 14–46) were found 1 to 2 h after ingestion (Kim and Yoon 1996). Similar THC and 11-OH-THC concentrations were observed with consistently higher THCCOOH concentrations. Interestingly, two THC peaks were frequently observed due to enterohepatic circulation. The onset, magnitude, and duration of pharmacodynamic effects generally occur later, are lower in magnitude, and have a delayed return to baseline when THC is administered by the oral as compared to the smoked route (Binitie 1975; Meier and Vonesch 1997).

In addition, THC-containing foods, i.e., hemp oil, beer, and other products, are commercially available for oral consumption. Hemp oil is produced from cannabis seed and is an excellent source of essential amino acids and omega-linoleic and linolenic fatty acids. THC content is dependent upon the effectiveness of cannabis seed cleaning and oil filtration processes. Hemp oil of greater than 300 μg THC/g was available in the U.S. and up to 1,500 μg THC/g in Europe. Currently, hemp oil THC concentrations in the U.S. are low, reflecting the efforts of manufacturers to reduce the amount of THC in hemp oil products.

In a recent controlled cannabinoid administration study of THC-containing hemp oils and dronabinol, the pharmacokinetics and pharmacodynamics of oral THC were evaluated. Up to 14.8 mg of THC was ingested by six volunteers each day in three divided doses with meals for five consecutive days (Nebro et al. 2004). There was a 10-day washout phase between each of the five dosing sessions. THC was quantified in plasma by solid-phase extraction followed by positive chemical ionization GC/MS. THC and 11-OH-THC were rarely detected in plasma following the two lowest doses of 0.39 and 0.47 mg/day THC, while peak plasma

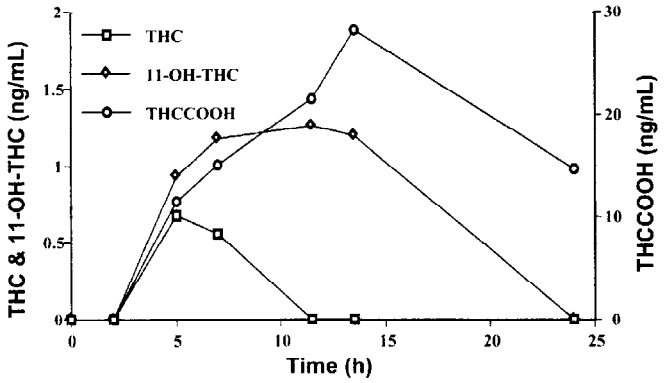

Fig. 3. Plasma Δ^9-tetrahydrocannabinol (*THC*), 11-hydroxy-Δ^9-tetrahydrocannabinol (*11-OH-THC*) and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (*THCCOOH*) concentrations in one participant over 24 h following administration of two 2.5-mg dronabinol (synthetic THC) doses. Time zero is the time of the first blood draw at 0730 hours. The 2.5-mg doses were administered with food at 1200 and 1800 (4.5 and 10.5 h after time zero). (Reprinted from Journal of Chromatography B, 789, Gustafson et al., Validated method for the simultaneous determination of delta-9-tetrahydrocannabinol (THC), 11-hydroxy-THC and 11-nor-9-carboxy-THC in human plasma using solid phase extraction and gas chromotography-mass spectrometry with positive chemical ionization, pp. 145, Fig. 2 therein, Copyright (2003) with permission from Elsevier)

concentrations of less than 6.5 ng/ml THC, less than 5.6 ng/ml 11-OH-THC, and less than 43.0 ng/ml THCCOOH were found after the two highest THC doses of 7.5 and 14.8 mg/day (Fig. 3). Interestingly, THCCOOH concentrations after the 7.5 mg/day dronabinol dose were greater than or equal to those of the high potency 14.8 mg/day hemp oil dose. Two possible reasons for the higher bioavailability of THC in dronabinol are greater protection from degradation in the acidic environment of the stomach due to encapsulation and improved absorption of THC from the sesame oil formulation. Plasma THC and 11-OH-THC concentrations fell below the method's limits of quantification of 0.5 ng/ml at 25 h, while THCCOOH was still measurable for more than 50 h after the last dose of the higher concentration hemp oils.

2.1.3 Rectal Administration

Several different suppository formulations were evaluated in monkeys to determine the formulation that maximized bioavailability and reduced first-pass metabolism of THC by the liver (Mattes et al. 1993, 1994); THC-hemisuccinate provided the highest bioavailability of 13.5%. Brenneisen et al. evaluated plasma THC concentrations in two patients who were prescribed THC hemisuccinate suppositories or Marinol for spasticity (Brenneisen et al. 1996). THC did not accumulate in the blood following 10 to 15 mg daily doses. THC concentrations peaked within 1 to 8 h after oral administration and ranged between 2.1 and 16.9 ng/ml. Rectal administration of 2.5 to 5 mg THC produced maximum plasma concentrations of 1.1 to 4.1 ng/ml within 2 to 8 h. The bioavailability of the rectal route was approximately twice that of the oral route due to higher absorption and lower first-pass metabolism.

2.1.4 Sublingual and Dermal Administration

Due to the chemical complexity of cannabis plant material as compared to synthetic THC, cannabis extracts are being explored as therapeutic medications. One reproducible extract of the *Cannabis sativa* plant contains approximately equal amounts of THC and CBD (see Pharmacokinetics of Cannabidiol, Sect. 3). The efficacy of cannabis extracts has been evaluated in clinical trials for analgesia (Holdcroft 1984; Vaughan and Christie 1984), spasticity, and other indications in affected patients (Zajicek et al. 2003). Cannabis extracts can be administered sublingually to avoid first-pass metabolism by the liver.

Another route of drug exposure that avoids first-pass metabolism is topical administration. Although still in the early stages of research, dermal administration of THC also is being explored as a means of improving bioavailability of THC (Stinchcomb et al. 2004).

2.2 Distribution

THC concentrations decrease rapidly after the end of smoking due to its rapid distribution into tissues and metabolism in the liver. THC is highly lipophilic and initially taken up by tissues that are highly perfused, such as the lung, heart, brain, and liver. In animals after i.v. administration of labeled THC, higher levels of radioactivity are present in the lung than in other tissues (Lemberger et al. 1970). Adams and Martin determined that a THC dose of 2 to 22 mg is necessary to produce pharmacological effects in humans (Adams and Martin 1996). Assuming that 10% to 25% of the available THC enters the circulation during smoking, the actual dose required was estimated as 0.2 to 4.4 mg. Furthermore, only about 1% of the dose at peak concentration was found in the brain, indicating that only 2 to 44 µg of THC penetrated the brain. Chiang et al. estimated that equilibration was reached between plasma and tissue THC approximately 6 h after an intravenous THC dose (Chiang and Rapaka 1987).

Metabolism of THC to 11-OH-THC, THCCOOH, and other analytes also contributes to the reduction of THC in the blood. Perez-Reyes et al. compared the pharmacokinetics and pharmacodynamics of tritiated THC and 11-OH-THC in 20 male volunteers (Perez-Reyes et al. 1972). Although equal doses produced equal psychoactive effects, drug effects were perceived more rapidly after 11-OH-THC than after THC. In addition, 11-OH-THC left the intravascular compartment faster than THC. These data suggest that 11-OH-THC diffuses into the brain more readily than THC. Another possible explanation is lower protein binding of 11-OH-THC, as compared to THC, in the blood. Further support for the faster penetration of brain by 11-OH-THC is found in studies documenting a more rapid diffusion of 11-OH-THC than THC into the brains of mice (Perez-Reyes et al. 1972).

THC's volume of distribution (V_d) is large, approximately 10 l/kg, despite the fact that it is 95% to 99% protein bound in plasma, primarily to lipoproteins (Hunt and Jones 1980; Kelly and Jones 1992). More recently, with the benefit of advanced analytical techniques, THC's steady state V_d was found to be 3.4 l/kg (Grotenhermen 2003). Less highly perfused tissues, including fat, accumulate drug more slowly as THC redistributes from the vascular compartment (Harvey 2001). With prolonged drug exposure, THC concentrates in fat and may be retained for extended periods of time (Johansson et al. 1989b; Kreuz and Axelrod 1973). It is suggested that fatty acid conjugates of THC and 11-OH-THC may be formed, increasing the stability of these compounds in fat (Grotenhermen 2003).

Distribution of THC into peripheral organs and brains was found to be similar in THC tolerant and non-tolerant dogs (Dewey et al. 1972). In addition, Dewey et al. found that tolerance to the behavioral effects of THC in pigeons was not due to decreased uptake of cannabinoids into brain (Dewey et al. 1972). Tolerance also was evaluated in humans by Hunt and Jones (1980). Tolerance in humans developed during oral administration of 30 mg of THC every 4 h for 10 to 12 days. Few pharmacokinetic changes were noted during chronic administration, although average total metabolic clearance and initial apparent volume of distribution increased from 605 to 977 ml/min and from 2.6 to 6.4 l/kg, respectively. The pharmacoki-

netic changes observed after chronic oral THC could not account for the observed behavioral and physiologic tolerance, suggesting rather that tolerance was due to pharmacodynamic adaptation.

THC rapidly crosses the placenta, although concentrations were lower in canine and ovine fetal blood and tissues than in maternal plasma and tissues (Lee and Chiang 1985). THC metabolites 11-OH-THC and THCCOOH crossed the placenta much less efficiently (Bailey et al. 1987; Martin et al. 1977). No THCCOOH was detected in fetal plasma and tissues, indicating a lack of transfer across the placenta and a lack of metabolism of THC in the fetal monkey (Bailey et al. 1987). Blackard and Tennes reported that THC in cord blood was three to six times less than in maternal blood (Blackard and Tennes 1984). Transfer of THC to the fetus was greater in early pregnancy. THC also concentrates into breast milk from maternal plasma due to its high lipophilicity (Atkinson et al. 1988; Perez-Reyes and Wall 1982).

2.3 Metabolism

2.3.1 Hepatic Metabolism

Burstein et al. were the first to show that 11-OH-THC and THCCOOH were primary metabolites of THC in rabbits and rhesus monkeys (Ben-Zvi et al. 1976; Ben-Zvi and Burstein 1974; Burstein et al. 1972). They also documented that THC could be metabolized in the brain. Harvey et al. monitored the metabolism of THC, CBD, and CBN in mice, rats, and guinea pigs and found extensive metabolism, but with inter-species variation (Harvey et al. 1979). Phase I oxidation reactions include allylic and aliphatic hydroxylations, oxidation of alcohols to ketones and acids, beta-oxidation, and degradation of the pentyl side chain. Conjugation with glucuronic acid is a common phase II reaction. 11-OH-THC was the primary metabolite in all three species, followed by 8α-OH-THC concentrations in the mouse and rat, and 8β-OH-THC in guinea pig. Side chain hydroxylation was common in all three species. THCCOOH concentrations were higher in the mouse and rat, while THCCOOH glucuronide concentrations predominated in the guinea pig. THC concentrations accumulated in the liver, lung, heart, and spleen.

