Cannabis (Marijuana) — Effects on Human Behavior and Performance

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ABSTRACT: Cannabis is one of the oldest and most commonly abused drugs in the world. Recently, tremendous advances have been made in our understanding of the endogenous cannabinoid system with the identification of cannabinoid receptors, cannabinoid receptor antagonists, endogenous neurotransmitters, metabolic enzymes, and reuptake mechanisms. These advances have helped us to elucidate the mechanisms of action of cannabis and the side effects and toxicities associated with its use. In addition, potential therapeutic applications are being investigated for the use of smoked cannabis and synthetic THC (dronabinol). Most workplace, military, and criminal justice positive urine drug tests are due to the use of cannabis. In addition, alternative matrices, including saliva, sweat, and hair, are being utilized for monitoring cannabis use in treatment, employment, and criminal justice settings. Experimental laboratory studies have identified cognitive, physiological, and psychomotor effects following cannabis. Epidemiological studies reveal that cannabis is the most common illicit drug world-wide in impaired drivers, and in motor vehicle injuries and fatalities. Driving simulator studies also indicate performance impairment following cannabis use; however, the results of open- and closed-road driving studies and of culpability studies do not consistently document increased driving risk. Clearly a combination of ethanol and cannabis use significantly increases risks. This article reviews the pharmacokinetics and pharmacodynamics of cannabis and places special emphasis on the effects of cannabis on complex tasks such as driving and flying.

KEY WORDS: cannabinoids, cannabis, driving, hair, impairment, marijuana, oral fluid, performance, plasma, sweat, tetrahydrocannabinol, urine, whole blood.

INTRODUCTION

Marijuana, hashish, sinsemilla, and other psychoactive products obtained from *Cannabis sativa* are the most widely used illicit drugs in the world. In the United States, smoked marijuana is the primary route of cannabinoid exposure, but in many countries, hashish predominates. The term cannabis will be used in this review, unless the reference is specifically to the leafy plant material termed marijuana. Cannabis has been used for its euphoric effects for over 4000 years [481]. The stout, aromatic, annual herb originated in Central Asia, but is now cultivated in many countries. A cane-like variety, devoid of psychoactive effects, provides an important source of hemp fiber. The Assyrians incorporated cannabis into their religious rites and as medicine for neurological and psychiatric diseases [293]. Cannabis was identified in plant ash on the skeleton of a young woman who died during childbirth in the 4th century A.D. [481]. Additional evidence of the use of cannabis during birthing comes from information documented in Egyptian papyri. Medicinal properties of the plant were recognized in China 2700 years ago for the relief of pain, muscle spasms, convulsions, epilepsy, asthma, and rheumatism. O'Shaughnessy, an Irish surgeon, introduced cannabis to Europe in 1842 after observing its therapeutic use in India and after completing toxicity experiments in animals [374]. He was impressed with the usefulness of cannabis as a muscle-relaxant, anticonvulsant, anti-emetic, and analgesic. However, similar to other herbal preparations, its potency was unreliable, contributing to the decline of its therapeutic value. In addition, physicians, including the French psychiatrist de Tour Moreau, became aware of the drug's psychoactive side effects and described it as "a gradual weakening of the power to direct thoughts at will" [302]. DeCourtive, a student of Moreau, conducted studies on the chemistry of hashish and its effects on animals and humans, including himself [401]. He believed that cannabis could be helpful in relieving the pain and suffering of his psychiatric patients. Today there is extensive research interest around the world in the therapeutic potential of cannabinoids and in understanding the endogenous cannabinoid system.

Cannabis grows in the wild in large areas of the Russian Federation, Kazakhstan, and Central Asia [450]. Asia, Africa and Latin America are the major producers of illicit cannabis [450]. The greatest period of cannabis use in the U.S. was in the 1960s and 1970s, followed by decreasing prevalence until the early 1990s, when marijuana use began to increase among the young. According to the 1999 National Household Survey, 34.6% of the total U.S. population age 12 or older reported use of marijuana at some time in their lives, with 8.9% and 5.1% stating that they used marijuana at least once in the past year and past month, respectively [447]. Currently, nearly 35% of

American males aged 12–17 smoke marijuana once a month [447]. Surprisingly, a slightly greater percentage of teen-age girls (39.6%) also report monthly smoking. Although there was an increase in marijuana use among American youth from 1991 to 1997 [426], according to the Monitoring the Future Survey, marijuana use began to decline among 8th graders in 1997, and among 10th and 12th graders in 1998 [218]. This decline continued only for 8th graders in 1999 and is accompanied by reductions in the perceived risk and personal disapproval of marijuana use among older teens. The total number of marijuana/hashish emergency room mentions in the U.S. has also increased from 11 (1992) to 36 (1999) per 100,000 people, according to the Drug Abuse Warning Network [139].

Cannabis is self-administered for its mood-altering properties, and has been described as an addictive, dependence-producing drug due to the production of euphoria, the presence of reversible psychological impairment, an abstinence syndrome, and tolerance [317]. A mixture of depressant and stimulant effects is noted at low doses; cannabis acts as a CNS depressant at high doses [13]. Cannabinoids share effects with other psychoactive drugs, yet possess a distinct pattern of effects that distinguishes this unique pharmacological drug class.

I. CHEMISTRY

A. Source

Cannabis preparations include loose marijuana plant material, kilobricks (the classical Mexican-produced material), buds, sinsemilla, Thai sticks, hashish (cannabis resin), and hash oil. The chemical composition of the different parts of the plant varies. Sinsemilla, a seedless and more potent form of cannabis produced from the unfertilized flowering tops of female *C. sativa* plants, first appeared in 1977 and is usually produced in the United States. Delta-9-tetrahydrocannabinol (THC), the primary psychoactive analyte, is found in the plant's flowering or fruity tops, leaves, and resin. The structure of THC is shown in **Figure 1**. Cannabinoid plant chemistry is far more complex than pure THC and different effects may be expected due to the presence of additional cannabinoids and other chemicals [442]. The ratio of cannabinoids in cannabis is dependent on the age of the sample, its geographic origin, and the plant strain. Cannabinol is essentially a chemical degradation product and its relative abundance increases as samples age [168,296]. The potency of a preparation is described by its THC concentration, usually as the % THC per dry weight of material. The actual amount of drug administered will depend upon the weight of the material and the route of drug administration. Potency has been increasing steadily over the years through selective cultivation. The potency of confiscated marijuana samples rose from less than 1.5% THC in 1980 to 4.2% THC in 1997 [113]. Marijuana represented the majority of seized specimens in the United States, with hash oil representing less than 1%, and hashish less than 5% of all samples over the last decade. Between 1990 and 1997, the mean percentages of THC in marijuana, hashish, and hash oil seizures were 3.5, 6.6, and 14.0%, respectively. The highest THC concentrations in seized materials were marijuana 29.9%, sinsemilla 33.1%, hashish 52.9%, and hash oil 47.0%.

B. Nomenclature

Cannabis contains over 421 different chemical compounds, including 61 cannabinoids [442]. During smoking, more than 2000 compounds may be produced by pyrolysis. Eighteen different classes of chemicals, including nitrogenous compounds, amino acids, hydrocarbons, sugars, terpenes, and simple and fatty acids contribute to cannabis's known pharmacological and toxicological properties. Other cannabinoids include cannabinol, which is approximately 10% as psychoactive as THC and cannabidiol, a non-psychoactive agent [342]. After years of effort, the structure of THC was elucidated in 1964 [292]. THC, a tricyclic 21-carbon structure, is a volatile, viscous oil with high lipid solubility and poor aqueous solubility. The pK_a of THC is 10.6. THC contains no nitrogen and has two chiral centers in trans-configuration. Two different numbering systems, the dibenzopyran or delta 9, and the monoterpene or delta 1 system, are utilized in the literature to describe THC [442]. The dibenzopyran system will be used throughout this chapter.

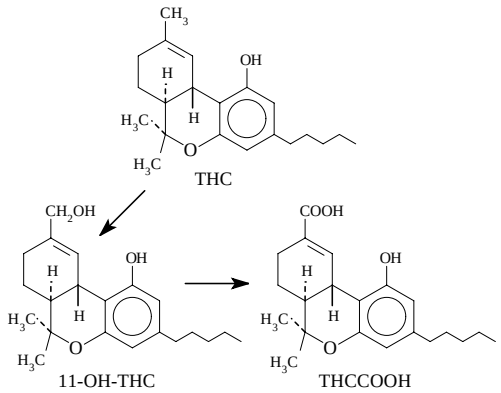


Figure 1. Major metabolic route for Δ^9-tetrahydrocannabinol (THC) including the primary active metabolite 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and the primary inactive metabolite, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH).

C. Structure-Activity Relationships

Early studies employing impure materials suggested that cannabinoid actions were not highly stereospecific; however, in the late 1980s and early 1990s, it became apparent that strict structural requirements were required for cannabinoid activity [293,294]. Cannabinoids are natural (–)-enantiomers with (3R,4R) stereochemistry. Until anandamide was identified as the first endogenous cannabinoid agonist [97], structure-activity studies of the classical THC agonist had indicated that the benzopyran ring structure, aliphatic side chain, and phenolic group were required for central activity [5,362,393]. More recent research has shown that anandamide, one of several unsaturated fatty acid ethanolamide endogenous ligands of the CB1 receptor, can assume a three-dimensional conformation that also successfully binds to the cannabinoid receptor [6,78,276]. Anandamide's hydroxyl group may be superimposed on the phenolic group of THC, its carboxyamide oxygen on the pyran oxygen, and its omega 6 aliphatic region may lie in the same position as THC's pentyl chain. Animal studies have shown that a C-5 hydroxy group confers potent peripheral activity [116]. The well-known tetrad of pharmacological effects in mice developed by Martin et al. [5] that includes catalepsy, reduced motility, hypothermia and antinociception, has been used extensively to characterize cannabinoid structure-activity relationships. Exposure of mice to compounds with cannabinoid-like activity reduces spontaneous locomotor activity and core body temperature, produces catalepsy (a rigidity of the limbs accompanied by a lack of response to stimuli and inactivity), and increases the threshold for pain perception. To date, activity in the mouse behavioral battery has been a reliable predictor of psychotomimetic activity in humans [98]; however, its usefulness will continue to be assessed with the discovery of many new endogenous cannabinoids.

D. Chemical Stability

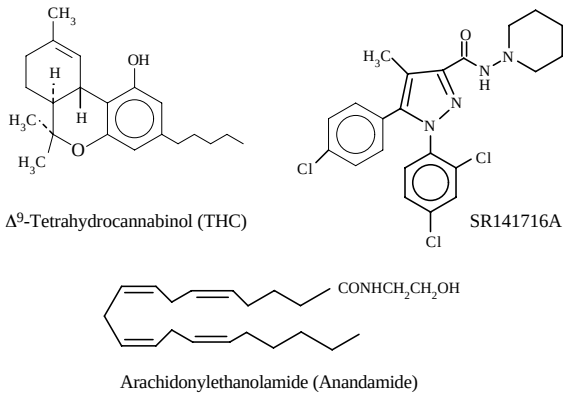
THC is usually present in C. *sativa* plant material as a mixture of monocarboxylic acids, which readily and efficiently decarboxylate upon heating [9,342,442]. THC decomposes when exposed to air, heat, or light; exposure to acid can oxidize the compound to cannabinol, a much less potent cannabinoid [168,320]. THC binds readily to glass and plastic, reducing recoveries during analytical procedures [38,141]. THC adsorption can be minimized with storage of solutions in amber silylated glassware and by maintenance of the compound in a basic solution or organic solvent [122,212].