The primary metabolic routes and metabolites of THC are depicted in Fig. 4. Hydroxylation of THC at C9 by the hepatic cytochrome P450 enzyme system leads to production of the equipotent metabolite 11-OH-THC (Iribarne et al. 1996; Matsunaga et al. 1995), believed by early investigators to be the true psychoactive analyte (Lemberger et al. 1970). Cytochrome P450 2C9, 2C19, and 3A4 are involved in the oxidation of THC (Matsunaga et al. 1995). More than 100 THC metabolites including di- and tri-hydroxy compounds, ketones, aldehydes, and carboxylic acids have been identified (Grotenhermen 2003; Harvey 2001; Harvey and Paton 1986). Although 11-OH-THC predominates as the first oxidation product, significant amounts of 8β-OH-THC and lower amounts of the 8α-OH-THC are formed. Much

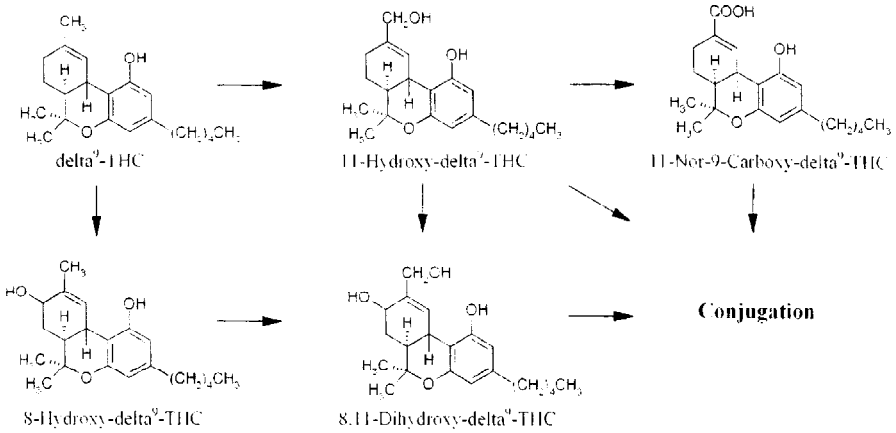

Fig. 4. Major metabolic routes for Δ^9-tetrahydrocannabinol (*THC*) in humans (M.A. Huestis, unpublished data)

lower plasma 11-OH-THC concentrations (approximately 10% of THC concentrations) are found after cannabis smoking than after oral administration (Wall et al. 1983). Peak 11-OH-THC concentrations occurred approximately 13 min after the start of smoking (Huestis et al. 1992b). Bornheim et al. reported that 11-OH-THC and 8-β-OH-THC were formed at the same rate in human liver microsomes, with smaller amounts of epoxy-hexahydrocannabinol, 8α-OH-THC and 8-keto-THC (Bornheim et al. 1992). Cytochrome P450 2C9 is believed to be primarily responsible for the formation of 11-OH-THC, whereas P450 3A catalyzes the formation of 8-β-OH-THC, epoxy hexahydrocannabinol, and other minor metabolites. Less than a fivefold variability in 2C9 rates of activity were observed, while much higher variability was noted for 3A. Dihydroxylation of THC yields 8β-11-di-OH-THC. Excretion of 8β-11-di-OH-THC in urine was reported to be a good biomarker for recent cannabis use (McBurney et al. 1986).

Oxidation of the active 11-OH-THC produces the inactive metabolite 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) (Lemberger et al. 1970; Mechoulam et al. 1973). THCCOOH and its glucuronide conjugate are the major end products of biotransformation in most species, including man (Halldin et al. 1982; Harvey and Paton 1986). THCCOOH concentrations gradually increase and are greater than THC concentrations 30 to 45 min after the end of smoking (Mason and McBay 1985). After ingestion of a single 10 mg oral dose of Marinol, plasma THCCOOH concentrations were higher than THC and 11-OH-THC concentrations as early as 1 h after dosing (Sporkert et al. 2001). Unlike after smoking, THC and 11-OH-THC concentrations are similar after oral THC administration. Phase II metabolism of THCCOOH involves addition of glucuronic acid, and less commonly, sulfate, glutathione, amino acids, and fatty acids via the C11 carboxyl group. The phenolic hydroxyl group may be a target as well. It is also possible to have two glucuronic acid moieties attached to THCCOOH, although steric hindrance at the phenolic hydroxyl group could be a factor. Addition of the glucuronide group improves water solubility facilitating excretion, but renal clear-

ance of these polar metabolites is low due to extensive protein binding (Hunt and Jones 1980). No significant differences in metabolism between men and women have been reported (Wall et al. 1983).

After the initial distribution phase, the rate-limiting step in the metabolism of THC is its redistribution from lipid depots into blood (Garrett and Hunt 1977). Lemberger et al. suggested that frequent cannabis smoking could induce THC metabolism (Lemberger et al. 1971). However, later studies did not replicate this finding (Agurell et al. 1986; Harvey and Paton 1986).

2.3.2
Extrahepatic Metabolism

Other tissues, including brain, intestine, and lung, may contribute to the metabolism of THC, although alternate hydroxylation pathways may be more prominent (Ben-Zvi et al. 1976; Greene and Saunders 1974; Krishna and Klotz 1994; Watanabe et al. 1988; Widman et al. 1975). An extrahepatic metabolic site should be suspected whenever total body clearance exceeds blood flow to the liver, or if severe liver dysfunction does not affect metabolic clearance (Krishna and Klotz 1994). Of the ten mammalian classes of cytochrome P450 systems, the cytochrome 1, 2, 3, and 4 families primarily metabolize xenobiotics and are found in the liver, small intestine, peripheral blood, bone marrow, and mast cells in decreasing concentrations, with the lowest concentrations in the brain, pancreas, gall bladder, kidney, skin, salivary glands, and testes. Within the brain, higher concentrations of cytochrome P450 enzymes are found in the brain stem and cerebellum (Krishna and Klotz 1994). The hydrolyzing enzymes, non-specific esterases, β-glucuronidases, and sulfatases, are primarily found in the gastrointestinal tract. Side chain hydroxylation of THC is prominent in THC metabolism by the lung. Metabolism of THC by fresh biopsies of human intestinal mucosa yielded polar hydroxylated metabolites that directly correlated with time and the amount of intestinal tissue (Greene and Saunders 1974).

In a study of the metabolism of THC in the brains of mice, rats, guinea pigs, and rabbits, Watanabe et al. found that brain microsomes oxidized THC to monohydroxylated metabolites (Watanabe et al. 1988). Hydroxylation of C4 of the pentyl side chain produced the most common THC metabolite in the brains of these animals, similar to THC metabolites produced in the lung. These metabolites are pharmacologically active, but their relative activity is unknown.

2.4
Elimination

Within 5 days, a total of 80% to 90% of a THC dose is excreted, mostly as hydroxylated and carboxylated metabolites (Halldin et al. 1982; Harvey 2001). More than 65% is excreted in the feces, with approximately 20% eliminated in the urine (Wall et al. 1983). Numerous acidic metabolites are found in the urine, many of which

are conjugated with glucuronic acid to increase their water solubility. The primary urinary metabolite is the acid-linked THCCOOH glucuronide conjugate (Williams and Moffat 1980), while 11-OH-THC predominates in the feces (Harvey 2001). The concentration of free THCCOOH and the cross-reactivity of glucuronide-bound THCCOOH enable cannabinoid immunoassays to be performed directly on non-hydrolyzed urine, but confirmation and quantification of THCCOOH is usually performed after alkaline hydrolysis or β-glucuronidase hydrolysis to free THC-COOH for measurement by GC/MS. It is generally thought that little to no THC or 11-OH-THC is excreted in the urine.

2.4.1 Terminal Elimination Half-Lives of THCCOOH

Another common problem with studying the pharmacokinetics of cannabinoids in humans is the need for highly sensitive procedures to measure low cannabinoid concentrations in the terminal phase of excretion, and the requirement for monitoring plasma concentrations over an extended period to adequately determine cannabinoid half-lives. Many studies utilized short sampling intervals of 24 to 72 h that underestimate terminal THC and THCCOOH half-lives. The slow release of THC from lipid storage compartments and significant enterohepatic circulation contribute to THC's long terminal half-life in plasma, reported as greater than 4.1 days in chronic cannabis users (Johansson et al. 1988). Isotopically labeled THC and sensitive analytical procedures were used to obtain this drug half-life. Garrett and Hunt reported that 10% to 15% of the THC dose is enterohepatically circulated in dogs (Garrett and Hunt 1977). Johansson et al. reported a THC-COOH plasma elimination half-life up to 12.6 days in a chronic cannabis user when monitoring THCCOOH concentrations for 4 weeks (Johansson et al. 1989a). Mean plasma THCCOOH elimination half-lives were 5.2±0.8 and 6.2±6.7 days for frequent and infrequent cannabis users, respectively. Similarly, when sensitive analytical procedures and sufficient sampling periods were employed for determining the terminal urinary excretion half-life of THCCOOH, it was estimated to be 3 to 4 days (Johansson and Halldin 1989). Urinary THCCOOH concentrations drop rapidly until approximately 20 to 50 ng/ml, and then decrease at a much slower rate. No significant pharmacokinetic differences between chronic and occasional users have been substantiated (Chiang and Rapaka 1987).

2.4.2 Percentage THC Dose Excreted as Urinary THCCOOH

An average of 93.9±24.5 µg THCCOOH (range 34.6–171.6) was measured in urine over a 7-day period following smoking of a single 1.75% THC cigarette containing approximately 18 mg THC (Huestis et al. 1996). The average amount of THCCOOH excreted in the same time period following the high dose (3.55% THC containing approximately 34 mg THC) was 197.4±33.6 µg (range 107.5–305.0). This represented an average of only 0.54±0.14% and 0.53±0.09% of the original amount of

THC in the low- and high-dose cigarettes, respectively. The small percentage of the total dose found in the urine as THCCOOH is not surprising considering the many factors that influence THCCOOH excretion after smoking. Prior to harvesting, cannabis plant material contains little active THC. When smoked, THC carboxylic acids spontaneously decarboxylate to produce THC with nearly complete conversion upon heating. Pyrolysis of THC during smoking destroys additional drug. Drug availability is further reduced by loss of drug in the side-stream smoke and drug remaining in the unsmoked cigarette butt. These factors contribute to high variability in drug delivery by the smoked route. It is estimated that the systemic availability of smoked THC is approximately 8% to 24% and that bioavailability depends strongly upon the experience of the cannabis user (Lindgren et al. 1981; Ohlsson et al. 1980; Perez-Reyes et al. 1981). THC bioavailability is reduced due to the combined effect of these factors; the actual available dose is much lower than the amount of THC and THC precursor present in the cigarette. Most of the THC dose is excreted in the feces (30%–65%), rather than in the urine (20%) (Wall and Perez-Reyes 1981; Wall et al. 1983). Another factor affecting the low amount of recovered dose is measurement of a single metabolite. Numerous cannabinoid metabolites are produced in humans as a result of THC metabolism, most of which are not measured or included in the percentage-of-dose-excreted calculations when utilizing GC/MS.