II. PHARMACOLOGY

A. Mechanisms of Action

Two hypotheses for THC's mechanisms of action were proposed for many years. One hypothesis suggested that THC exerted its effects through non-specific interactions of the drug with cellular and organelle membranes [181,274]. The other hypothesis suggested that THC interacted with specific cannabinoid receptors [96,98,349]. Delineating mechanisms of action was difficult due to demonstrated THC activity at many sites, including the opioid and benzodiazepine receptors, and noted effects on prostaglandin synthesis, DNA, RNA, and protein metabolism [55,334,464]. Cannabinoids inhibit macromolecular metabolism in a dose-related manner and have a wide range of effects on enzyme systems, hormone secretion, and neurotransmitters [37,60,88,90,99,300,350]. These numerous and diffuse effects lent support to the non-specific interaction hypothesis. However, in the last 10 years our knowledge of cannabinoid pharmacology has increased tremendously. Central (CB1) [282,314] and peripheral (CB2) [314] cannabinoid receptors have been characterized, endogenous ligands (e.g., anandamide [97], 2-arachidonyl glycerol [422]) have been identified, and specific CB1 [366,368] and CB2 receptor antagonists [358] have been synthesized. The structures of THC, the endogenous neurotransmitter anandamide, and the first CB1 cannabinoid receptor antagonist SR141716 are shown in **Structure 1**. There are indications that additional non-CB1, non-CB2 cannabinoid receptors may also be present in the brain and body [44,464].

CB1 receptors in the brain were mapped indicating that the distribution of the high-affinity, stereoselective, and pharmacologically distinct brain receptors is anatomically selective [180,273,282]. A high density of receptors in the caudate nucleus and cerebellum are consistent with the marked effects of cannabinoids on motor behavior [377,385,454]. Significant binding has been documented in the striatum, cerebral cortex, and hippocampus correlating with cannabinoid effects on perception, cognition, memory, learning, endocrine function, food intake, and regulation of body temperature [59,78,161, 275]. Cannabinoid receptors belong to the G protein class of receptors and have seven trans-membrane domains [147,188]. The intracellular surface of the CB1 receptor interacts with G proteins to regulate effector proteins such as adenylate cyclase, calcium and potassium ion channels, and the mitogen-activated protein kinase pathway [24,29,367]. The distinct CB2 peripheral cannabinoid receptor appears to play an important immunomodulatory



Structure 1. Chemical structures of Δ^9-tetrahydrocannabinol (THC), anandamide (the first endogenous cannabinoid neurotransmitter), and SR141716 (the first CB1 cannabinoid receptor antagonist).

role [264,365]. CB2 receptors have been localized in the spleen, thymus, tonsils, and on mast cells and plasmocytes. A 44% homology in the amino acid sequence exists between the CB1 and CB2 cannabinoid receptors [399].

The first endogenous cannabinoid ligand to be identified, anandamide (Sanskrit term for bliss) or arachidonylethanolamide, is an arachidonic acid derivative [97]. It mimics THC binding at both the CB1 and CB2 receptor subtypes, and possesses similar pharmacological activity, although with reduced potency for some effects [133,187,297]. Anandamide also appears to function as a neurotransmitter in some systems where THC is inactive, e.g., activity at vanilloid (VR1) receptors, to produce other pharmacological effects including vasodilation [484] and to reduce glioma cell proliferation [207]. Deutsch et al. proposed a biosynthetic route for anandamide [95]; however, it appears that anandamide may be released from cell membranes following depolarization due to the influx of calcium [100,115,423]. Anandamide can be inactivated by enzymatic hydrolysis with fatty acid amide hydrolase [95,276,352] or by a specific transporter reuptake mechanism [101], further substantiating that this endogenous cannabinoid ligand functions as a biological neurotransmitter. Other ethanolamines, e.g., palmitoyl and stearoylethanolamine, are not active at cannabinoid receptors themselves, but appear to greatly increase the activity of endogenous ligands and have, therefore, earned the title of "entourage compounds" [94,276,295].

SR141716, the first specific CB1 cannabinoid receptor antagonist, has been shown to block acute effects of THC and other CB1 agonists in vitro and in animals [4,248,366,368]. The first clinical studies of the pharmacokinetic and pharmacodynamic effects of oral SR141716 in combination with smoked marijuana have recently been reported [195]. Smoked marijuana alone produced expected physiological and psychological responses reflecting intoxication. In combination with SR141716, there was a dose-dependent blockade of marijuana effects on subjective effects and heart rate. The 90-mg dose produced significant 38% to 43% reductions in Visual Analog Scale ratings of "How high do you feel now?" "How stoned on marijuana are you now?" and "How strong is the drug effect you feel now?" and a 75% reduction ($p<0.06$) in the marijuana subscale peak effects. Heart rate increases were also substantially reduced by SR141716. SR141716 alone produced no significant physiological and psychological effects in human volunteers, although inverse agonism and/or disruption of endogenous cannabinoid tone by the antagonist have been described in some in vitro and animal studies [39,195]. A pharmacokinetic interaction between THC and SR141716 was not likely to account for the effects of SR141716 on human THC pharmacodynamics because no significant difference in the mean THC AUC or peak THC plasma concentration after placebo or 90 mg SR141716 was observed. These findings confirmed, for the first time in humans, the important role of CB1 receptors in mediating the cardiovascular and behavioral effects of cannabis.

The significant advances in cannabinoid research have opened new frontiers and are leading to a better understanding of cannabis's effects and the role of the endogenous cannabinoids in humans. It is suggested that THC may act as an indirect dopamine agonist to stimulate electrical brain reward circuits [138]. Stimulation of the brain reward circuits is an essential characteristic of drugs of abuse. Cannabis produces substantial changes in human behavior that are linked to physiologic and biochemical changes [201]. Subjective responses and performance effects are interrelated with other body functions; behavior being the highest level of human response.

B. Effects

Cannabis's behavioral and physiologic effects have been well described [5,98,220]. Behavioral effects include feelings of euphoria and relaxation, altered time perception, lack of concentration, impaired learning and memory, and mood changes such as panic reactions and paranoia. Cannabis's spectrum of behavioral effects is unique, preventing classification of the drug as a stimulant, sedative, tranquilizer, or hallucinogen [448]. Subjective effects of cannabis, such as drug "liking" and "feel drug" may appear after the first or second puff of a cannabis cigarette [201]. Cannabis was also found to produce rapid changes in some physiologic effects includ-

ing heart rate and diastolic blood pressure [26,184,219,347]. Other frequent physiological effects include conjunctival suffusion, dry mouth and throat, increased appetite, vasodilatation, and decreased respiratory rate. Cannabis affects the immune and endocrine systems, produces lung damage and EEG alterations, and influences neonatal and child development [61,92,134–136,165,431,433,482].

Acute toxic effects of cannabis include behavioral effects, e.g., panic attacks and psychosis, increased heart rates, and CNS depression [144,155,185,420]. NIDA's Drug Abuse Warning Network (DAWN) reported a threefold increase in cannabis-related hospital emergency room visits from 1992 to 1999 that may be related to the increased potency of cannabis and the increase in use among the young [139]. Children have experienced serious CNS depression following ingestion or inhalation of cannabis [266,379,392]. Usually, with supportive care, these cases have resolved successfully with few residual effects.

Acute cannabis consumption may impair cognitive and performance tasks, including memory, altered time sense, reaction time, learning, perception, motor coordination, and attention [17,34–36,175,225,281,356,387, 472]. Numerous investigators have observed the disruption in free recall of previously learned items and other components of memory [161,391,417,425,439]. Cannabis is frequently included as a contributing factor to motor vehicle accidents and is one of the most commonly found drugs in multiple-drug cases (*see* Section IX for further discussion) [85,108,143,410]. In 2001, Shope et al., in a study of high-risk driving behaviors in 4,403 young adults, found that substance use, including tobacco cigarettes, marijuana, and alcohol, at age 15 was an important predictor of subsequent excess risk of serious offenses and car crashes for men and women [400].

There are conflicting reports on chronic toxic effects of cannabis in the literature [158,184,356,413]. This may be due in part to different experimental protocols, type and potency of cannabis, schedule and length of exposure, subject characteristics and defined endpoint of effect. Impaired health, including lung damage, behavioral changes, reproductive, cardiovascular, and immunological effects, has been associated with cannabis use [157,398]. The ability of cannabinoids to readily cross placental membranes to expose the developing fetus has led to additional health concerns [164]. Cannabinoids can be embryocidal, affect gestational length and labor, induce maturational delays, and may have effects on behavioral parameters in the human neonate [89,134,388]. Furthermore, recent research points to an important role for endogenous cannabinoids in the successful implantation of embryos [332,333]. CB1 cannabinoid receptors are present in high concentrations in the developing embryo and high concentrations of anandamide have been found in the uterus. Cannabinoids were found to interfere with implantation in wild type, but not with CB1/CB2 receptor knock-out mice. There are indications that cannabis also inhibits the human immune system [53,239,305,315,430, 432]. The smoke condensate yield of cannabis, which includes potential mutagens, was more than 50% higher than that of tobacco cigarette smoke [463]. Some of the most reproducible findings suggest that THC inhibits the progression of responsive macrophages to full activation by limiting their capacity to respond to immunogenic signals [56]. Reports indicate that exposure to cannabis also impairs alveolar macrophage function and cytokine production [19].

Acute effect vs. time curves for heart rate and subjective "high" display a counter-clockwise hysteresis, indicating a delay between effects and plasma concentrations [20,63,76,79]. A counter-clockwise hysteresis is generally indicative of a prominent distribution phase, perhaps due to redistribution of drug from the vascular compartment to the drug's site of action, the brain. The subjective "high" effect was found to be directly proportional to the mean plasma concentration of THC from approximately 1–4 h after cannabis smoking [64]. Domino et al. [104] determined that THC plasma concentrations at 50% maximal effect were 7.2 and 16.8 ng/mL in light and heavy cannabis users, respectively. In a controlled clinical study of marijuana smoking, initial changes in THC blood concentrations were reported to be out of phase with physiological and behavioral changes (hysteresis); however, after blood/tissue equilibrium was established, a direct correlation of THC blood concentrations and effects was observed [79].

Most behavioral and physiological effects of THC return to baseline levels within 3–6 h after exposure [59,186,395], although, some investigators have demonstrated residual effects in specific behaviors up to 24 h after drug [176,250]. More research is needed to define the onset, magnitude, and duration of cannabis's behavioral effects, especially following long-term, frequent use of the drug. Pope et al. recently reported that significant neurocognitive deficits were observed in long-term marijuana users who had smoked more than 5000 times in their lives as compared to occasional marijuana users [355]. This impairment continued to be significantly different from controls after 7 days of abstinence, but had resolved by 28 days of marijuana abstinence.

III. THERAPEUTIC POTENTIAL

A. Cannabinoid Agonists

A small number of cancer, glaucoma, and AIDS patients have been supplied with marijuana by the U.S. government and have been permitted to smoke marijuana legally [41]. In a 1991 survey of oncologists, physicians indicated their willingness to prescribe marijuana for therapeutic purposes if it were legal to do so [102]. Although the Public Health Service initially indicated that it would accept new applications for supply of therapeutic marijuana in response to the HIV epidemic, this policy was reversed in 1992, and no new applications have been approved [41]. The possibility of lung cancer, dysfunction of the immune system, and behavioral effects of the drug were listed as reasons for the policy reversal. In 1997, the National Institutes of Health reviewed the state of research on the therapeutic benefits and risks of cannabis and determined that additional clinical studies on its therapeutic uses were needed. Clinical studies of the therapeutic benefit of cannabis and THC are currently underway in many countries including Great Britain, Canada, and the U.S.

Potential therapeutic uses have been actively pursued despite removal of THC from the British and U.S. pharmacopoeias in the 1930s and 1940s due to central hallucinogenic actions of the drug. In 1996, California and Arizona passed referenda to permit physicians to write prescriptions for the therapeutic use of cannabinoids. Additional states have followed with similar legislation. Clinical trials into the effectiveness of THC delivered by the smoked, oral, rectal, and nasal spray routes are currently in progress. Dronabinol (Marinol®), a synthetic THC, is licensed for the treatment of nausea and vomiting associated with cancer chemotherapy. Some oncologists have indicated that smoked cannabis is more effective than the synthetic oral medication due to dronabinol's low and less reliable bioavailability, some patients' inability to tolerate the oral medication, and the absence of other active compounds found in cannabis plant material [2,103,389,409]. Another prominent use of dronabinol or smoked cannabis is to enhance appetite in AIDS wasting disease [287,396,421]. Other studies have indicated that cannabinoids may be efficacious as analgesic [45,137,152, 277], anti-inflammatory [130], anti-tumor [207], anti-epileptic [374,412], anti-hypertensive (management of glaucoma) [50,357,480], and anti-spasmodic [312,313] agents.

Extensive efforts have focused on the synthesis of cannabinoid analogs that produce beneficial responses with minimal undesirable side effects, e.g., psychoactivity. To date, these efforts have been relatively unsuccessful. Additional therapeutic approaches include self-administration of cannabis-based medicines sublingually in a spray or rectally to better balance analgesic and psychoactive drug effects and to avoid the toxic effects of cannabis smoke [46,284,374].

B. Cannabinoid Antagonists, Reuptake Inhibitors, and Enzyme Inhibitors

Increasing knowledge of the endogenous cannabinoid system has provided new opportunities for therapeutic interventions with cannabinoid receptor antagonists, anandamide hydrolase inhibitors, and anandamide reuptake inhibitors. SR141716, the first CB1 cannabinoid receptor antagonist, is being developed by Sanofi-Synthelabo Inc. as an anorectic medication to reduce food intake in obese individuals. Preliminary data in current phase II trials demonstrate effective weight loss over a six-month period without the development of tolerance to the medication [248]. Other potential uses for cannabinoid receptor antagonists include tobacco cessation and as a therapeutic aid in the treatment of cannabinoid dependence [195].

IV. PHARMACOKINETICS

A. Absorption

Smoking, the principal route of cannabis administration, provides a rapid and highly efficient method of drug delivery. Approximately 30% of the THC in marijuana or hashish cigarettes is estimated to be destroyed by pyrolysis during smoking [3,91]. Smoked drugs are highly abused, in part, due to the efficiency and speed of delivery of drug from the lungs to the brain. Intense pleasurable and strongly reinforcing effects may be produced due to almost immediate drug exposure to the central nervous system. Drug delivery during cannabis smoking is characterized by rapid absorption of THC with slightly lower peak concentrations than those found after intravenous administration [328]. Bioavailability following the smoking route has been reported to be 18–50%, due in part to the intra- and intersubject variability in smoking dynamics that contribute to uncertainty in dose delivery [8,330]. The number, duration, and spacing of puffs, hold time, and inhalation volume greatly influences the degree of drug exposure [16,179,341]. THC can be measured in the plasma within seconds after inhalation of the first puff of marijuana smoke [196]. 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 (1.75% THC, approximately 16 mg) or high (3.55% THC, approxi-

mately 30 mg) dose cigarette, respectively [196]. Concentrations continued to increase rapidly and peak concentrations occurred at 9.0 min, prior to initiation of the last puff sequence at 9.8 min.

Ingestion of cannabis is also common. Absorption is slower following the oral route of administration with lower, more delayed peak THC concentrations [246,328,329,457]. Wall et al. found peak THC concentrations approximately 4–6 h after ingestion of 15–20 mg of THC in sesame oil [457]. Peak THC concentrations ranged from 4.4–11 ng/mL and occurred 1–5 h following ingestion of 20 mg of THC in a chocolate cookie [328]. Bioavailability is reduced to 4–20% following oral use [328,457], due in part to degradation of drug in the stomach [348]. Also, there is significant first-pass metabolism to active (11-hydroxy-tetrahydrocannabinol, 11-OH-THC) and inactive metabolites. Plasma 11-OH-THC concentrations range from 50 to 100% of THC concentrations following the oral route of cannabis administration compared to only about 10% after smoking [457]. 11-OH-THC is equipotent to THC, explaining the fact that pharmacodynamic effects after oral cannabis appear to be greater than at the same THC concentration after smoked drug administration [328].

B. Distribution

THC has a large volume of distribution, 10 L/Kg, and is 97–99% protein bound in plasma, primarily to lipoprotein [202,224]. Highly perfused organs, including the brain, are rapidly exposed to the drug. Less highly perfused tissues accumulate drug more slowly as THC redistributes from the vascular compartment to tissue [167]. THC's high lipid solubility results in concentration and prolonged retention of the drug in fat [215]. Low concentrations of THC in brain tissue have been documented in distribution studies in rats [242]. Slow release of drug from fat and significant enterohepatic recirculation contribute to THC's long terminal half-life in plasma, reported as greater than 4.1 days in chronic marijuana users [213]. Isotopically labeled THC and sensitive analytical procedures were used to obtain this estimate of drug half-life. Use of less sensitive assays results in much lower estimates of the terminal half-life, and therefore, a more simplified description of the drug's pharmacokinetics.

C. Metabolism

Hydroxylation of THC by the hepatic cytochrome P450 enzyme system leads to production of the active metabolite, 11-OH-THC [204,283], believed by early investigators to be the true active analyte [253]. Much lower concentrations (approximately 10% of the THC concentration) of 11-OH-THC were noted after marijuana smoking [196]. Peak concentrations occurred approximately 13 min after the start of smoking and averaged 7 ng/mL after a single marijuana cigarette. Other tissues, including brain, intestine, and lung, may contribute to the metabolism of THC, although alternate hydroxylation pathways may be more prominent [25,151,243,461,468]. Further metabolism to di- and tri-hydroxy compounds, ketones, aldehydes, and carboxylic acids has been documented [167,169]. Oxidation of active 11-OH-THC produces the inactive metabolite, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THCCOOH) [252,298]. In a study of the pharmacokinetics of a single oral 10-mg dose of Marinol®, the concentration of the inactive THCCOOH metabolite predominated from as early as 1 h after dosing, and the concentrations of parent THC and 11-OH-THC were similar [415]. The inactive THCCOOH metabolite and its glucuronide conjugate have been identified as the major end products of biotransformation in most species, including man [159,169]. Renal clearance of these polar metabolites is low due to extensive protein binding [202]. THCCOOH concentrations gradually increase and are greater than THC concentrations shortly after smoking. Plasma concentrations of THC decrease rapidly once smoking is finished [196]. The time course of detection of THCCOOH is much longer than either that of THC or 11-OH-THC. After the initial distribution phase the rate-limiting step in the metabolism of THC is its redistribution from lipid depots to blood [140]. Early studies showed that 15 to 20% of a smoked THC dose was eliminated as acidic urinary metabolites, while 30–35% were excreted in the feces as 11-OH-THC and THCCOOH [167]. Approximately 20% of the acidic urinary metabolites are estimated to be conjugated and non-conjugated THCCOOH. No significant difference in metabolism between men and women has been reported [457]. Figure 1 illustrates the major metabolic pathway for THC.

D. Elimination

More than 65% of the drug is excreted in the feces, with approximately 20% excreted in the urine [457]. A total of 80–90% of the drug is excreted within 5 days, mostly as hydroxylated and carboxylated metabolites [167]. Halldin et al. have identified 18 acidic metabolites of THC in urine, most of which are hydroxylated or beta-oxidized analogs of THC [160]. Many of these metabolites are conjugated with glucuronic acid, which increases the compounds' water solubility. The primary urinary metabolite is the acid-linked THCCOOH glucuronide conjugate [471], while 11-OH-THC predominates in the

feces [167]. Mean peak urinary concentrations of THCCOOH were 89.8±31.9 ng/mL and 153.4±49.2 ng/mL approximately 8–14 h after smoking a single 1.75% or 3.55% THC cigarette [200]. THCCOOH was detected in urine at a concentration greater than or equal to 15 ng/mL for 33.7±9.2 h and 88.6±9.5 h after these doses. When sensitive analytical procedures and sufficient sampling periods have been employed, the terminal urinary excretion half-life of THCCOOH in man has been estimated to be 3–4 days [214].

E. Plasma Concentrations

1. Smoked Cannabis

Many of the available analytical methods for early THC or cannabis administration studies measured THC and metabolites as aggregate acidic and neutral fractions rather than individual analytes. Other common problems with determining the pharmacokinetics of THCCOOH in humans include the necessity of rapid sampling during cannabis smoking to capture the absorption phase, 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 24–72 h that underestimate terminal THC and THCCOOH half-lives.

Huestis et al. [196] characterized the absorption of THC and formation of 11-OH-THC and THCCOOH during marijuana smoking, and followed the time course of detection of these compounds over 7 days. THC was detected in the plasma immediately after the first marijuana puff (**Figure 2** [191]). Concentrations continued to increase rapidly. Following smoking of one 1.75% or 3.55% (**Figure 3** [196]) THC cigarette, peak THC concentrations ranges were 50–129 ng/mL (mean 84.3 ng/mL) and 76–267 ng/mL (mean 162.2 ng/mL), respectively. 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 3–12 h after the low-dose and from 6 to 27 h after the high-dose marijuana cigarette.

These peak THC plasma concentrations are in good agreement with the results of other controlled cannabis smoking studies. Perez-Reyes et al. reported mean peak THC concentrations of 94.3, 107.4, and 155.1 ng/mL after smoking a single 1.32, 1.97, or 2.54% THC cigarette, respectively. Peak THC concentrations ranged between 45.6 to 187.8 ng/mL following smoking of an approximately 1% THC cigarette [347] and 33–118 ng/mL 3 minutes after ad lib smoking of an approximate 2% THC cigarette[328]. THC detection times in plasma of 3.5–5.5 h were reported in individuals who smoked two marijuana cigarettes containing a total of approximately 10 mg of THC (GC/MS LOD 0.8 ng/mL) [287] 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) [213]. 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 [7,251,457] that lacked the sensitivity and the lengthy monitoring window of the radio-labeled protocol.