2.4.3 Cannabinoid Glucuronide Conjugates

Specimen preparation for cannabinoid testing frequently includes a hydrolysis step to free cannabinoids from their glucuronide conjugates. Most GC/MS confirmation procedures in urine measure total THCCOOH following either an enzymatic hydrolysis with β-glucuronidase, or more commonly, an alkaline hydrolysis with sodium hydroxide. Alkaline hydrolysis appears to efficiently hydrolyze the ester THCCOOH glucuronide linkage.

2.4.4 Urinary Biomarkers of Recent Cannabis Use

Significantly higher concentrations of THC and 11-OH-THC in urine are observed when *Escherichia coli* β-glucuronidase is employed in the hydrolysis method compared to either *Helix pomatia* β-glucuronidase or base (Kemp et al. 1995a,b). THC and 11-OH-THC are primarily excreted in urine as glucuronide conjugates that are resistant to cleavage by alkaline hydrolysis and by enzymatic hydrolysis procedures employing some types of β-glucuronidase. Kemp et al. demonstrated that β-glucuronidase from *E. coli* was needed to hydrolyze the ether glucuronide linkages of the active cannabinoid analytes. Mean THC concentration in urine specimens from seven subjects collected after each had smoked a single 3.58% marijuana cigarette was 22 ng/ml using the *E. coli* β-glucuronidase hydrolysis

method, while THC concentrations using either *H. pomatia* β-glucuronidase or base hydrolysis methods were near zero (Kemp et al. 1995a,b). Similar differences were found for 11-OH-THC with a mean concentration of 72 ng/ml from the *E. coli* method and concentrations less than 10 ng/ml from the other methods. The authors suggested that finding THC and/or 11-OH-THC in the urine might provide a reliable marker of recent cannabis use, but adequate data from controlled drug administration studies were not yet available to support or refute this observation. Using a modified analytical method with *E. coli* β-glucuronidase, we have analyzed hundreds of urine specimens collected following controlled THC administration. We found that 11-OH-THC may be excreted in the urine of chronic cannabis users for a much longer period of time, beyond the period of pharmacodynamic effects and performance impairment. However, it does appear that THC is only present in urine for a short period after use. Additional research is necessary to determine the validity of estimating time of cannabis use from THC and 11-OH-THC concentrations in urine.

3 Pharmacokinetics of Cannabidiol

Cannabidiol (CBD) is a natural constituent of *Cannabis sativa* that is not psychoactive (Benowitz et al. 1980; Perez-Reyes et al. 1973b; Pertwee 2004), but possesses pharmacological activity that is being explored for therapeutic applications (Pertwee 2004). CBD has been reported to be neuroprotective (Hampson et al. 1998), analgesic (Holdcroft 1984; Karst et al. 2003; Vaughan and Christie 1984), sedating (Holdcroft 1984; Melamede 1984; Plasse 1984; Vaughan and Christie 1984), antiemetic (Plasse 1984), anti-spasmodic (Baker et al. 2000), and anti-inflammatory (Malfait et al. 2000). In addition, it has been reported that CBD blocks the anxiety produced by THC (Zuardi et al. 1982) and is useful in the treatment of autoimmune diseases (Melamede 1984). These potential therapeutic applications alone warrant investigation of CBD pharmacokinetics, but also, the controversy over whether CBD alters the pharmacokinetics of THC in a clinically significant manner needs to be resolved (Agurell et al. 1984; McArdle et al. 2001).

Cannabidiol metabolism is similar to that of THC, with primary oxidation of C9 to the hydroxy and carboxylic acid moieties (Agurell et al. 1986; Harvey and Mechoulam 1990) and side chain oxidation (Harvey et al. 1979; Harvey and Mechoulam 1990). Like THC, CBD is subjected to a significant first-pass effect; however, unlike THC, a large proportion of the dose is excreted unchanged in the feces (Wall et al. 1976). Benowitz et al. reported that CBD was an in vitro inhibitor of liver microsomal drug-metabolizing enzymes and inhibited hexobarbital metabolism in humans (Benowitz et al. 1980). Others have reported that CBD selectively inhibits THC metabolite formation in vitro (McArdle et al. 2001). Hunt et al. reported that THC's pharmacokinetic properties were not affected by CBD, except for a slight slowing of the metabolism of 11-OH-THC to THCCOOH (Hunt et al. 1981). Co-administration of CBD did not significantly affect the total clearance, volume of distribution, and terminal elimination half-lives of THC metabolites.

The bioavailability of CBD following the smoked route averaged 31% (range 11%–45%) as compared to intravenously administered drug (Ohlsson et al. 1986).

Similar results were obtained when comparing the sublingual administration of 25 mg THC to 25 mg THC and 25 mg CBD in cannabis-based medicinal extracts (Guy and Robson 2004a). There were no statistically significant differences in mean THC C_{max}, half-life, or AUC for THC and 11-OH-THC following administration of these two compounds. The only statistically significant difference was in the time of maximum THC concentration. Despite administration of equivalent amounts of THC and CBD, lower plasma concentrations of CBD were always observed. In a separate evaluation of 10 mg THC and 10 mg CBD from a cannabis-based medicine extract, the pharmacokinetics of THC, 11-OH-THC, and CBD were determined after sublingual, buccal, oro-pharyngeal, and oral administration (Guy and Robson 2004b). All three analytes were measurable approximately 30 min after dosing with higher THC than CBD concentrations. 11-OH-THC generally exceeded THC concentrations within 45 min of dosing. Mean C_{max} concentrations for THC, CBD, and 11-OH-THC were less than 5, less than 2, and less than 7 ng/ml across all administration routes. High intra- and inter-subject variability was noted.

4 Pharmacokinetics of Cannabinol

Cannabinol (CBN) is a natural constituent of *Cannabis sativa* with approximately 10% of the activity of THC (Perez-Reyes 1985; Perez-Reyes et al. 1973b). CBN metabolism is also similar to that of THC with the hydroxylation of C9 yielding the primary metabolite (Wall et al. 1976). Due to the fact that one additional ring is aromatic, CBN is metabolized less extensively and more slowly than THC (Harvey et al. 1979). The average bioavailability of a smoked CBN dose, as compared to intravenous CBN, was 41% with a range of 8% to 77% (Ohlsson et al. 1985).

5 Interpretation of Cannabinoid Concentrations in Biological Fluids

5.1 Plasma Concentrations of THC, 11-OH-THC, and THCCOOH

Compared to other drugs of abuse, analysis of cannabinoids presents some difficult challenges. THC and 11-OH-THC are highly lipophilic and present in low concentrations in body fluids. Complex specimen matrices, i.e., blood, sweat, and hair, may require multi-step extractions to separate cannabinoids from endogenous lipids and proteins. Care must be taken to avoid low recoveries of cannabinoids due to their high affinity to glass and plastic containers, and to collection devices for alternate matrices (Blanc et al. 1993; Bloom 1982; Christophersen 1986; Joern 1992). THC and THCCOOH are predominantly found in the plasma fraction of blood, where 95% to 99% are bound to lipoproteins. Only about 10% of either

compound is found in the erythrocytes (Garrett and Hunt 1974; Widman et al. 1974). Whole blood cannabinoid concentrations are approximately one-half the concentrations found in plasma specimens, due to the low partition coefficient of drug into erythrocytes (Huang et al. 2001; Mason and McBay 1985; Owens et al. 1981; Widman et al. 1974).

5.1.1 Following Intravenous THC Administration

Kelly et al. intravenously administered 5 mg of THC to eight males and periodically monitored THC, THCCOOH, and THCCOOH-glucuronide conjugates by GC/MS [limit of detection (LOD) 1 ng/ml for THC and THCCOOH] in plasma with and without alkaline hydrolysis for up to 10 h, and then once daily for up to 12 days (Kelly and Jones 1992). The elimination half-lives of THC, THCCOOH, and THCCOOH-glucuronide in the plasma of frequent cannabis users were 116.8 min, 5.2 days, and 6.8 days, respectively, and 93.3 min, 6.2 days and 3.7 days in infrequent users. Conjugated THCCOOH was detected in the plasma of 75% of the frequent and 25% of the infrequent users at day 12.

5.1.2 Following Smoked Cannabis Administration

THC detection times in plasma of 3.5 to 5.5 h were reported in individuals who smoked two cannabis cigarettes containing a total of approximately 10 mg of THC (GC/MS LOD 0.8 ng/ml) (McBurney et al. 1986) and up to 13 days for deuterated THC in the blood of chronic cannabis users who smoked four deuterium-labeled THC cigarettes (GC/MS LOD = 0.02 ng/ml) (Johansson et al. 1988). In the latter study, the terminal half-life of THC in plasma was determined to be approximately 4.1 days, as compared to frequent estimates of 24 to 36 h in several other studies (Agurell et al. 1984; Lemberger et al. 1972; Wall et al. 1983) that lacked the sensitivity and the lengthy monitoring window of the radio-labeled protocol.

Few controlled drug administration studies have monitored active 11-OH-THC plasma concentrations. Huestis et al. found plasma 11-OH-THC concentrations to be approximately 6% to 10% of the concurrent THC concentrations for up to 45 min after the start of smoking (Huestis et al. 1992b). Mean peak 11-OH-THC concentrations occurred 13.5 min (range 9.0–22.8) after the start of smoking and were 6.7 ng/ml (range 3.3–10.4) and 7.5 ng/ml (range 3.8–16) after one 1.75% or 3.55% THC cigarette, respectively. 11-OH-THC concentrations decreased gradually with mean detection times of 4.5 h and 11.2 h after the two doses.

THCCOOH concentrations were monitored in human plasma for 7 days after controlled cannabis smoking (Huestis et al. 1992b). This inactive metabolite was detected in all subjects' plasma by 8 min after the start of smoking. THCCOOH concentrations in plasma increased slowly and plateaued for up to 4 h. Peak concentrations were consistently lower than peak THC concentrations, but

were higher than peak 11-OH-THC concentrations. Mean peak THCCOOH concentrations were 24.5 ng/ml (range 15–54) and 54.0 ng/ml (range 22–101) after the 1.75% and 3.55% THC cigarettes, respectively. Following smoking of the lower dose, THCCOOH was detected from 48 to 168 h, with a mean of 84 h. Detection times ranged from 72 to 168 h with a mean of 152 h following smoking of the higher dose. The time course of detection of THCCOOH is much longer than either that of THC or 11-OH-THC. The area under the curve for the mean data from 0 to 168 h was 36.5 and 72.2 ng-h/ml, respectively, for the low- and high-dose conditions, demonstrating a dose–response relationship for the mean data (Huestis et al. 1992b). Figure 2 shows individual THC concentration time profiles for six subjects and demonstrates the large inter-subject variability of the smoked route of drug administration. Moeller et al. measured serum THC and THCCOOH concentrations in 24 experienced users from 40 to 220 min after smoking 300-μg/kg cannabis cigarettes (Moeller et al. 1992). Mean serum THC and THCCOOH concentrations were approximately 13 and 22 ng/ml at 40 min and 1 and 13 ng/ml at 220 min after smoking. The half-life of the rapid distribution phase of THC was estimated to be 55 min over this short sampling interval.