Figure 2. Mean (n = 6) Δ^9-tetrahydrocannabinol (THC), 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) concentrations during smoking of a 3.55% THC cigarette. Each arrow represents one inhalation or puff on the cannabis cigarette. (Reproduced with permission from *Principles of Forensic Toxicology* [191].)

Figure 3. Mean (n = 6) concentrations of Δ^9-tetrahydrocannabinol (THC, closed triangles), 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC, open circles), and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH, closed squares) during and following smoking of a 3.55% THC cigarette. (Reproduced with permission from *J Anal Toxicol* [196].)

Few controlled drug administration studies have monitored the active 11-OH-THC plasma concentration. Huestis et al. found plasma 11-OH-THC concentrations to be approximately 6-10% of the concurrent THC concentrations for up to 45 min after the start of smoking [196]. 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 ng/mL) and 7.5 ng/mL (range 3.8–16 ng/mL) 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.

Huestis et al. monitored THCCOOH concentrations in human plasma for 7 days after controlled cannabis smoking [196]. This inactive metabolite was detected in all subjects' plasma by 8 min after the start of smoking. THCCOOH concentrations in plasma increased slowly, then held for up to 4 h. Peak concentrations were consistently lower than peak THC concentrations, but were higher than 11-OH-THC peak 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 48–168 h (mean 84 h). Detection times ranged 72–168 h (mean 152 h) following smoking of the higher dose.

Kelly et al. [225] intravenously administered 5 mg of THC to eight males and periodically monitored THC, THCCOOH, and THCCOOH-glucuronide conjugates by GC/MS (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. 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. Moeller et al. measured serum THC and THCCOOH concentrations in 24 experienced users from 40–220 min after smoking 300 μg/Kg cannabis cigarettes [303]. 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 THC-, 11-OH-THC-, or THCCOOH-glucuronides. 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 [121,127,150,224,226,227,246,271,287,456,458,467]. In general, the conjugates are believed to be of less importance in plasma following intravenous or smoked cannabis than after oral drug administration. Also, alkaline hydrolysis and beta-glucuronidase from *Helix pomatia* are less efficient than beta-glucuronidase from *E. coli* in hydrolyzing the ether glucuronide linkages of THC and 11-OH-THC glucuronide [227].

2. Cannabis Ingestion

There are fewer studies on the disposition of THC and metabolites after the oral as compared to the smoked route of cannabis administration. Recently, there has been renewed interest in oral THC pharmacokinetics due to the therapeutic value (*see* Section III) of orally administered THC and to the production of positive urine cannabinoid tests following ingestion of THC-containing foods, e.g., hemp oil. Peak THC plasma concentrations are much lower and occur later after ingestion as compared to smoking due to erratic absorption, degradation of THC by stomach acids and extensive first-pass metabolism [346,457]. Also, the choice of vehicle has been shown to be an important variable in determining the bioavailability following oral administration [382,412,443]. Ohlsson et al. [328] reported peak THC plasma concentrations of 4.4–11 ng/mL 2–3 h after eating a cookie containing 20-mg of THC; Law et al. [246] observed THC peaks of less than 10 ng/mL 4–6 h after ingestion of a similar amount. A higher peak concentration of 21.2 ng/mL 2 h after ingestion of 20 mg THC was suggested to be due to improved availability of THC when administered in sesame oil [382]. In a study of THC, 11OH-THC and THCCOOH concentrations in 17 volunteers after a single 10-mg Marinol capsule, peak plasma THC concentrations of 4.7±3 ng/mL were found 1–2 h after ingestion. Similar THC and 11-OH-THC concentrations were observed with consistently higher THCCOOH concentrations [415]. Interestingly, two THC peaks frequently were observed due to enterohepatic circulation. The onset, magnitude, and duration of pharmacodynamic effects are affected greatly by the concentration and route of THC administration, but certainly can occur following THC or cannabis ingestion [30,299]. Cone et al. [82] reported increases in subjective behavioral measures following the ingestion of marijuana-laced brownies in a controlled clinical study. Peak effects occurred 2.5 to 3.5 h after dosing.

3. Frequent Cannabis Use

Most THC plasma data have been collected following acute exposure; less is known of plasma THC concentrations in frequent users. Peat [337] 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±13.1 ng/mL, respectively, a minimum of 12 h after smoking. Furthermore, THC was detectable for up to 6 days after smoking cannabis in frequent users, and less than 1 day for infrequent users; no difference was observed in terminal half-life for frequent vs. infrequent users. Johansson et al. [213] 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.

F. Urine Concentrations

1. THCCOOH Excretion

Interpretation of positive urine tests requires an understanding of the excretion pattern of metabolites in humans. However, limited urinary excretion data from controlled clinical studies of cannabis use are available to aid interpretation. 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 appears in urine. Mean first urine THCCOOH concentrations were 47 ng/mL±22.3 and 75.3±48.9 ng/mL after smoking one 1.75 or 3.55% THC cigarette, respectively [200]. Fifty percent of the subjects' first urine specimens after the low dose and 83% of the first urine specimens 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 on 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 mg 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.

2. Detection Windows

Drug detection time, or the duration of time after drug administration that an individual tests positive, 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. After smoking a 1.75% THC cigarette, three of six subjects had additional positive urine samples interspersed between negative urine samples [198]. This had the effect of producing much longer detection times for the last positive specimen. Using the 15 ng/mL cutoff for THCCOOH currently required by the U.S. Department of Health and Human Services, Department of Transportation, and Department of Defense for regulated 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 h) and 88.6±23.2 h (range 57–122.3 h) [198].

3. Cannabinoid Immunoassays

Knowledge of the sensitivity and specificity of cannabinoid immunoassays for different cannabinoid analytes is essential for their proper use, since these assay characteristics differ and affect detection times. Reports of prolonged drug excretion have provided the basis for the common assumption that cannabinoid metabolites may be detected in urine for a week or longer. The accuracy, sensitivity, and specificity of immunoassays for the detection of cannabinoids and metabolites are unique for a specific assay and may change over time. It is important that individuals who select assays and those who interpret test results be aware of qualitative and quantitative changes that occur. In general, detection times of cannabinoid metabolites in urine monitored by immunoassay have decreased over the past two decades as the specificities of the assays for THCCOOH have increased. Periodically, this variability should be assessed by determining individual cannabinoid excretion profiles with available cannabinoid immunoassays.

Urinary cannabinoid detection times vary substantially across assays, subjects, doses, and cutoff concentrations. Mean detection times across nine commercial cannabinoid assays were found to range from a maximum of 0.5 days after smoking one 1.75% THC cigarette and up to 1.5 days after one 3.55% THC cigarette using a 100-ng/mL immunoassay cutoff [199]. Monitoring acute cannabis usage with a commercial cannabinoid immunoassay with a 50-ng/mL cutoff concentration provides only a narrow window of detection of 1–2 days. Mean detection times were less than 1 day following the low-dose and less than 2 days following the high-dose exposure with the 50 ng/mL cutoff [198]. Mean detection times were longer, 1–

6 days after smoking, with a 20 ng/mL cutoff. GC/MS detection times were approximately twice as long as mean detection times with an immunoassay cutoff of 50 ng/mL [199]. Consecutive urine voids may produce either positive or negative results when drug concentrations approach the cutoff concentration. Quantitative results, not adjusted for creatinine concentration, are subject to normal variation in excretion of cannabinoids due to differences in an individual's state of hydration, and subsequently, the water content of the urine specimens.

4. Percentage Dose Excreted

An average of 93.9±24.5 μg THCCOOH (range 34.6–171.6 μg) was measured in urine over a 7-day period following smoking of a single 1.75% THC cigarette [200]. The average amount of THCCOOH excreted in the same time period following the high dose was 197.4±33.6 μg (range 107.5–305.0 μg). 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 sidestream smoke. 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 on the experience of the cannabis user [256,328,347]. 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. The major route of excretion of THC and metabolites is in the feces (30 to 65%), rather than in the urine (20%) [455,457]. In addition, numerous cannabinoid metabolites are produced in humans as a result of THC metabolism, most of which are not measured or included in the % dose excreted calculations.

V. ANALYSIS

A. Initial Testing

1. Urine Testing

Selection of an appropriate testing method requires knowledge of the type of available specimen, the analyte's metabolic profile, and the assay's characteristics. The nature and abundance of specific metabolites in different body fluids is best achieved through controlled drug administration studies. Initial testing or screening methods for cannabinoids in body fluids include immunoassays and thin layer chromatography (TLC). A wide variety of immunoassays are available, including enzyme immunoassays (EIA), fluorescence polarization immunoassays (FPIA), radioimmunoassays (RIA), cloned enzyme donor immunoassays (CEDIA) and kinetic interaction of microparticles in solution (KIMS) assays. Urine is usually tested without specimen preparation due to high concentrations of drug and/or metabolites and low concentrations of other interfering components such as proteins and lipids. If commercial urine immunoassays are used to screen blood, plasma, or other complex matrices for cannabinoids, it may be necessary to use a pre-extraction step because of potential interferences. The cross-reactivity of the immunoassay's antibodies to drug metabolites, including glucuronides, is important in method selection. Immunoassays developed for urine testing contain antibodies directed toward THCCOOH, the primary urinary metabolite, although cross-reactivity of the different immunoassays varies considerably toward other THC metabolites [258,265]. This specificity for THCCOOH was appropriate for the analysis of urine because little free parent THC and 11-OH-THC metabolite were originally believed to be present in urine. However, THC and 11-OH-THC have been identified in urine specimens, albeit for a shorter time after drug administration than the more abundant THCCOOH metabolite [226] (*see* Section V-B). Although a high percentage of cannabinoid metabolites are excreted in the urine as glucuronides, the combined cross-reactivity of THCCOOH glucuronide and the abundance of free THCCOOH have provided adequate sensitivity to forego hydrolysis of urine during screening.

Initial test cutoffs for screening cannabinoids in urine include 20, 50, and 100 ng/mL. In April 1988, the Health and Human Services guidelines for testing urine for the federal sector established the initial test (screen) cutoff for cannabinoids at 100 ng/mL [445]. HHS subsequently lowered the required initial test cutoff for cannabinoids to 50 ng/mL [446]. Lowering the urine cannabinoid initial test cutoff from 100 to 50 ng/mL significantly increased the identification of true positive specimens and drug detection time after cannabis exposure [199]. The more sensitive 20-ng/mL cutoff is utilized in many treatment settings and in some workplace testing environments, e.g., nuclear power plant testing programs. Commercially available immunoassays for cannabinoids can be modified to provide better sensitivity for the detection of in utero drug exposure in maternal and neonatal urine specimens [28,170,474,475]. In addition, many on-site drug-testing

devices for cannabinoids in urine have been developed [48,49,52,86,336,390,441].