Most plasma or whole blood cannabinoid analytical methods have not included measurement of the glucuronide conjugates of THC, 11-OH-THC, or THCCOOH. The relative percentages of free and conjugated cannabinoids in plasma after different routes of drug administration are unclear. Even the efficacy of alkaline and enzymatic hydrolysis procedures to release analytes from their conjugates is not fully understood (Feng et al. 2000; Foltz 1984; Green et al. 1997; Kelly and Jones 1992; Kemp et al. 1995a,b; Law et al. 1984; Manno et al. 2001; McBurney et al. 1986; Wall and Perez-Reyes 1981; Wall and Taylor 1984; Widman et al. 1974). In general, conjugate concentrations are believed to be lower in plasma following intravenous or smoked cannabis, but may be of much greater magnitude after oral drug administration. There is no indication that the glucuronide conjugates are active, although supporting data are lacking.

5.1.3 Oral THC

After oral and sublingual administration of THC, THC-containing food products, or cannabis-based extracts, concentrations of THC and 11-OH-THC are much lower than after smoked administration. Plasma concentrations of THC in patients receiving 10 to 15 mg of Marinol as an anti-emetic were low to non-measurable in 57 patients (Shaw et al. 1991). Brenneisen et al. found peak plasma concentrations of THC and THCCOOH after daily oral 10 to 15 mg Marinol doses of 2.1 to 16.9 ng/ml within 1 to 8 h and 74.5 to 244 ng/ml within 2 to 8 h, respectively (Brenneisen et al. 1996). In our oral THC controlled administration studies, peak plasma THC, 11-OH-THC, and THCCOOH concentrations were less than 6.5, 5.6, and 24.4 ng/ml, respectively, following up to 14.8 mg/day of THC in the form of THC-containing food products or Marinol (Nebro et al. 2004). Peak concentrations and time to peak concentrations varied, sometimes considerably, between subjects. Plasma

THC and 11-OH-THC were negative for all participants and for all doses by 16 h after the last THC dose. Plasma THCCOOH persisted for a longer period of time following the two highest doses of 7.5 mg/day dronabinol and 14.8 mg/day THC in hemp oil. Ohlsson et al. reported that orally administered THC (20 mg in a cookie) yielded low and irregular plasma concentrations compared to intravenous and inhaled THC (Ohlsson et al. 1980).

5.1.4
Cannabinoid Concentrations After Frequent Use

Most THC plasma data have been collected following acute exposure; less is known of plasma THC concentrations in frequent users. Peat reported THC, 11-OH-THC, and THCCOOH plasma concentrations in frequent cannabis users of 0.86±0.22, 0.46±0.17, and 45.8±3.1 ng/ml, respectively, a minimum of 12 h after the last smoked dose (Peat 1989). No difference in terminal half-life in frequent or infrequent users was observed. Johansson et al. administered radiolabeled THC to frequent cannabis users and found a terminal elimination half-life of 4.1 days for THC in plasma due to extensive storage and release from body fat (Johansson et al. 1988).

5.1.5
Prediction Models for Estimation of Cannabis Exposure

Although there continues to be controversy in the interpretation of blood cannabinoid results, some general concepts have wide support. A dose–response relationship has been demonstrated for smoked THC and THC plasma concentrations (Perez-Reyes et al. 1981, 1982). It is well established that plasma THC concentrations begin to decline prior to the time of peak effects, although it has been shown that THC effects appear rapidly after initiation of smoking (Huestis et al. 1992d). Individual drug concentrations and ratios of cannabinoid metabolite to parent drug concentration have been suggested as potentially useful indicators of recent drug use (Hanson et al. 1983; Law et al. 1984). The ratio of plasma THCCOOH to THC was found to exceed 1 at 45 min after cannabis smoking (Kelly and Jones 1992). This is in agreement with results reported by Mason and McBay (1985) and Huestis et al. (1992d) who found that peak effects occurred when THC and THCCOOH concentrations reached equivalency, within 30 to 45 min after initiation of smoking. Measurement of cannabinoid analytes with short time courses of detection (e.g., 8β, 11-dihydroxy-tetrahydrocannabinol) as a marker of recent exposure has not found widespread use (Mason and McBay 1985). Recent exposure (6 to 8 h) and possible impairment have been linked to plasma THC concentrations in excess of 2 to 3 ng/ml (Huestis et al. 1992b; Mason and McBay 1985). Gjerde et al. (1993) suggested that 1.6 ng/ml THC in whole blood might indicate possible impairment. This correlates well with the suggested concentration of plasma THC, due to the fact that THC in hemolyzed blood is approximately one-half the concentration of

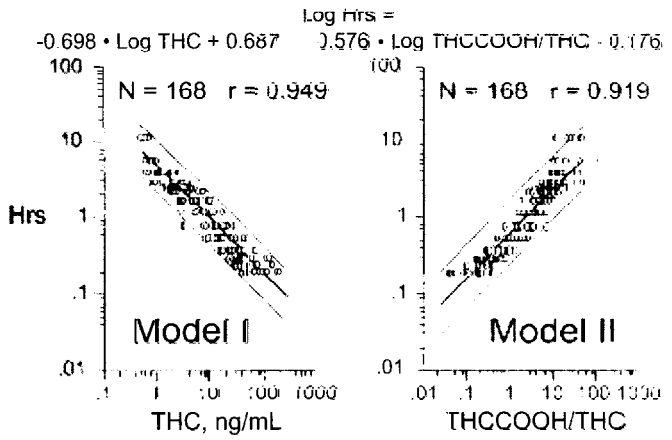

Fig. 5. Predictive mathematical models for estimating the elapsed time in hours (*Hrs*) of last cannabis use based on plasma Δ^9-tetrahydrocannabinol (*THC*) and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (*THCCOOH*) concentrations. (Reproduced from the *Journal of Analytic Toxicology*, by permission of Preston Publications, a division of Preston Industries; Huestis et al. 1992c, Fig. 1 therein)

plasma THC (Mason and McBay 1984). Interpretation is further complicated by residual THC and THCCOOH concentrations found in blood of frequent cannabis users. In general, it is suggested that chronic cannabis smokers may have residual plasma THC concentrations of less than 2 ng/ml 12 h after smoking cannabis (Peat 1989). Significantly higher residual concentrations of THCCOOH may be found.

Having an accurate prediction of the time of cannabis exposure would provide valuable information in establishing the role of cannabis as a contributing factor to events under investigation. Two mathematical models for the prediction of time of cannabis use from the analysis of a single plasma specimen for cannabinoids were developed (Huestis et al. 1992c). Model I was based on THC concentrations and model II was based on the ratio of THCCOOH to THC in plasma (Fig. 5). Both correctly predicted the times of exposure within the 95% confidence interval for more than 90% of the specimens evaluated. Furthermore, plasma THC and THCCOOH concentrations reported in the literature following oral and smoked cannabis exposure, in frequent and infrequent cannabis smokers, and with measurements obtained by a wide variety of methods, including radioimmunoassay and GC/MS, were evaluated with the models. Plasma THC concentrations less than 2.0 ng/ml were excluded from use in both models due to the possibility of residual THC concentrations in frequent smokers. Manno et al. evaluated the models' usefulness in predicting the time of cannabis use in a controlled cannabis smoking study (Manno et al. 2001). The models were found to accurately predict the time of last use within the 95% confidence intervals. Due to the limited distribution of THC and THCCOOH into red blood cells, it is important to remember that when comparing whole blood THC and/or THCCOOH concentrations to plasma concentrations, it is necessary to double the whole blood concentration prior to comparison.

5.2 Urinary THCCOOH Concentrations

Detection of cannabinoids in urine is indicative of prior cannabis exposure, but the long excretion half-life of THCCOOH in the body, especially in chronic cannabis users, makes it difficult to predict the timing of past drug use. In a single extreme case, one individual's urine was positive at a concentration greater than 20 ng/ml by immunoassay up to 67 days after last drug exposure (Ellis et al. 1985). This individual had used cannabis heavily for more than 10 years. However, a naïve user's urine may be found negative by immunoassay after only a few hours following the smoking of a single cannabis cigarette (Huestis et al. 1995). Assay cutoff concentrations and the sensitivity and specificity of the immunoassay affect drug detection times. A positive urine test for cannabinoids indicates only that drug exposure has occurred. The result does not provide information on the route of administration, the amount of drug exposure, when drug exposure occurred, or the degree of impairment.

To date, there are too few urinary THC and 11-OH-THC data to guide interpretation of positive urine cannabinoid tests; however, data are available for guiding interpretation of total urinary THCCOOH concentrations. Total THCCOOH concentrations include both the free THCCOOH and THCCOOH-glucuronide concentrations that are obtained after alkaline or enzymatic hydrolysis. Substantial intra- and inter-subject variability occurs in patterns of THCCOOH excretion. THCCOOH concentration in the first specimen after smoking is indicative of how rapidly the metabolite can appear in urine. Mean first urine THCCOOH concentrations were 47±22.3 ng/ml and 75.3±48.9 ng/ml after smoking one 1.75% or 3.55% THC cigarette, respectively (Huestis et al. 1996). Of the subjects' first urine specimens, 50% after the low dose and 83% after the high dose were positive by GC/MS at a 15 ng/ml THCCOOH cutoff concentration. Thus, THCCOOH concentrations in the first urine specimen are dependent upon the relative potency of the cigarette, the elapsed time following drug administration, smoking efficiency, and individual differences in drug metabolism and excretion. Mean peak urine THCCOOH concentrations averaged 89.8±31.9 ng/ml (range 20.6–234.2) and 153.4±49.2 ng/ml (range 29.9–355.2) following smoking of approximately 15.8 and 33.8 mg THC, respectively. The mean times of peak urine concentration were 7.7±0.8 h after the 1.75% THC and 13.9±3.5 h after the 3.55% THC dose. Although peak concentrations appeared to be dose related, there was a 12-fold variation between individuals.

5.2.1 THCCOOH Detection Windows in Urine

Drug detection time, or the duration of time after drug administration that an individual's urine tests positive for cannabinoids, is an important factor in the interpretation of urine drug results. Detection time is dependent on pharmacological factors (e.g., drug dose, route of administration, rates of metabolism and excretion)

and analytical factors (e.g., assay sensitivity, specificity, accuracy). Mean detection times in urine following smoking vary considerably between subjects, even in controlled smoking studies where cannabis dosing is standardized and smoking is computer-paced. During the terminal elimination phase, consecutive urine specimens may fluctuate between positive and negative as THCCOOH concentrations approach the cutoff concentration. It may be important in drug treatment settings or in clinical trials to differentiate between new drug use and residual excretion of previously used cannabinoids. After smoking a 1.75% THC cigarette, three of six subjects had additional positive urine samples interspersed between negative urine samples (Huestis et al. 1995). This had the effect of producing much longer detection times for the last positive specimen. Using the 15 ng/ml confirmation cutoff for THCCOOH currently used for most urine drug testing, the mean GC/MS THCCOOH detection times for the last positive urine sample following the smoking of a single 1.75% or 3.55% THC cigarette were 33.7±9.2 h (range 8–68.5) and 88.6±23.2 h (range 57–122.3), respectively.