TLC is also used as a screening method for cannabinoids in urine. Early studies of THC metabolism utilized classical TLC methods. Commercial applications of these systems are available for the identification of THCCOOH in urine, and although the time required for testing and the hands-on technologist time may be greater than with immunoassays, a number of specimens may be tested simultaneously and at a reduced cost in some instances [129]. TLC methods are specific for the THCCOOH metabolite and include alkaline hydrolysis, extraction, concentration, and separation. Fast Blue BB staining reagent is the reagent of choice for visualization; sensitivity limits of 5–10 ng/mL THCCOOH have been achieved [232].

2. Oral Fluid Testing

Oral fluid also is a suitable specimen for screening for the presence of cannabinoids [57,153,154,316,407,408] and is being considered for approval for federally mandated workplace drug testing programs. Adequate sensitivity would be achieved best by an immunoassay directed toward detection of the parent THC, rather than the 11-OH-THC or THCCOOH metabolites. 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 the oral fluid [174]. Following intravenous administration of radiolabeled THC, no radioactivity could be demonstrated in oral fluid [173]. No measurable 11-OH-THC or THCCOOH were found in the oral fluid for 7 days following cannabis smoking by GC/MS with a LOQ of 0.5 ng/mL [192], or in oral fluid from 22 subjects positive for THCCOOH in the urine [233]. Oral fluid collected with the Salivette collection device was positive for THC in 14 of the 22 participants. In a recent study of oral fluid from 10 cannabis users, frequent false negative and false positive results were obtained with the Drugwipe® device as compared to GC/MS analysis [384]. As previously observed, no 11-OH-THC or THCCOOH was found in the oral fluid by GC/MS after cannabis smoking, although THC, cannabinol, and cannabidiol were identified. It appears that initially THC in cannabis smoke contaminates oral fluid with high drug concentrations. Hours after smoking, the oral mucosa serves as a depot for release of THC into the oral fluid.

New enzyme-immunoassays are available for detecting cannabinoids in oral fluid that require little to no specimen preparation [210,233,290]. Mura et al. evaluated six rapid screening tests for identifying cannabinoids in oral fluid [316]. The results of testing the Syva® Rapidtest, Biomedix®, Frontline®, Drug Wipe®, Cortez®, and Dako® devices for cannabinoids in saliva were disappointing, with numerous false positive and false negative test results. The proposed DHHS guidelines for cannabinoid testing of oral fluid recommends 4 ng/mL THC as the cutoff for the initial screening test, and 2 ng/mL THC as the confirmatory cutoff. In a new study of smoked and oral cannabis use, the Intercept DOA Oral Specimen Collection Device and Intercept MICRO-PLATE EIA initial test for cannabinoids were evaluated [323]. A cannabinoid screening cutoff of 1.0 ng/mL and a GC/MS/MS THC confirmation cutoff of 0.5 ng/mL were employed to test consecutive oral fluid specimens from 10 participants following drug use. Oral fluid specimens tested positive following smoked cannabis for an average of 15±2 (range 1–24) h by EIA and 13±3 (range 1–24) h by GC/MS/MS. After these times, occasional positive oral fluid results were interspersed with negative tests for up to 34 h. Oral fluid specimens also tested positive immediately after cannabis smoking, providing an advantage over urine testing for detecting very recent cannabis use. The performance of the Cozart RapiScan collection device was evaluated in three volunteers who smoked cannabis and provided oral fluid for up to 24 h [210]. The 10 ng/mL THCCOOH cutoff was determined to be too high to detect cannabis use for more than 2 h after smoking. Lower cutoff concentrations were suggested 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 [156].

3. Blood and Tissue Testing

Whole blood, plasma, and tissues may also be screened for the presence of cannabinoids. Whole blood cannabinoid concentrations are approximately one-half the concentrations found in plasma specimens due to the low partition coefficient of drug into erythrocytes [189,279,331, 467]. Simple preparation steps, such as protein precipitation or single-step solvent extraction, may be required with some methods; more extensive extraction and concentration schemes may be required for the use of other immunoassays [65,206,228,331,403]. Some immunoassay reagents contain antibodies that cross-react with the parent THC compound; other reagents contain antibodies to the inactive THCCOOH metabolite. THC cross-reacts poorly with antibodies found in most of the commercially available reagents; however, THCCOOH appears during smoking, increases over time, and has a much longer time course of detection than the parent compound.

4. Sweat Testing

There are few data on the excretion of cannabinoids in sweat, although sweat is being considered as an alternate matrix for some types of federally mandated workplace drug testing [192,229]. In 1989, Balabanova and Schneider reported the presence of THC in apocrine sweat by RIA [18]. Mura et al. evaluated six rapid screening tests for identifying cannabinoids in sweat [316]. The DrugWipe® test was found to be useful in identifying cannabis in sweat within 2 h of use. In another study, the reliability of the DrugWipe test for identifying cannabinoid use was questioned due to several false positive and false negative results in a study of 15 cannabis users [384]. Kintz et al. identified THC (4–38 ng/patch) in a study of 20 known heroin abusers attending a detoxification center who wore the PharmChek patch for 5 days [236]. 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 [233]. THC, but not 11-OH-THC or THCCOOH metabolites, was detected (4–152 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 also has been used to measure cannabinoids in sweat collected with the PharmChek sweat patch [109]. THC was reliably detected at a limit of 1 ng/patch. Proposed U.S. guidelines for oral fluid cannabinoid testing include cutoff concentrations of 4 ng/mL THC for the initial test and 2 ng/mL for THC in the confirmatory test.

5. Hair Testing

Radioimmunoassay, enzyme multiplied immunoassay and fluorescence polarization immunoassay screening methods have been employed with sensitive GC/MS or GC/MS/MS confirmation methodologies in the analysis of cannabinoids in hair [71,72,172,221,234,380,419, 469]. Cirimele et al. developed a rapid, simple GC/MS screening method for THC, cannabinol, and cannabidiol in hair that did not require derivatization prior to analysis [73]. The method was found to be a sensitive screen for cannabis detection, with GC/MS identification of THCCOOH recommended as a confirmatory procedure. Most studies have focused on identifying the most abundant cannabinoid analyte in hair, the more neutral and lipophilic parent compound, THC. However, other methods target THCCOOH, which is present in much lower concentrations in the hair [58,70,235,307]. An advantage of measuring THCCOOH in hair is that cannabis use can be more effectively documented than with detection of parent THC. THC could be deposited in hair following environmental exposure to cannabis smoke. Analysis of cannabinoids in hair has challenged the sensitivity limits of immunoassay and confirmation assays; GC/MS/MS has been required in most cases to increase the confirmation rate of presumptive positive results [58,444]. At the current time, the proposed U.S. guidelines for cannabinoid testing in hair include cutoff concentrations of 1 picogram/mg (pg/mg) of hair for THC for the initial test and 0.05 pg/mg for THCCOOH in the confirmatory test.

B. Confirmatory Testing

A chemical technique that is based on a different scientific principle from the chemical technique used in the initial test is required for confirmation of cannabinoid results, e.g., immunoassay for the initial test and chromatography for confirmation. Numerous confirmation methodologies have been developed for cannabinoids, including TLC [11,129,222,231,232,241], gas chromatography (GC) [278,335,354,361,465], high performance liquid chromatography (HPLC) [10,27,40,111,124,143,149,183, 202,205,223,318,324,338,384,437], liquid chromatography/mass spectrometry (LC/MS) [44], liquid chromatography tandem mass spectrometry (LC/MS/MS) [321], capillary electrophoresis/mass spectrometry (CE/MS) [87,190,429], gas-chromatography/mass spectrometry (GC/MS) [75,84,120,127,148,156,216,222,303,381,397, 416,469,478], and GC/MS/MS [58,77,322,444]. Cannabinoid confirmations also are available for ion trap GC/MS instruments [156,289,351,473]. Confirmation of forensic specimens almost always includes mass spectrometric or tandem mass spectrometric identification due to the improved specificity of these techniques. Ideally, the sensitivity of the confirmation assay should be equal to or greater than the sensitivity of the initial test method. Selected ion monitoring (SIM), full-scan ion monitoring, chemical ionization methods, direct probe insertion GC/MS, and neutral loss and product ion methods have been utilized for the confirmation of cannabinoids in body fluids and tissues.

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 NaOH. Alkaline hydrolysis appears to efficiently hydrolyze the ester THCCOOH glucuronide linkage. The efficiency of glucuronide hydrolysis in cannabinoid extraction methods should be routinely evaluated by inclusion of a THCCOOH glucuronide quality control sample. This sample can be prepared from a pool of cannabinoid-positive urine specimens, or from THCCOOH glucu-

ronide-spiked specimens. THC and 11-OH-THC primarily are 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 rather than the more commonly employed *Helix pomatia* (mollusk) β-glucuronidase [227]. Evaluation of the efficiency of the *E. coli* β-glucuronidase to cleave the hydroxy-glucuronide ether linkage requires a pooled urine specimen collected within 24 h of smoking when 11-OH-THC is expected to still be present or a quality-control urine specimen spiked with THC-glucuronide. Some methods also utilize a hydrolysis step in the analysis of cannabinoids in blood [121,224,226,227]. The importance of glucuronide derivatives of cannabinoids in blood remains a contested issue.

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, plasma, hair, may require multi-step extractions to separate cannabinoids from lipids and proteins. Cannabinoid extraction techniques include liquid-liquid extractions, as well as solid-phase extraction with bonded silica, XAD-2, anion exchange and many new mixed-mode columns [120,231,289,319,325,378,402,466,478]. Care must be taken to avoid low recoveries of cannabinoids due to their high affinity to glass and plastic containers [32,38, 66,212].

Several GC methods for both packed and capillary columns are available, although for forensic purposes, GC/MS has supplanted GC analyses. One of the first widely used GC methods for THCCOOH in urine utilized flame ionization detection of the methyl ether-methyl ester derivative (detection limit 20 ng/mL) [465]. More sensitive electron impact [120,121,148,226,303], chemical ionization [128,171,397], GC/MS and GC/MS/MS [322] confirmation procedures have been developed for THC, 11-OH-THC, and THCCOOH in a wide variety of biological tissues. Several deuterated THCCOOH materials are available as internal standards and are recommended for the highest accuracy of results [257,303]. Compounds with multiple deuterium ions are available and provide adequate resolution between the deuterated and native ions for use in full-scan ion monitoring techniques [112,211].

Usually, two separate extracts and two GC/MS injections are made for analysis of acidic and neutral cannabinoids. Huang et al. have developed a simultaneous method for analysis of THC and THCCOOH in plasma following solid-phase extraction and negative chemical ionization GC/MS [189]. Although recovery was poor for THCCOOH (17%), a LOQ of 2.5 ng/mL for THCCOOH was achieved. Another creative approach for the analysis of cannabinoids utilized immunoaffinity extraction of cannabinoids from plasma, urine, and meconium; however, the LOQ for THC was 1.5 ng/mL [121]. Limits of quantitation in plasma need to be as low as possible for both pharmacokinetic studies and forensic analyses due to rapid metabolism and distribution of THC. Excellent reviews of cannabinoid analyses in whole blood and other biological matrices have been published [120,127,304,416].