5.2.2 Normalization of Cannabinoid Urine Concentrations to Urine Creatinine Concentrations

Normalization of the cannabinoid drug concentration to the urine creatinine concentration aids in the differentiation of new vs prior cannabis use and reduces the variability of drug measurement due to urine dilution. Due to the long half-life of drug in the body, especially in chronic cannabis users, toxicologists and practitioners are frequently asked to determine if a positive urine test represents a new episode of drug use or represents continued excretion of residual drug. Random urine specimens contain varying amounts of creatinine depending on the degree of concentration of the urine. Hawks first suggested creatinine normalization of urine test results to account for variations in urine volume in the bladder (Hawks 1983). Whereas urine volume is highly variable due to changes in liquid, salt, and protein intake, exercise, and age, creatinine excretion is much more stable. Manno et al. recommended that an increase of 150% in the creatinine normalized cannabinoid concentration above the previous specimen be considered indicative of a new episode of drug exposure (Manno et al. 1984). If the increase is greater than or equal to the threshold selected, then new use is predicted. This approach has received wide attention for potential use in treatment and employee assistance programs, but there has been limited evaluation of the usefulness of this ratio under controlled dosing conditions. Huestis et al. conducted a controlled clinical study of the excretion profile of creatinine and cannabinoid metabolites in a group of six cannabis users who smoked two different doses of cannabis separated by weekly intervals (Huestis and Cone 1998b). As seen in Fig. 6, normalization of urinary THCCOOH concentration to the urinary creatinine concentration produces a smoother excretion pattern and facilitates interpretation of consecutive urine drug test results. A relative operating characteristic (ROC) curve was constructed from sensitivity and specificity data for 26 different cutoffs ranging from 10% to

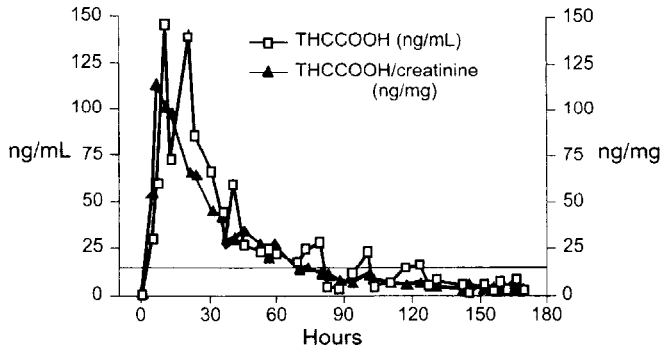

Fig. 6. Urine concentrations of 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (*THCCOOH*; ng/ml, and ng/mg creatinine) for one subject after smoking a single 3.55% THC cigarette. (Reproduced from the *Journal of Analytic Toxicology* by permission of Preston Publications, a division of Preston Industries; Huestis and Cone 1998b, Fig. 3 therein)

200%. The most accurate ratio (85.4%) was 50%, with a sensitivity of 80.1% and a specificity of 90.2%, with 5.6% false-positive and 7.4% false-negative predictions. If the previously recommended increase of 150% was used as the threshold for new use, sensitivity of detecting new use was only 33.4%, specificity was high at 99.8%, and there was an overall accuracy prediction of 74.2%. To further substantiate the validity of the derived ROC curve, urine cannabinoid metabolite and creatinine data from another controlled clinical trial that specifically addressed water dilution as a means of specimen adulteration were evaluated (Cone et al. 1998). Sensitivity, specificity, accuracy, percentage false positives, and percentage false negatives were 71.9%, 91.6%, 83.9%, 5.4%, and 10.7%, respectively, when the 50% criterion was applied. These data indicate selection of a threshold to evaluate sequential creatinine-normalized urine drug concentrations can improve the ability to distinguish residual excretion from new drug usage.

5.3 Oral Fluid Testing

Oral fluid is also a suitable specimen for monitoring cannabinoid exposure and is being evaluated for driving under the influence of drugs, drug treatment, workplace drug testing, and for clinical trials (Cairns et al. 1990; Gross and Soares 1978; Gross et al. 1985; Mura et al. 1999; Soares et al. 1976, 1982). Adequate sensitivity is best achieved with an assay directed toward detection of THC, rather than 11-OH-THC or THCCOOH. The oral mucosa is exposed to high concentrations of THC during smoking and serves as the source of THC found in oral fluid. Only minor amounts of drug and metabolites diffuse from the plasma into oral fluid (Hawks 1983). Following intravenous administration of radiolabeled THC, no radioactivity could be demonstrated in oral fluid (Hawks 1982). No measurable 11-OH-THC or THCCOOH was found in oral fluid collected immediately following and up to

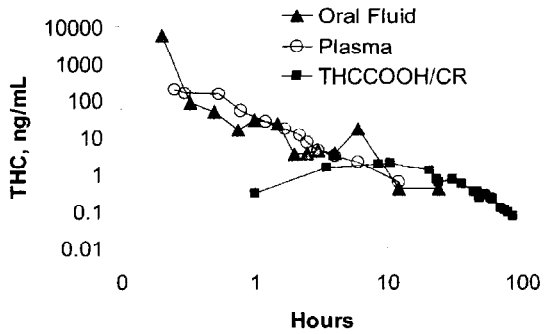

Fig. 7. Excretion patterns of Δ^9-tetrahydrocannabinol (THC) concentrations (ng/ml) in oral fluid and plasma, and urinary 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (ng THCCOOH/mg creatinine) in one human subject following smoking of a single cannabis cigarette (3.55%). The ng THCCOOH/mg creatinine ratio is illustrated for all urine specimens collected through the last positive specimen. Analyses were performed by GC-MS at cutoff concentrations of 0.5 ng/ml for oral fluid and plasma and 15 ng/ml for urine. (Reproduced from the *Journal of Analytic Toxicology* by permission of Preston Publications, a division of Preston Industries; Huestis and Cone 2004, Fig. 2 therein)

7 days after cannabis smoking with a GC/MS LOQ of 0.5 ng/ml (Huestis and Cone 1998a). Similarly, 11-OH-THC and THCCOOH were not detected in the oral fluid of 22 subjects who were documented cannabis users (Kintz et al. 2000). Oral fluid collected with the Salivette collection device was positive for THC in 14 of these 22 participants. Although no 11-OH-THC or THCCOOH was identified by GC/MS, cannabinol and cannabidiol were found in addition to THC. Hours after smoking, the oral mucosa serves as a depot for release of THC into the oral fluid. In addition, as detection limits continue to decrease with the development of new analytical instrumentation, it may be possible to measure low concentrations of THCCOOH in oral fluid.

Detection times of cannabinoids in oral fluid are shorter than in urine, and more indicative of recent cannabis use (Cairns et al. 1990; Gross et al. 1985). Oral fluid THC concentrations temporally correlate with plasma cannabinoid concentrations and behavioral and physiological effects, but wide intra- and inter-individual variation precludes the use of oral fluid concentrations as indicators of drug impairment (Huestis and Cone 1998a; Huestis et al. 1992a). THC may be detected at low concentrations by radioimmunoassay for up to 24 h after use. Figure 7 depicts excretion of THC in oral fluid and plasma and creatinine-normalized THCCOOH excretion in urine in one subject after smoking a single 3.55% cannabis cigarette (Huestis and Cone 2004). After smoking cannabis, oral fluid cannabinoid tests were positive for THC by GC/MS/MS with a cutoff of 0.5 ng/ml for 13±3 h (range 1–24) (Niedbala et al. 2001). After these times, occasional positive oral fluid results were interspersed with negative tests for up to 34 h. Peel et al. tested oral fluid samples from 56 drivers suspected of being under the influence of cannabis with the enzyme-multiplied immunoassay test (EMIT) screening test and GC/MS confirmation (Peel et al. 1984). They suggested that the ease and non-invasiveness of sample collection made oral fluid a useful alternative matrix for detection of

recent cannabis use. Oral fluid samples also are being evaluated in the European Union's Roadside Testing Assessment (ROSITA) Project to reduce the number of individuals driving under the influence of drugs and to improve road safety. The ease and non-invasiveness of oral fluid collection, reduced hazards in specimen handling and testing, and shorter detection window are attractive attributes of this method for identifying the presence of potential performance-impairing drugs.

In a recent study of smoked and oral cannabis use, the Intercept DOA Oral Specimen Collection Device and GC/MS/MS (cutoff 0.5 ng/ml) were paired to monitor oral fluid cannabinoids in ten participants (Niedbala et al. 2001). Oral fluid specimens tested positive following smoked cannabis for an average of 13±3 h (range 1–24). After these times, occasional positive oral fluid results were interspersed with negative tests for up to 34 h. A different oral fluid collection device, the Cozart RapiScan device, utilizes a 10 ng/ml cannabinoid cutoff to screen for cannabis use (Jehanli et al. 2001). Positive oral fluid cannabinoid tests were not obtained more than 2 h after last use, suggesting that much lower cutoff concentrations were needed to improve sensitivity. A procedure for direct analysis of cannabinoids in oral fluid with solid-phase microextraction and ion trap GC/MS has been developed with a limit of detection of 1.0 ng/ml (Hall et al. 1998). Detection of cannabinoids in oral fluid is a rapidly developing field; however, there are many scientific issues to resolve. One of the most important is the degree of absorption of the drug to oral fluid collection devices.

5.4 Cannabinoids in Sweat

To date, there are no published data on the excretion of cannabinoids in sweat following controlled THC administration. Sweat testing is being applied to monitor cannabis use in drug treatment, criminal justice, workplace drug testing, and clinical studies (Huestis and Cone 1998a; Kidwell et al. 1998). In 1989, Balabanova and Schneider utilized radioimmunoassay to detect cannabinoids in apocrine sweat (Balabanova and Schneider 1989). Currently, there is a single commercially available sweat collection device, the PharmCheck patch, offered by PharmChem Laboratories in Texas, USA. Generally, the patch is worn for 7 days and exchanged for a new patch once each week during visits to the treatment clinic or parole officer. Theoretically, this permits constant monitoring of drug use throughout the week, extending the window of drug detection and improving test sensitivity. As with oral fluid testing, this is a developing analytical technique with much to be learned about the pharmacokinetics of cannabinoid excretion in sweat, potential reabsorption of THC by the skin, possible degradation of THC on the patch, and adsorption of THC onto the patch collection device. It is known that THC is the primary analyte detected in sweat, with little 11-OH-THC and THCCOOH. Several investigators have evaluated the sensitivity and specificity of different screening assays for detecting cannabinoids in sweat (Mura et al. 1999; Samyn and van Haeren 2000). Kintz et al. identified THC (4–38 ng/patch) in 20 known heroin abusers who wore the PharmChek patch for 5 days while attending a detoxification center (Kintz

et al. 1997). Sweat was extracted with methanol and analyzed by GC/MS. The same investigators also evaluated forehead swipes with cosmetic pads for monitoring cannabinoids in sweat from individuals suspected of driving under the influence of drugs (Kintz et al. 2000). THC, but not 11-OH-THC or THCCOOH, was detected (4 to 152 ng/pad) by electron impact GC/MS in the sweat of 16 of 22 individuals who tested positive for cannabinoids in urine. Ion trap tandem mass spectrometry has also been used to measure cannabinoids in sweat collected with the PharmChek sweat patch with a limit of detection of 1 ng/patch (Ehorn et al. 1994).