Carboxyl and hydroxyl groups on the THC, 11-OH-THC, and THCCOOH molecules require derivatization to improve chromatographic performance. A wide variety of different derivatizing reagents have been used in the analysis of cannabinoids to achieve acceptable chromatography, stability, and sensitivity including silyl [148,166,226], methyl [303,335], trifluro [128,189,224, 322,397], and pentafluoro [120,224,287] derivatizing reagents. Electron impact mass spectrometry of cannabinoids following alkaline hydrolysis and derivatization with one of a wide variety of derivatization reagents is achievable for most forensic toxicology laboratories due to the availability of low-cost, bench-top GC/MS instruments.

VI. INTERPRETATION

A. Urine

Detection of cannabinoids in urine is indicative of prior cannabis exposure, but the long excretion half-life of THC 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 [110]. This individual had used cannabis heavily for more than 10 years. However, a naive user's urine may be found negative by immunoassay after only a few h following the smoking of a single cannabis cigarette [198]. Assay cutoff concentrations affect drug detection times. Other components to the detection of cannabis use are the sensitivity and specificity of the immunoassay system used. In general, immunoassay reagents have become more specific for THCCOOH as newer assays have been developed. This has resulted in improved correlations between immunoassays, and also between immunoassays utilizing 50-ng/mL initial test cutoffs and confirmation procedures with a 15-ng/mL cutoff concentration [198]. This improved specificity would be expected to shorten the urine

detection window. Nevertheless, 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.

1. Creatinine Normalization

Normalization of the cannabinoid drug concentration to the urine creatinine concentration aids in the differentiation of new from 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 [174] first suggested creatinine normalization of urine test results to account for variations in urine volume in the bladder. 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 [268]. 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 associated with workplace drug testing.

Unfortunately, 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 marijuana users who smoked two different doses of marijuana separated by weekly intervals [193]. A relative operating characteristic (ROC) curve was constructed from sensitivity and specificity data for 26 different cutoffs ranging from 10 to 200%. The most accurate ratio (85.4%) was 50% with a sensitivity of 80.1% and a specificity of 90.2%. Use of the 50% threshold to evaluate whether new drug use had occurred between two urine drug specimens generated 5.6% false positive and 7.4% false negative predictions for this clinical study. 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%, for 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 [83]. Sensitivity, specificity, accuracy, % false positives and % false negatives were 71.9%, 91.6%, 83.9%, 5.4%, and 10.7%, respectively, when the 50% criterion was applied. These data compare favorably with the results from the first clinical study, with the exception of slightly lower sensitivity and higher false negative percentages in the water dilution study. This would be expected due to the ingestion of large amounts of water and consequent dilution of urine drug concentration. 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.

2. Presence of THC and 11-OH-THC in Urine

It has been proposed that the amount of THC and 11-OH-THC measured in urine samples can be related to the elapsed time after cannabis smoking. Hydrolysis of urinary cannabinoid glucuronides with β-glucuronidase from *E. coli* (bacteria) prior to GC/MS analysis resulted in higher concentrations of THC and 11-OH-THC than with beta-glucuronidase from *Helix pomatia* [227]. In the controlled clinical study of Kemp et al., the time course of excretion of THC-glucuronide and 11-OH-THC-glucuronide in urine was much shorter than THCCOOH-glucuronide, potentially indicating recent cannabis use. Ongoing research in our laboratory indicates that 11-OH-THC may be excreted in the urine of chronic cannabis users for a much longer period of time, perhaps beyond the period of pharmacodynamic effects and performance impairment. Additional research is necessary to determine the validity of estimating time of cannabis use from THC and 11-OH-THC concentrations in urine.

B. Oral Fluid

Detection times of cannabinoids in oral fluid are shorter than in urine, and are more indicative of recent cannabis use [57,154]. 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 [192,194]. THC may be detected at low concentrations by radioimmunoassay for up to 24 h after use. A study of oral fluid THC concentrations after smoked cannabis, reported positive cannabinoid tests for 15±2 (range 1–24) h by EIA and 13±3 h (range 1–24) with a screening cutoff of 1.0 ng/mL and a GC/MS/MS THC confirmation cutoff of 0.5 ng/mL [323]. 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 for cannabinoids with the EMIT screening test and GC/MS confirmation [340]. 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 are also being evaluated in the European Union's Roadside Testing Assessment (ROSITA) Project whose goals are reduce the number of individuals driving under the influence and to improve road safety. Urine, sweat, and oral fluid on-site tests are being evaluated for the rapid and accurate detection of impairing drugs. The ease and non-invasiveness of oral fluid collection, reduced hazards in specimen handling and testing, and a shorter detection window are attractive attributes to the use of this specimen for identifying the presence of potentially performance impairing drugs.

C. Blood, Plasma, and Serum

Scientific advances have improved our ability to identify and quantitate cannabinoids in body fluids; however, the interpretation of results remains a difficult task. Forensic scientists receive frequent requests to interpret the significance of cannabinoid concentrations in blood specimens from individuals involved in accidents, criminal investigations, and traffic violations. Relevant facts, such as the amount of drug used, route of administration, and history of use, generally are unknown. To date, a practical presumptive concentration of blood THC cannot be related to a measurable level of impairment such as the situation with blood ethanol concentrations [33,173]. Due to chemical and pharmacokinetic differences between cannabis and ethanol, we cannot use ethanol as a model for relating drug concentrations to effects. Consequently, the pattern of distribution to and elimination from active sites of these two molecules are quite different. Pharmacokinetic and pharmacodynamic models that account for the dispositional differences of THC may be more successful in defining blood concentrations that can be associated with the psychoactive effects of THC [79].

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 [343,347]. 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 [201]. Individual drug concentrations and ratios of cannabinoid metabolite to parent drug concentration have been suggested as potentially useful indicators of recent drug use [162,246]. The ratio of plasma THCCOOH to THC was found to exceed 1 at 45 min after cannabis smoking [224]. This is in agreement with results reported by Mason and McBay [279] and Huestis et al. [201] who found that peak effects occurred when THC and THCCOOH concentrations reached equivalency, within 30–45 min after initiation of smoking. Measurement of cannabinoid analytes with short time courses of detection, e.g., 8β, 11-dihydroxytetrahydrocannabinol, as markers of recent exposure has not found wide spread use [287]. Recent exposure (6–8 h) and possible impairment have been linked to plasma THC concentrations in excess of 2–3 ng/mL [22,196,279]. Gjerde [146] suggested that 1.6 ng/mL THC in whole blood may 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 plasma THC [280]. 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 [337]. Significantly higher residual concentrations of THCCOOH may be found.

1. Prediction Models for Estimation of Cannabis Exposure

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. Huestis et al. developed two mathematical models for the prediction of time of cannabis use from the analysis of a single plasma specimen for cannabinoids [197]. Model I was based on THC concentrations and Model II was based on the ratio of THCCOOH to THC in plasma. 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 [271]. The models were found to accurately predict the time of use within the 95% confidence intervals. The

models are being used in many criminal and accident investigations and may be beneficial to forensic scientists in the interpretation of cannabinoid plasma concentrations.

VII. IN VITRO STABILITY

A. Whole Blood, Plasma, and Serum

One concern in the analysis of THC and metabolites in biological specimens is the stability of these compounds over time. THC is a lipophilic molecule and binds to hydrophobic surfaces. This can potentially cause a reduction in concentration depending on the type of storage container. It is recommended that blood or plasma specimens be stored in glass tubes rather than plastic tubes, as THC may adsorb to plastic tubes, thus reducing the measured concentration. However, stability studies in blood or plasma have found that, in general, the concentration of THC remains unchanged over time. THC was stable in blood stored at 5, –5, and –20 °C for up to 17 weeks [474]. Degradation began to occur after this time and the drug was not detected by 23 weeks. Temperature conditions did not influence recovery of the drug, nor did repetitive freeze-thaw cycles. The authors hypothesized that decreasing THC concentrations may have been due to unsuccessful extractions of the drug due to irretrievable binding to degrading proteins. Another study on the stability of THC, 11-OH-THC, and THCCOOH in blood and plasma found no significant changes in concentrations for the first month of storage at room temperature, 4, or –10 °C [217]. However, THC and 11-OH-THC concentrations decreased significantly after storing for 2 months at room temperature. Blood stored at 4 °C showed no significant changes for 4 months, but extractions after 6 months demonstrated poor precision and inefficient extraction. Cannabinoid concentrations in blood and plasma stored at –10 °C and plasma stored at 4 °C were stable for up to 6 months. Furthermore, studies evaluating contact between the specimen and the collection tube's rubber stopper noted that the size of the blood specimen, storage temperature, and extent of contact with the rubber stopper did not affect cannabinoid concentration for up to 24 h.

THCCOOH was found to be stable for up to 30 days in blood collection tubes containing EDTA, heparin, or sodium fluoride, and in tubes with no anticoagulant at refrigerated and room temperatures [288]. In addition, repetitive freeze-thaw cycles did not contribute to loss of this analyte. THC, 11-OH-THC, and THCCOOH concentrations in blood and plasma are stable for at least 1 month when stored refrigerated, frozen or at room temperature. After this time period, reductions may be seen if the blood is stored at room temperature. This stability in blood or plasma possibly may be attributed to extensive protein binding, which may limit loss via adsorption to container surfaces.

B. Urine

Romberg [375] evaluated the stability of THCCOOH-spiked urine specimens stored at room temperature, under nitrogen, in the dark, or exposed to light. THCCOOH concentrations were within 10% of the initial level after 4 weeks of storage and within 20% after 7 weeks. In another study by Romberg [376], THCCOOH concentrations in frozen routine urine specimens stored over variable time periods were noted to decrease an average of 24%, although considerable variability was observed. The percent change in concentration ranged from +28% to –80%. There was no correlation between the decrease in concentration and the time in frozen storage. The stabilities of in-house prepared frozen control solutions also were evaluated at pH 6.0, 7.5, and 9.0. THCCOOH concentrations were stable over the 9-month evaluation period, except for the pH 9.0 control that decreased by 30%. Thawing and refreezing did not affect the stability of the drug in the control solutions. Other studies have indicated that THCCOOH is stable for at least 6 months at –20 °C [127]. The most consistent results were obtained by thoroughly thawing the urine and sonicating prior to extraction. THCCOOH can concentrate in urine sediment and in foam formed upon shaking.

VIII. Passive Inhalation

Environmental exposure to cannabis smoke can occur through passive inhalation of side-stream and exhaled smoke by non-users. Several research studies have indicated that it is possible to produce detectable concentrations of cannabinoid metabolites in the urine and plasma after passive inhalation of cannabis smoke. Perez-Reyes et al. exposed non-smokers to marijuana smoke from two to four cigarettes for 1 h in confined environments (one in a small automobile and two studies in a 640 cu ft room) and collected urine samples for the following 24 h [344]. Exposure was repeated in one study on 3 consecutive days. Only 2 urine specimens screened positive at 20 ng/mL with the EMIT test. One of the urine specimens contained 3.9 ng/mL THCCOOH by GC/MS. Law et al. exposed four non-smoking volunteers to cannabis smoke from six cannabis smokers; all remained within a small room for 3 h [247]. All blood specimens were negative for cannabinoids, while urine specimens taken up to 6 h after exposure had cannabinoid metabolites up to 6.8 ng/mL by

a radioimmunoassay. Morland et al. exposed five naïve cannabis users to cannabis smoke for 30 min in a small closed car and found RIA total blood cannabinoid concentrations of 13 ng/mL; THC concentrations of 1.3–6.3 ng/mL were measured by GC/MS immediately after passive exposure [308]. Some of the urine cannabinoid concentrations exceeded 20 ng/mL by EMIT.