5.5 Cannabinoids in Hair

There are multiple mechanisms for the incorporation of cannabinoids in hair. THC and metabolites may be incorporated into the hair bulb that is surrounded by capillaries. Drug may also diffuse into hair from sebum that is secreted onto the hair shaft and from sweat that is excreted onto the skin surface. Drug may also be incorporated into hair from the environment. Cannabis is primarily smoked, providing an opportunity for environmental contamination of hair with THC in cannabis smoke. Basic drugs such as cocaine and methamphetamine concentrate in hair due to ionic bonding to melanin, the pigment in hair that determines hair color. The more neutral and lipophilic THC is not highly bound to melanin, resulting in much lower concentrations of THC in hair as compared to other drugs of abuse. Usually THC is present in hair at a higher concentration than its THCCOOH metabolite (Cairns et al. 1995; Cirimele 1996; Kintz et al. 1995; Moore et al. 2001). An advantage of measuring THCCOOH in hair is that THCCOOH is not present in cannabis smoke, avoiding the issue of passive exposure from the environment. Analysis of cannabinoids in hair is challenging due to the high analytical sensitivity required. THCCOOH is present in the femtogram to picogram per milligram of hair range. GC/MS/MS is required in most analytical techniques. A novel approach to the screening of hair specimens for the presence of cannabinoids in hair was proposed by Cirimele et al. (1996). They developed a rapid, simple GC/MS screening method for THC, cannabinol, and cannabidiol in hair that did not require derivatization prior to analysis. The method was found to be a sensitive screen for cannabis detection with GC/MS identification of THCCOOH recommended as a confirmatory procedure.

It is difficult to conduct controlled cannabinoid administration studies on the disposition of cannabinoids in hair because of the inability to differentiate administered drug from previously self-administered cannabis. If isotopically labeled drug were administered, it would be possible to identify newly administered drug in hair. There are advantages to monitoring drug use with hair testing including a wide window of drug detection, a less invasive specimen collection procedure, and the ability to collect a second specimen at a later time. However, one of the weakest aspects of testing for cannabinoids in hair is the low sensitivity of drug detection in this alternate matrix. In controlled cannabinoid administration studies conducted by Huestis et al., only about one-third of non-daily users and two-thirds

of daily cannabis users had positive cannabinoid hair tests by GC/MS/MS with detection limits of 1 ng/mg for THC and 0.1 ng/mg for THCCOOH. All participants had positive urine cannabinoid tests at the time of hair collection (unpublished data).

References

Adams IB, Martin BR (1996) Cannabis: pharmacology and toxicology in animals and humans. Addiction 91:1585–1614

Agurell S, Leander K (1971) Stability, transfer and absorption of cannabinoid constituents of cannabis (hashish) during smoking. Acta Pharm Suec 8:391–402

Agurell S, Gillespie H, Halldin M, Hollister LE, Johansson E, Lindgren JE, Ohlsson A, Szirmai M, Widman M (1984) A review of recent studies on the pharmacokinetics and metabolism of delta-1-tetrahydrocannabinol, cannabidiol and cannabinol in man. In: Paton SW, Nahas GG (eds) Marijuana '84. IRL Press, Oxford, pp 49–62

Agurell S, Halldin M, Lindgren JE, Ohlsson A, Widman M, Gillespie H, Hollister L (1986) Pharmacokinetics and metabolism of delta-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev 38:21–43

Atkinson HC, Begg EJ, Darrlow BA (1988) Drugs in human milk clinical pharmacokinetic considerations. Clin Pharmacokinet 14:217–240

Azorlosa JL, Heishman SJ, Stitzer ML, Mahaffey JM (1992) Marijuana smoking: effect of varying delta 9-tetrahydrocannabinol content and number of puffs. J Pharmacol Exp Ther 261:114–122

Bailey JR, Cunny HC, Paule M, Slikker W Jr (1987) Fetal disposition of delta-9-tetrahydrocannbinol (THC) during late pregnancy in the rhesus monkey. Toxicol Appl Pharmacol 90:315–321

Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, Layward L (2000) Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature 404:84–87

Balabanova S, Schneider E (1989) Nachweis von drogen im schweis. Beitr Gerichtl Med 48:45–49

Ben-Zvi Z, Burstein S (1974) 7-Oxo-delta-1-tetrahydrocannabinol: a novel metabolite of delta 1 tetrahydrocannabinol. Int J Clin Pharmacol Ther 8:223–229

Ben-Zvi Z, Bergen JR, Burstein S, Sehgal PK, Varanelli C (1976) The metabolism of delta-tetrahydrocannabinol in the rhesus monkey. In: Braude MC, Szara S (eds) The pharmacology of marijuana. Raven Press, New York, pp 63–75

Benowitz NL, Nguyen TL, Jones RT, Herning RI, Bachman J (1980) Metabolic and psychophysiologic studies of cannabidiol-hexobarbital interaction. Clin Pharmacol Ther 28:115–117

Binitie A (1975) Psychosis following ingestion of hemp in children. Psychopharmacologia 44:301–302

Blackard C, Tennes K (1984) Human placental transfer of cannabinoids. N Engl J Med 311:797

Blanc JA, Manneh VA, Ernst R, Berger DE, de Keczer SA, Chase C, Centofanti JM, DeLizza AJ (1993) Adsorption losses from urine-bases cannabinoid calibrators during routine use. Clin Chem 39:1705–1717

Bloom AS (1982) Effect of delta-9-tetrahydrocannabinol on the synthesis of dopamine and norepinephrine in mouse brain synaptosomes. J Pharmacol Exp Ther 221:97–103

Bornheim LM, Lasker JM, Raucy JL (1992) Human hepatic microsomal metabolism of delta-1-tetrahydrocannabinol. Drug Metab Dispos 20:241–246

Brenneisen R, Egli A, ElSohly MA, Henn V, Spiess Y (1996) The effect of orally and rectally administered delta-9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int J Clin Pharmacol Ther 34:446–452

Burstein S, Rosenfeld J, Wittstruck T (1972) Isolation and characterization of two major urinary metabolites of delta-1-tetrahydrocannabinol. Science 176:422–424

Cairns ER, Howard RC, Hung CT, Menkes DB (1990) Saliva THC levels and cannabis intoxication. Report No. 2411, Chemistry Division, Division of Scientific and Industrial Research, Lower Hutt, New Zealand, pp 1–71

Cairns T, Kippenberger DJ, Scholtz H, Baumgartner WA (1995) determination of carboxy-THC in hair by mass spectrometry/mass spectrometry. In: de Zeeuw RA, Al Hosani I, Al Munthiri S, Maqbool A (eds) Hair Analysis in Forensic Toxicology: proceedings of the 1995 international conference and workshop. The Organizing Committee of the conference, Abu Dhabi, pp 185–193

Cami J, Guerra D, Ugena B, Segura J, de La Torre R (1991) Effect of subject expectancy on the THC intoxication and disposition from smoked hashish cigarettes. Pharmacol Biochem Behav 40:115–119

Chiang CN, Rapaka RS (1987) Pharmacokinetics and disposition of cannabinoids. In: Rapaka RS, Makriyannis A (eds) NIDA research monograph—structure-activity relationships of the cannabinoids. National Institute on Drug Abuse, Rockville, pp 173–188

Christophersen AS (1986) TetraHydroCannabinol stability in whole blood: plastic versus glass containers. J Anal Toxicol 10:129–131

Cirimele V (1996) Cannabis and amphetamine determination in human hair. In: Kintz P (ed) Drug testing in hair. CRC Press, Boca Raton, pp 181–189

Cirimele V, Sachs H, Kintz P, Mangin P (1996) Testing human hair for cannabis. III. Rapid screening procedure for the simultaneous identification of delta9-tetrahydrocannabinol, cannabinol, and cannabidiol. J Anal Toxicol 20:13–16

Claussen U, Korte F (1968) Uber das verhalten von hanf und von delta-9-6a, 10a-trans-tetrahydrocannabinol biem rauchen. Justus Liebigs Ann Chem 713:162–165

Cone EJ, Lange R, Darwin WD (1998) In vivo adulteration: excess fluid ingestion causes false-negative marijuana and cocaine urine test results. J Anal Toxicol 22:460–473

Dewey WL, McMillan DE, Harris LS, Turk RF (1972) Distribution of radioactivity in brain of tolerant and nontolerant pigeons treated with 3-H-delta-9-tetrahydrocannabinol. Biochem Pharmacol 22:399–405

Ehorn C, Fretthold D, Maharaj M (1994) Ion trap GC/MS/MS for analysis of THC from sweat. Abstract presented at the Society of Forensic Toxicologists annual meeting, Tampa, 31 October–4 November, p 11

Ellis GM, Mann MA, Judson BA, Schramm NT, Tashchian A (1985) Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. Clin Pharmacol Ther 38:572–578

ElSohly HN, Boeren EG, Turner CE, ElSohly MA (1984) Constituents of cannabis sativa L. XXIV: Cannabitetrol, a new polyhydroxylated cannabinoid. In: Agurell S, Dewey WL, Willette RE (eds) The cannabinoids: chemical, pharmacologic and therapeutic aspects. Academic Press, Orlando, pp 89–96

Feng S, ElSohly MA, Salamone S, Salem MY (2000) Simultaneous analysis of delta-9-THC and its major metabolites in urine, plasma, and meconium by GC-MS using an immunoaffinity extraction procedure. J Anal Toxicol 24:395–402

Foltz RL (1984) Analysis of cannabinoids in physiological specimens by gas chromatography/mass spectrometry. In: Baselt RC (ed) Advances in analytical toxicology. Biomedical Publications, Foster City, pp 125–157

Garrett ER, Hunt CA (1974) Physiochemical properties, solubility, and protein binding of delta-9-tetrahydrocannabinol. J Pharm Pharm Sci 63:1056–1064

Garrett ER, Hunt CA (1977) Pharmacokinetics of delta-9-tetrahydrocannabinol in dogs. J Pharm Pharm Sci 66:395–406

Gjerde H, Beylich KM, Morland J (1993) Incidence of alcohol and drugs in fatally injured car drivers in Norway. Accid Anal Prev 25:479–483

Green MD, Belanger G, Hum DW, Belanger A, Tephly TR (1997) Glucuronidation of opioids, carboxylic acid-containing drugs, and hydroxylated xenobiotics catalyzed by expressed monkey UDP-glucuronosyltransferase 2B9 protein. Drug Metab Dispos 25:1389–1394

Greene ML, Saunders DR (1974) Metabolism of tetrahydrocannabinol by the small intestine. Gastroenterology 66:365–372

Gross SJ, Soares JR (1978) Validated direct blood delta-9-THC radioimmune quantitation. J Anal Toxicol 2:98–100

Gross SJ, Worthy TE, Nerder L, Zimmermann EG, Soares JR, Lomax P (1985) Detection of recent cannabis use by saliva delta-9-THC radioimmunoassay. J Anal Toxicol 9:1–5

Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 42:327–360

Gustafson RA, Moolchan ET, Barnes A, Levine B, Huestis MA (2003) Validated method for the simultaneous determination of delta-9-tetrahydrocannabinol (THC), 11-hydroxy-THC and 11-nor-9-carboxy-THC in human plasma using solid phase extraction and gas chromatography-mass spectrometry with positive chemical ionization. J Chromatogr B Analyt Technol Biomed Life Sci 798:145–154