Cone et al. exposed five volunteers to sidestream smoke from 4 and 16 marijuana cigarettes in a small-unventilated room for 1 h for 6 consecutive days [81]. Urine specimens were analyzed by EMIT (20 ng/mL cutoff), Abuscreen RIA (10 ng/mL cutoff), and GC/MS (5 ng/mL cutoff). Few urine specimens were positive following the 4-cigarette exposure condition with concentrations close to the cutoff levels, while many more specimens were positive and at higher concentrations after the 16-cigarette exposure condition. THCCOOH concentrations after the first day of high exposure ranged from 0–39 ng/mL by GC/MS. The maximum THCCOOH concentration observed was 87 ng/mL. The last positive urine specimen with a GC/MS cutoff of 5 ng/mL THCCOOH occurred from 25.4–123.1 h after six consecutive passive inhalation exposures to 16 marijuana cigarettes for 1 h per day. Although positive urine tests can be obtained after passive inhalation in a laboratory setting, exposure conditions included heavy marijuana smoke (smoke of such intensity that goggles were required to protect the eyes), a non-ventilated, tightly sealed room, and multiple daily exposures [80]. It is generally agreed that passive inhalation of cannabis smoke under normal exposure conditions, i.e., an outdoor stadium or an open room within a home, is not a valid explanation for a positive urine cannabinoid test [312].

IX. IMPAIRMENT

It would be helpful if a driver's drug concentration in blood were directly related to a specific degree of driving impairment. However, the relationship between drug concentrations and physiological and behavioral impairment is complex. With the exception of ethanol, few experimental data are available correlating drug concentrations in blood to driving impairment. Interpretation of the contribution of drug use to accident causation and determination of the relative importance of a drug's quantitative concentration in plasma or whole blood is complicated by a multitude of factors including drug interactions, drug tolerance, driving experience, road and weather conditions, and the age and health of the driver.

The effects of a drug on driving performance can be studied using three different approaches that are discussed below. Each of these approaches has been used to study cannabis's effects on driving and each has offered a different perspective on potential impairment.

- Epidemiological studies to determine the incidence of the drug in fatal and non-fatal motor vehicle accidents and in driving under the influence cases. These studies can also evaluate the causal effect of the drug using culpability or responsibility analysis.
- Performance impairment studies, particularly those in which the effect of the drug on cognitive and/or psychomotor tasks is measured.
- Driving simulator and closed and open-road driving studies in which the drug's effects in situations more closely resembling real driving are monitored.

A. Epidemiological Studies

Epidemiological studies of cannabis use and motor vehicle fatalities and injuries, trauma patients, driving under the influence of drugs (DUID), tractor-trailer drivers, and occupational fatalities are included in **Table 1** (A–F). Most statistical studies that examine the frequency of accidents or fatalities in individuals who have consumed drugs lack proper control groups. The value of these studies in predicting possible impairment and linking drug use to increased accidents or fatalities is weakened because incidence rates of cannabis use in control populations are poorly defined [23]. Some data are available on cannabis usage rates in the general population, and on usage rates shortly before or while driving. More than one-fourth of drivers over the age of 16 reported occasional driving under the influence of alcohol, marijuana, or both in the 1996 National Household Survey on Drug Abuse, reflecting the magnitude of this important public health safety issue [449]. In the 1990s, cannabis use was identified in 7–15% of injured drivers in the U.S., Canada and Australia [261,418]. In 1995, 17.3% of U.S. college students reported use of marijuana within the preceding 30 days [118]. Random stops of tractor-trailer drivers indicated a 15% positive rate for cannabinoids, with 3% positive for blood THC exceeding 2.5 ng/mL [263]. Cannabis is not the drug of choice for professional drivers due to its sedative effects; therefore, this rate may not reflect general population use.

Incidence rates were higher at the height of marijuana usage from 1960 to 1980. Driving shortly after marijuana smoking was reported by 29% and 21% of Massachusetts teen-agers in 1979 and 1981, respectively [182]. In another study of young adults in Boston, 43% reported driving or riding with a driver under the influence of marijuana [462], while 6.3% of University of Illinois students stated that they operated a motor vehicle on a weekly/daily basis shortly after or while using cannabis [451].

Table 1. Epidemiological studies examining the presence of cannabinoids in various population groups

Population description	Findings[a,b]	Blood level[a–c]	Year	Ref.
A. Motor vehicle fatalities				
Motor vehicle fatalities, Ontario, Canada (*n* = 401)	3.7% THC; 0.2% only THC; usually THC with ethanol; 10.7% positive for urine cannabinoids, no THC in blood	13/15 blood THC <5 ng/mL	1982	[69]
Single vehicle fatalities, NC (*n* = 600)	7.8% THC; 0.7% only THC	RIA and EMIT screen >3 ng/mL (range 3.1–37 ng/mL)	1984	[280]
Fatalities in young male CA drivers (*n* = 440)	37% THC or metabolite; 4.3% THC only drug; cannabinoids' role in crash responsibility undetermined	THC (ng/mL): 38% 0.2–0.9; 22% 1.0–1.9; 26% 2.0–4.9; 14% >5.0	1985	[470]
Fatalities, AL	17% positive for cannabinoids	N/A	1986	[132]
Fatalities, TX (*n* = 199)	34% of homicide victims, 25% of car/truck drivers, and 38% of motorcycle drivers positive for cannabinoids; cannabinoid drivers at fault about 52% of cases	GC/MS for THC, 11-OH-THC or THC-COOH in blood or urine	1986	[142]
Motor vehicle fatalities, Los Angeles, CA (*n* = 594)	18.8% THC positive	RIA (50 ng/mL) and GC/MS	1986	[51]
Fatalities, Ontario, Canada (*n* = 1,169)	10.9% THC; 1.7% only THC; 7.6% in pedestrian fatalities	RIA and GC/MS THC 0.2–37 ng/mL	1990	[68]
Motor vehicle fatalities: Norway (*n* = 159)	5% THC, most common drug; 3–6% drugs alone; 20% impaired by alcohol; 8% by alcohol and drugs	Blood screened by immunoassay, confirmed by GC/MS	1992	[145]
Fatalities in U.S. truck drivers (*n* = 168)	12.5% positive cannabinoids in blood; 70% THC; 30% THCCOOH; All THC positives found to be responsible for crash	GC/MS: mean THC 4.1 ng/mL (range 1–12); mean THCCOOH 20 ng/mL (range 5–174)	1993	[85]
Motor vehicle fatalities, Australia (*n* = 1,045)	11% positive for cannabinoids in blood or urine; lower odds ratio for accident risk when cannabis alone; higher odds for cannabis and ethanol combined	Primarily THCCOOH in urine; sometimes blood; few THC in blood	1994	[107]
Motor vehicle fatalities, BC, Canada (*n* = 227)	13% THC or THCCOOH of drivers dying within 24 h of accident; 5% THC	Blood THCCOOH mean 15.9 ng/mL; blood THC mean 3.6 ng/mL	1995	[301]
Motor vehicle fatalities, WA (*n* = 318)	11% of drivers had cannabinoids in blood or urine	Blood and urine screened by EMIT®; TLC confirmation	1996	[259]
B. Motor vehicle injuries				
Motor vehicle injuries, Rochester, NY (*n* = 497); culpability study	Increased odds ratio for cannabinoids alone 2.1; alcohol alone 5.4	N/A	1982	[435]
Motor vehicle injuries, Tasmania (*n* = 200)	6% THC	Blood RIA screen; GC/MS confirmation	1987	[291]
Motor vehicle injuries, Knoxville, TN (*n* = 164)	BAC 37%; other drugs 40%; >50% of BAC positive also positive for other drugs	Urine EMIT® 50 ng/mL	1992	[238]
Motor vehicle injuries, 7 U.S. states (*n* = 1,882)	6.7% positive for cannabinoids, 2/3 THC positive; cannabinoid positive less risk than drug-free	Blood RIA screens for THC and THCCOOH (13 ng/mL); GC/MS confirmation (THC = 1 ng/mL, THCCOOH = 2 ng/mL)	1992	[436]
Motor vehicle injuries, Toronto, Canada (*n* = 339)	13.9% THC; 40.5% positive for drug beside ethanol	N/A	1993	[418]
Motor vehicle injuries, Baltimore, MD (*n* = 331)	2.7% automobile drivers and 32.0% of motorcyclists positive serum THC	Serum RIA for THC (2 ng/mL)	1995	[410]
Motor vehicle injuries, Ann Arbor, MI (*n* = 894)	13.8% blood positive for cannabinoids, drawn within 6 h of crash (mean <1 h)	Serum THC and THCCOOH; higher odds ratio when THC = 2.1 ng/mL and THCCOOH = 31 ng/mL	1998	[203]
Motor vehicle injuries, South Australia (*n* = 2,500)	Odds ratios increased with increasing serum THC, not significantly different from drug-free; greater risk with THC and ethanol	Blood RIA screen (10 ng/mL); GC/MS confirmation (THC = 1 ng/mL, THCCOOH = 2 ng/mL)	1997	[459]
Motor vehicle injuries, Australia (*n* = 2,500)	10.8% positive cannabinoids; 2.8% THC and THC-COOH, 8% THCCOOH only; 7.1% cannabinoids only drug	Immunoassay screen (40 ng/mL); GC/MS confirmation (0.5 ng/mL); mean time prior to blood draw 2.7±3 h	2000	[260, 261]

Table 1. (Continued)