Guy GW, Robson PJ (2004a) A phase I, double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK0215). J Cannabis Ther 3:121–152

Guy GW, Robson PJ (2004b) A phase I, open label, four-way crossover study to compare the pharmacokinetic profiles of a single dose of 20 mg of a cannabis based medicine extract (CBME) administered on 3 different areas of the buccal mucosa and to investigate the pharmacokinetics of CBME per oral in healthy male and female volunteers (GWPK0112). J Cannabis Ther 3:79–120

Hall BJ, Satterfield-Doerr M, Parikh AR, Brodbelt JS (1998) Determination of cannabinoids in water and human saliva by solid-phase microextraction and quadrupole ion trap gas chromatography-mass spectrometry. Anal Chem 70:1788–1796

Halldin MM, Widman M, Bahr CV, Lindgren JE, Martin BR (1982) Identification of in vitro metabolites of delta-tetrahydrocannabinol formed by human livers. Drug Metab Dispos 10:297–301

Hampson AJ, Grimaldi M, Axelrod J, Wink D (1998) Cannabidiol and (–) delta-9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci U S A 95:8268–8273

Hanson VW, Buonarati MH, Baselt RC, Wade NA, Yep C, Biasotti AA, Reeve VC, Wong AS, Orbanowsky MW (1983) Comparison of 3H-and 125I-radioimmunoassay and gas chromatography/mass spectrometry for the determination of delta-9-tetrahydrocannabinol and cannabinoids in blood and serum. J Anal Toxicol 7:96–102

Harder S, Rietbrock S (1997) Concentration-effect relationship of delta-9-tetrahydrocannabiol and prediction of psychotropic effects after smoking marijuana. Int J Clin Pharmacol Ther 35:155–159

Harvey DJ (2001) Absorption, distribution, and biotransformation of the cannabinoids. In: Nahas GG, Sutin KM, Harvey DJ, Agurell S (eds) Marijuana and medicine. Humana Press, Totowa, pp 91–103

Harvey DJ, Mechoulam R (1990) Metabolites of cannabidiol identified in human urine. Xenobiotica 20:303–320

Harvey DJ, Paton WDM (1986) Metabolism of the cannabinoids. Rev Biochem Toxicol 6:221–264

Harvey DJ, Martin BR, Paton WDM (1979) Identification and measurement of cannabinoids and their in vivo metabolites in liver by gas chromatography-mass spectrometry. In: Nahas GG, Paton WDM (eds) Marijuana: biological effects. Pergamon Press, Oxford, pp 45–62

Hawks RL (1982) The constituents of cannabis and the disposition and metabolism of cannabinoids. In: Hawks R (ed) The analysis of cannabinoids in biological Fluids. Research Monograph 42. National Institute on Drug Abuse, Rockville, pp 125–137

Hawks RL (1983) Developments in cannabinoid analyses of body fluids: implications for forensic applications. In: Agurell S, Dewey W, Willette R (eds) The cannabinoids: chemical, pharmacologic, and therapeutic aspects. Academic Press, Rockville, pp 1–12

Heishman SJ, Stitzer ML, Yingling JE (1989) Effects of tetrahydrocannabinol content on marijuana smoking behavior, subjective reports, and performance. Pharmacol Biochem Behav 34:173–179

Holdcroft A (1984) Pain therapy. In: Grotenhermen F, Russo E (eds) Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. The Haworth Integrative Healing Press, New York, pp 181–186

Huang W, Moody DE, Andrenyak DM, Smith EK, Foltz RL, Huestis MA, Newton JF (2001) Simultaneous determination of delta-9-tetrahydrocannabinol and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol in human plasma by solid phase extraction and gas chromatography—negative ion chemical ionization—mass spectrometry. J Anal Toxicol 25:531–537

Huestis MA, Cone EJ (1998a) Alternative testing matrices. In: Karch SB (ed) Drug abuse handbook. CRC Press, Boca Raton, pp 799–857

Huestis MA, Cone EJ (1998b) Differentiating new marijuana use from residual drug excretion in occasional marijuana users. J Anal Toxicol 22:445–454

Huestis MA, Cone EJ (2004) Relationship of Delta-9-tetrahydrocannabinol concentrations in oral fluid and plasma after controlled administration of smoked cannabis. J Anal Toxicol 28:394–399

Huestis MA, Dickerson S, Cone EJ (1992a) Can saliva THC levels be correlated to behavior? American Academy of Forensic Sciences Annual Meeting, New Orleans, p 190

Huestis MA, Henningfield JE, Cone EJ (1992b) Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Anal Toxicol 16:276–282

Huestis MA, Henningfield JE, Cone EJ (1992c) Blood cannabinoids. II. Models for the prediction of time of marijuana exposure from plasma concentrations of delta-9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THCCOOH). J Anal Toxicol 16:283–290

Huestis MA, Sampson AH, Holicky BJ, Henningfield JE, Cone EJ (1992d) Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther 52:31–41

Huestis MA, Mitchell JM, Cone EJ (1995) Detection times of marijuana metabolites in urine by immunoassay and GC-MS. J Anal Toxicol 19:443–449

Huestis MA, Mitchell JM, Cone EJ (1996) Urinary excretion profiles of 11-nor-9-carboxy-Δ9-tetrahydrocannabinol in humans after single smoked doses of marijuana. J Anal Toxicol 20:441–452

Hunt CA, Jones RT (1980) Tolerance and disposition of tetrahydrocannabinol in man. J Pharmacol Exp Ther 215:35–44

Hunt CA, Jones RT, Herning RI, Bachman J (1981) Evidence that cannabidiol does not significantly alter the pharmacokinetics of tetrahydrocannabinol in man. J Pharmacokinet Biopharm 9:245–260

Iribarne C, Berthou F, Baird S, Dreano Y, Picart D, Bail JP, Beaune P, Menez JF (1996) Involvement of cytochrome P450 3A4 enzyme in the N-demethylation of methadone in human liver microsomes. Chem Res Toxicol 9:365–373

Jehanli A, Brannan S, Moore L, Spiehler VR (2001) Blind trials of an onsite saliva drug test for marijuana and opiates. J Forensic Sci 46:1214–1220

Joern WA (1992) Surface adsorption of the urinary marijuana carboxy metabolite: the problem and a partial solution. J Anal Toxicol 16:401

Johansson E, Halldin MM (1989) Urinary excretion half-life of delta1-tetrahydrocannabinol-7-oic acid in heavy marijuana users after smoking. J Anal Toxicol 13:218–223

Johansson E, Agurell S, Hollister LE, Halldin MM (1988) Prolonged apparent half-life of delta-1-tetrahydrocannabinol in plasma of chronic marijuana users. J Pharm Pharmacol 40:374–375

Johansson E, Halldin MM, Agurell S, Hollister LE, Gillespie HK (1989a) Terminal elimination plasma half-life of delta-1-tetrahydrocannabinol (selta-1-THC) in heavy users of marijuana. Eur J Clin Pharmacol 37:273–277

Johansson E, Noren K, Sjovall J, Halldin MM (1989b) Determination of delta-1-tetrahydrocannabinol in human fat biopsies from marihuana users by gas chromatography-mass spectrometry. Biomed Chromatogr 3:35–38

Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U (2003) Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain. J Am Med Assoc 290:1757–1762

Kelly P, Jones RT (1992) Metabolism of tetrahydrocannabinol in frequent and infrequent marijuana users. J Anal Toxicol 16:228–235

Kemp PM, Abukhalaf IK, Manno JE, Manno BR, Alford DD, Abusada GA (1995a) Cannabinoids in humans. I. Analysis of delta-9-tetrahydrocannabinol and six metabolites in plasma and urine using GC-MS. J Anal Toxicol 19:285–291

Kemp PM, Abukhalaf IK, Manno JE, Manno BR, Alford DD, McWilliams ME, Nixon FE, Fitzgerald MJ, Reeves RR, Wood MJ (1995b) Cannabinoids in humans. II. The influence of three methods of hydrolysis on the concentration of THC and two metabolites in urine. J Anal Toxicol 19:292–298

Kidwell DA, Holland JC, Athanaselis S (1998) Testing for drugs of abuse in saliva and sweat. J Chromatogr 713:111–135

Kim KR, Yoon HR (1996) Rapid screening for acidic non-steroidal anti-inflammatory drugs in urine by gas chromatography-mass spectrometry in the selected-ion monitoring mode. J Chromatogr B Biomed Appl 682:55–66

Kintz P, Cirimele V, Mangin P (1995) Testing human hair for cannabis II. Identification of THC-COOH by GC-MS-NCI as a unique proof. J Forensic Sci 40:619–622

Kintz P, Brenniesen R, Bundeli P, Mangin P (1997) Sweat testing for heroin and metabolites in a heroin maintenance program. Clin Chem 43:736–739

Kintz P, Cirimele V, Ludes B (2000) Detection of cannabis in oral fluid (saliva) and forehead wipes (sweat) from impaired drivers. J Anal Toxicol 24:557–561

Kreuz DS, Axelrod J (1973) Delta-9-tetrahydrocannabinol: localization in body fat. Science 179:391–393

Krishna DR, Klotz U (1994) Extrahepatic metabolism of drugs in humans. Clin Pharmacokinet 26:144–160

Law B, Mason PA, Moffat AC, Gleadle RI, King LJ (1984) Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin. J Pharm Pharmacol 36:289–294

Lee CC, Chiang CN (1985) Appendix. Maternal-fetal transfer of abused substances: pharmacokinetic and pharmacodynamic data. In: Chiang CN, Lee CC (eds) NIDA Research monograph 60. U.S. Department of Health and Human Services, Rockville, pp 110–147

Lemberger L, Silberstein SD, Axelrod J, Kopin IJ (1970) Marihuana: studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. Science 170:1320–1322

Lemberger L, Tamarkin NR, Axelrod J (1971) Delta-9-tetrahydrocannabinol: metabolism and disposition in long-term marihuana smokers. Science 173:72–74

Lemberger L, Crabtree RE, Rowe HM (1972) 11-hydroxy-delta-9-tetrahydrocannabinol: pharmacology, disposition, and metabolism of a major metabolite of marijuana in man. Science 177:62–64

Lindgren JE, Ohlsson A, Agurell S, Hollister L, Gillespie H (1981) Clinical effects and plasma levels of delta-9-tetrahydrocannabinol (delta-9-THC) in heavy and light users of cannabis. Psychopharmacology (Berl) 74:208–212

Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldmann M (2000) The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A 97:9561–9566

Manno JE, Ferslew KE, Manno BR (1984) Urine excretion patterns of cannabinoids and the clinical application of the EMIT-d.a.u. cannabinoid urine assay for substance abuse treatment. In: Agurell S, Dewey WL, Willette RE (eds) The cannabinoids: chemical, pharmacologic, and therapeutic aspects. Harcourt Brace Jonanovich, Orlando, pp 281–290

Manno JE, Manno BR, Kemp PM, Alford DD, Abukhalaf IK, McWilliams ME, Hagaman FN, Fitzgerald MJ (2001) Temporal indication of marijuana use can be estimated from plasma and urine concentrations of delta-9-tetrahydrocannabinol, 11-hydroxy-delta-9-tetrahydrocannabinol, and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid. J Anal Toxicol 25:538–549

Martin BR, Dewey WL, Harris LS, Beckner JS (1977) 3H-Delta-9-tetrahydrocannbinol distribution in pregnant dogs and their fetuses. Res Commun Chem Pathol Pharmacol 17:457–470

Mason AP, McBay AJ (1984) Ethanol, marijuana, and other drug use in 600 drivers killed in single-vehicle crashers in North Carolina, 1978–1981. J Forensic Sci 29:987–1026

Mason AP, McBay AJ (1985) Cannabis: pharmacology and interpretation of effects. J Forensic Sci 30:615–631

Matsunaga T, Iwawaki Y, Watanabe K, Yamamoto I, Kageyama T, Yoshimura H (1995) Metabolism of delta-9-tetrahydrocannabinol by cytochrome P450 isozymes purified from hepatic microsomes of monkeys. Life Sci 56:2089–2095

Mattes RD, Shaw LM, Edling-Owens J, Engelman K, ElSohly MA (1993) Bypassing the first-pass effect for the therapeutic use of cannabinoids. Pharmacol Biochem Behav 44:745–747

Mattes RD, Engelman K, Shaw LM, ElSohly MA (1994) Cannabinoids and appetite stimulation. Pharmacol Biochem Behav 49:187–195

McArdle K, Mackie P, Pertwee R, Guy G, Whittle B, Hawksworth G (2001) Selective inhibition of delta-9-tetrahydrocannabinol metabolite formation by cannabidiol in vitro (abstract) in Proceedings of the BTS Annual Congress. Toxicology 168:133–134

McBurney LJ, Bobbie BA, Sepp LA (1986) GC/MS and Emit analyses for delta-9-tetrahydrocannabinol metabolites in plasma and urine of human subjects. J Anal Toxicol 10:56–64

Mechoulam R (1970) Marihuana chemistry. Science 168:1159–1166

Mechoulam R, Zvi ZB, Agurell S, Nilsson IM, Nilsson JLG, Edery H, Grunfeld Y (1973) Delta-6 tetrahydrocannabinol-7-oic acid, a urinary delta-6-THC metabolite: isolation and synthesis. Experientia 29:1193–1195

Meier HJ, Vonesch HJ (1997) Cannabis-intoxikation nach salatgenuss. Schweiz Med Wochenschr 127:214–218

Melamede R (1984) Possible mechanisms in autoimmune diseases. In: Grotenhermen F, Russo E (eds) Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. The Haworth Integrative Healing Press, New York, pp 111–122

Moeller MR, Doerr G, Warth S (1992) Simultaneous quantitation of delta-9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) in serum by GC/MS using deuterated internal standards and its application to a smoking study and forensic cases. J Forensic Sci 37:969–983

Moore C, Guzaldo F, Donahue T (2001) The determination of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) in hair using negative ion gas chromatography-mass spectrometry and high-volume injection. J Anal Toxicol 25:555–558

Mura P, Kintz P, Papet Y, Ruesch G, Piriou A (1999) Evaluation of six rapid tests for screening of cannabinoids in sweat, saliva and urine. Acta Clin Belg 1:35–38

Nebro W, Barnes A, Gustafson R, Moolchan E, Huestis M (2004) Delta-9-tetrahydrocannabinol (THC), 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THCCOOH) in human plasma following oral administration of hemp oil. 2004 FBI/SOFT/TIAFT Meeting

Niedbala RS, Kardos KW, Fritch DF, Kardos S, Fries T, Waga J (2001) Detection of marijuana use by oral fluid and urine analysis following single-dose administration of smoked and oral marijuana. J Anal Toxicol 25:289–303

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK (1980) Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther 28:409–416

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK (1981) Plasma levels of delta-9-tetrahydrocannabinol after intravenous, oral and smoke administration. NIDA Res Monogr 34:250–256

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK (1982) Single dose kinetics of deuterium labelled delta-1-tetrahydrocannabinol in heavy and light cannabis users. Biomed Environ Mass Spectrom 9:6–10

Ohlsson A, Agurell S, Londgren JE, Gillespie HK, Hollister LE (1985) Pharmacokinetic studies of delta-1-tetrahydrocannabinol in man. In: Barnett G, Chiang CN (eds) Pharmacokinetics and pharmacodynamics of psychoactive drugs. Mosby Yearbook, St Louis, pp 75–92

Ohlsson A, Lindgren JE, Andersson S, Agurell S, Gillespie H, Hollister LE (1986) Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. Biomed Environ Mass Spectrom 13:77–83

Owens SM, McBay AJ, Reisner HM, Perez-Reyes M (1981) 125 I radioimmunoassay of delta-9-tetrahydrocannabinol in blood and plasma with a solid-phase second-antibody separation method. Clin Chem 27:619–624

Peat MA (1989) Distribution of delta-9-tetrahydrocannabinol and its metabolites. In: Baselt RC (ed) Advances in analytical toxicology II. Year Book Medical Publishers, Chicago, pp 186–217

Peel HW, Perrigo BJ, Mikhael NZ (1984) Detection of drugs in saliva of impaired drivers. J Forensic Sci 29:185–189

Perez-Reyes M (1985) Pharmacodynamics of certain drugs of abuse. In: Barnett G, Chiang CN (eds) Pharmacokinetics and pharmacodynamics of psychoactive drugs. Biomedical Publications, Foster City, pp 287–310

Perez-Reyes M (1990) Marijuana smoking: factors that influence the bioavailability of tetrahydrocannabinol. In: Chiang CN, Hawks RL (eds) Research findings on smoking of abused substances. NIDA Research Monograph 99, Rockville, pp 42–62

Perez-Reyes M, Wall ME (1982) Presence of delta-9-tetrahydrocannabinol in human milk. N Engl J Med 307:819–820

Perez-Reyes M, Timmons MC, Lipton MA, Davis KH, Wall ME (1972) Intravenous injection in man of delta-9-tetrahydrocannabinol and 11-OH-delta-9-tetrahydrocannabinol. Science 177:633–635

Perez-Reyes M, Lipton MA, Timmons MC, Wall ME, Brine DR, Davis KH (1973a) Pharmacology of orally administered delta-9-tetrahydrocannabinol. Clin Pharmacol Ther 14:48–55

Perez-Reyes M, Timmons MC, Davis KH, Wall EM (1973b) A comparison of the pharmacological activity in man of intravenously administered delta-9-tetrahydrocannabinol, cannabinol and cannabidiol. Experientia 29:1368–1369

Perez-Reyes M, Owens SM, Di Guiseppi S (1981) The clinical pharmacology and dynamics of marijuana cigarette smoking. J Clin Pharmacol 21:201S–207S

Perez-Reyes M, Di Guiseppi S, Davis KH, Schindler VH, Cook CE (1982) Comparison of effects of marijuana cigarettes of three different potencies. Clin Pharmacol Ther 31:617–624

Pertwee RG (2004) The pharmacology and therapeutic potential of cannabidiol. In: Di Marzo V (ed) Cannabinoids. Kluwer Academic/Plenum Publishers, New York, pp 32–83

Plasse T (1984) Antiemetic effects of cannabinoids. In: Grotenhermen F, Russo E (eds) Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. The Haworth Integrative Healing Press, New York, pp 165–180

Samyn N, van Haeren C (2000) On-site testing of saliva and sweat with Drugwipe and determination of concentrations of drugs of abuse in saliva, plasma and urine of suspected users. Int J Legal Med 113:150–154

Shaw LM, Edling-Owens J, Mattes R (1991) Ultrasensitive measurement of delta-9-tetrahydrocannabinol with a high energy dynode detector and electron-capture negative chemical-ionization mass spectrometry. Clin Chem 37:2062–2068

Soares JR, Gross SJ (1976) Separate radioimmune measurements of body fluid delta-9THC and 11-nor-9-carboxy-delta-THC. Life Sci 19:1711–1717

Soares JR, Grant JD, Gross SJ (1982) Significant developments in radioimmune methods applied to delta-9-THC and its 9-substituted metabolites. In: Hawks R (ed) NIDA Research Monograph 42: National Institute on Drug Abuse, Bethesda, pp 44–55

Sporkert F, Pragst F, Ploner CJ, Tschirch A, Stadelmann AM (2001) Pharmacokinetic investigations and delta-9-tetrahydrocannabinol and its metabolites after single administration of 10 mg Marinol in attendance of a psychiatric study. The Annual Meeting of The International Association of Forensic Toxicologists, Prague, pp 1–62

Stinchcomb AL, Valiveti S, Hammell DC, Ramsey DR (2004) Human skin permeation of delta-8-tetrahydrocannabinol, cannabidiol and cannabinol. J Pharm Pharmacol 56:291–297

Turner CE, ElSohly MA, Boeren EG (1980) Constituents of cannabis sativa L. XVII. A review of the natural constituents. J Nat Prod 43:169–234

Vaughan CW, Christie MJ (1984) Mechanisms of cannabinoid analgesia. In: Grotenhermen F, Russo E (eds) Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. The Haworth Integrative Healing Press, New York, pp 89–100

Wall ME, Perez-Reyes M (1981) The metabolism of delta-9-tetrahydrocannabinol and related cannabinoids in man. J Clin Pharmacol 21:178S–189S

Wall ME, Taylor HL (1984) Conjugation of acidic metabolites of delta-8 and delta-9-THC in man. In: Harvey DJ, Paton SW, Nahas GG (eds) Marihuana 84 Proceedings of the Oxford Symposium on Cannabis. IRL Press Limited, Oxford, pp 69–76

Wall ME, Brine DR, Perez-Reyes M (1976) Metabolism of cannabinoids in man. In: Braude MC, Szara S (eds) The Pharmacology of marihuana. Raven Press, New York, pp 93–113

Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M (1983) Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther 34:352–363

Watanabe K, Tanaka T, Yamamoto I, Yoshimura H (1988) Brain microsomal oxidation of delta-8- and delta-9-tetrahydrocannabinol. Biochem Biophys Res Commun 157:75–80

Widman M, Agurell S, Ehrnebo M, Jones G (1974) Binding of (+) and (−)-delta1-tetrahydrocannabinols and (−)-7-hydroxy-delta1-tetrahydrocannabinol to blood cells and plasma proteins in man. J Pharm Pharmacol 26:914–916

Widman M, Nordqvist M, Dollery CT, Briant RH (1975) Metabolism of delta-1-tetrahydrocannabinol by the isolated perfused dog lung. Comparison with in vitro liver metabolism. J Pharm Pharmacol 27:842–848

Williams PL, Moffat AC (1980) Identification in human urine of delta-9-tetrahydrocannabinol-11-oic glucuronide: a tetrahydrocannabinol metabolite. J Pharm Pharmacol 32:445–448

Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A (2003) Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 362:1517–1526

Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG (1982) Action of cannabidiol on the anxiety and other effects produced by delta-9-THC in normal subjects. Psychopharmacology (Berl) 76:245–250

View publication stats