Population description	Findings[a,b]	Blood level[b,c]	Year	Ref.
Motor vehicle injuries, CO (*n* = 414)	17% urine positive cannabinoid; cannabinoids only not associated with increased risk	Urine collected within 1 h; initially screened; later analyzed urine for THC and THCCOOH to estimate time of use	2001	[262]
Motor vehicle injuries, Canada (*n* = 1,158)	40.2% of injured patients positive for blood THC and/or THCCOOH; 58.8% of cannabinoid positive had THC, 71.3% of these also positive for ethanol; 41.2% positive for THCCOOH only, of these 77.2% also positive for ethanol	Usually BAC <0.10 g%	1996	[209]
C. Trauma patients				
Trauma patients, MD (*n* = 1023)	37.4% THC; 16.5% alcohol and THC; 18.3% THC alone; Similar % in vehicular and non-vehicular trauma patients	RIA (2 ng/mL), some GC/MS confirmation; THC (ng/mL): 39.7% 2–4.9; 25.6% 5–9.9; 34.6% ≥ 10.0	1988	[411]
Trauma patients, WA (*n* = 452)	27% urine cannabinoid positive	Urine EMIT® (100 ng/mL)	1989	[370]
Trauma patients, Chicago, IL (*n* = 654)	37% positive urine cannabinoids	Urine EMIT®	1989	[404]
Trauma patients, Pittsburgh, PA (*n* = 177)	24% urine cannabinoid positive; 45% with ethanol	Urine EMIT®	1991	[74]
Trauma patients, New South Wales, Australia (*n* = 164)	15.2% positive urine cannabinoids; 68% >400 ng/mL	Urine semi-quantitative EMIT® screen (100 ng/mL)	1995	[424]
D. Driving under the influence of drug (DUID)				
DUID, CA (*n* = 1,792)	14.4% THC; 23% ethanol negative ; all THC positives failed roadside sobriety test	Blood THC ≥ 5.5 ng/mL Range 5.5–23 ng/mL, RIA, some GC/MS	1983	[483]
DUID, St. Louis, MO (*n* = 184)	47% of positive drug cases THC; negative BAC Impaired driving resulted in police stop	Urine EMIT® screen, TLC confirmation	1987	[353]
DUID, Los Angeles, CA (*n* = 173)	43.9% THC in blood	<1.0 to 12.4 ng/mL	1987	[54]
DUID, Norway (*n* = 270)	26% suspected alcohol were positive for cannabinoids; 13% confirmed THC; 43% DUID positive for THC; 15-20% with BAC <0.05% influenced by drugs	Blood RIA screen (0.5 μM); GC/MS confirmation (0.001 μM)	1990	[67]
DUID, negative for ethanol, Norway (*n* = 425)	56% THC; 82% positive for more than one drug	EMIT® and GC/MS, 50% <5 ng/mL THC	1991	[146]
DUID, PA (*n* = 39)	39% THC; 50% THC; 50% THC metabolite (GC/MS); 3.1% THC only	RIA (10 ng/mL), GC/MS confirmation	1992	[428]
DUID, NM (*n* = 2,023)	16.8% cannabinoid positive	Blood screen EMIT®; GC/MS confirmation	1992	[371]
DUID, Memphis, TN (*n* = 150)	33% positive for cannabinoids; 88% considered moderately or severely impaired; 100% of cannabinoid only failed sobriety tests	On-site urine screening with GC/MS confirmation, 30% failed to confirm	1994	[47]
DUID, Denver, CO (*n* = 242)	66.9% urine positive for cannabinoids	Urine EMIT® screen (20 ng/mL); GC/MS confirmation (5 ng/mL)	1996	[440]
DUID, Canada (*n* = 1,158)	62.1% of DUID positive for blood THC and/or THCCOOH; 81.5% of cannabinoid positive had THC, 49.5% of these also positive for ethanol; 18.5% positive for THCCOOH only, of these 53.3% also positive for ethanol	BAC <0.10 g%	1996	[209]
DUID, Switzerland (*n* = 641)	57.3% positive for cannabinoids; 20.6% cannabinoids and ethanol, 19.2% cannabinoids and opiates	Blood and/or urine, RIA screen, GC/MS confirmation	1997	[15]

Table 1. (Continued)

Population description	Findings[a,b]	Blood level[a–c]	Year	Ref.
DUID, Vienna, Austria (n = 205)	65.8% urine positive for cannabinoids in drivers testing negative for breath ethanol	Urine FPIA screen (25 ng/mL); GC/MS confirmation (THCCOOH 1 ng/mL)	1998	[369]
DUID, Ontario, Canada (n = 4,670)	1.9% of adult driving population and 22.8% of cannabis users drove within 1 h of cannabis use within the past 12 months; frequently combined with alcohol	Self-reported questionnaire	1999	[460]
E. Tractor-trailer drivers				
Tractor-trailer drivers (n = 317)	15% cannabinoids; 3% blood THC; ethanol <1%	Blood or serum THC 2.5–12 ng/mL; urine EMIT screen; GC/MS or HPTLC confirmation	1988	[263]
F. Occupational fatalities				
Occupational fatalities, Alberta, Canada (n = 82)	8.5% positive urine cannabinoids; only illicit drug	Urine cannabinoids ≥ 5 ng/mL	1991	[12]
Occupational fatalities, Ontario, Canada (n = 470)	17% cannabinoid positive	N/A	1993	[394]

[a] THC = Δ^9-Tetrahydrocannabinol; THCCOOH = 11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol.
[b] BAC = Blood alcohol concentration.
[c] RIA = Radioimmunoassay; EMIT = Enzyme-multiplied immunoassay test; GC/MS = Gas chromatography/mass spectrometry; FPIA = Fluorescence polarization immunoassay.

Other difficulties in interpreting epidemiological data relate to the selection of assay methods, cutoff concentrations, and specimens to be tested for drugs. Additionally, cannabinoid measurements sometimes are not included due to the difficulty and expense of analysis. Many studies only evaluated specimens for drugs if the blood alcohol concentration (BAC) was less than the legal limit, or after negative results were obtained on a breath alcohol test. Alcohol intoxication is a major contributing factor to traffic accidents; however, the role of other illicit drugs, including cannabis, is less well defined. From 40 to 80% of drivers in culpability studies are positive for blood or breath alcohol, complicating the assignment of crash responsibility to illicit drugs that may also be present [262].

Specimens may be treated differently in different studies; i.e., specimens may be screened for cannabinoids in whole blood, plasma, or serum, or qualitatively or quantitatively tested for cannabinoids, THC, and/or THCCOOH. Sometimes only urine specimens are evaluated. The long elimination half-life of cannabinoids makes the relationship between a positive urine test and accident risk difficult to interpret. Furthermore, in many cases published data are unclear as to whether THC or its inactive metabolite THCCOOH, or both, are considered a positive result. Rarely are quantitative data available, and, in many studies, no confirmatory procedures are performed, raising the issue of false positive and false negative tests. Another consideration is the variability in limits of detection and cutoff concentrations employed in different studies that limit data comparison.

In motor vehicle accidents, 40 to 50% of casualties were positive for at least one drug other than ethanol, cannabis being the most common. In a prospective study of 1023 trauma cases in Maryland, 34.7% of subjects had greater than 2 ng/mL THC in their serum; more than one-third had serum THC concentrations of 10 ng/mL or more [411]. Although a high percentage of DUID cases also are positive for cannabinoids, especially in specimens negative for BAC, if the active compound (THC) was detected, its concentration was usually low, <5 ng/mL. Sutton et al. suggested this was due to the rapid decline of THC concentrations after smoking and the time required obtaining blood specimens [428]. Delays in specimen collection may reduce cannabinoid concentrations below analytical detection limits. Thus, there may be a potential for bias in epidemiological studies due to inclusion of cases in the drug-free group that are intoxicated from cannabis, yet are negative for blood cannabinoids.

In two studies of occupational fatalities in Canada [12,394], cannabinoids were found in 8.5 to 17% of those tested; cannabis use in the general population was judged to equal or exceed these rates. These incident rates were based in part on urine cannabinoid studies. The authors concluded that cannabis's contribution to the cause of the fatalities was limited.

Although laboratory performance measures and driving behavior have shown alterations following cannabis, few studies unequivocally link increased accident rates with cannabis [310]. It is difficult to determine if observed decrements in laboratory performance are large enough to account for actual driving impairment. A promising approach to determining a drug's contribution to accident causation is to calculate the culpability rates for drug-exposed and non-drug-exposed drivers. These studies are difficult and expensive to conduct, but in conjunction with blood drug concentrations, may help to elucidate cannabis's role in driving impairment. Culpability studies compare the relative degree of responsibility for crashes between groups of cases and determine the odds ratios for crashes based on toxicological results. If cannabis contributes to crash risk, then the proportion of drivers who are culpable will be greater among cannabinoid-positive drivers than among those with negative test results.

Lowenstein et al. found in a study of 414 injured drivers in Colorado who were admitted to the emergency room within 1 h of the accident that cannabis alone was not associated with crash responsibility (odds ratio 1.1, 95% confidence interval 0.5–2.4) [262]. In this same study, cannabis in combination with alcohol was found to impair driving skills and increase accident risk. In a study of 2,500 injured drivers in Australia, 2.8% of the drivers' blood specimens were positive for THC and THCCOOH, and 8% were positive for THCCOOH only [261]. Most of the crashes also involved alcohol, making it difficult to determine the contribution of cannabis to the event. Further investigations by Longo et al. found that drivers with alcohol or benzodiazepines alone, and those with combinations of alcohol and THC or benzodiazepines, were significantly more likely to be culpable; however, the increased odds ratios were not greater than for alcohol alone [260]. Motorists positive for THC only did not have an increased risk ratio. Terhune et al. reported similar results in a study of 1,882 drivers in 7 U.S. states [436] and by Williams in a study of 440 fatally injured young male drivers in California (cannabinoids detected in 37% of blood specimens) [470]. Higher risk was associated with alcohol, but a lower odds ratio was found for drivers with cannabis only. Inclusion of fatalities up to 4 h from the time of the crash provided sufficient time for THC concentrations to fall below analytical detection limits and potentially bias results. Of the drivers identified as cannabis users, two-thirds had detectable THC in their blood.

In 1982, Terhune et al. reported that 9.5% of 497 drivers injured in motor vehicle accidents in Rochester, NY, had THC in their blood, 51% in combination with ethanol [435]; 52.9% of the THC-only positive drivers were judged to be culpable for the accident, as compared to 34% of drug-free drivers. For comparison, drivers positive for ethanol >0.10% had a culpability rate of 73.8%; those with ethanol and THC did not have a significantly higher culpability rate than those positive for ethanol alone, although the number of samples in this category was small. Another possibility is that increased culpability could be related to higher concentrations of blood THC. In a study of hospitalized drivers in Australia, higher odds ratios for accident risk were found with THC >2.1 ng/mL and THCCOOH exceeding 31 ng/mL, although this trend did not reach statistical significance. [203]. Drummer et al. found lower odds ratios for the 11% cannabis-positive drivers in a study of 1,045 fatalities in Australia in 1990–1993, although alcohol- and THC-positive drivers had significantly increased risk [107].

Marowitz et al. compared the driving records of 106,214 persons arrested for drug offenses in California in 1989 to 41,493 drivers from the general population [272]. Drug arrestees had significantly more traffic violations and total accidents and were found to be more responsible for their accidents than the control group. The authors concluded that individuals arrested for drug offenses posed an elevated safety risk. Furthermore, individuals arrested for misdemeanor marijuana had twice the 1-year post-arrest accident rate of the control group.

B. Performance Studies

Controlled clinical studies of cognitive and psychomotor performance following cannabis use are included in **Table 2**. Translating the importance of cannabis-induced performance effects observed in a controlled laboratory study to impairment of specific driving skills or other complex behavior is difficult. Furthermore, some results indicating impairing effects of cannabis have not been replicated in other laboratories. In 1993 Foltin and Evans reviewed numerous studies of performance effects of drugs of abuse and found consistent decrements in tracking, digit symbol substitution, list recall, arithmetic, memory recall, vigilance, divided attention, circular lights, paired associates, digit span, list learning, stroop, and list recognition tasks after cannabis [125]. Inconsistent results were obtained for choice and other reaction time tasks. Laboratory performance studies help us to understand drug effects and to predict possible impairment in performance of complicated tasks. These results also provide the basis for additional studies utilizing driving and flying simulators, as well as closed and open course driving trials that more closely reflect actual driving conditions.

Review of the literature requires careful evaluation of study design, including whether appropriate placebo controls were incorporated, whether doses were presented in

Table 2. Controlled administration studies of cannabis with psychomotor and cognitive effects

Task[a]	Findings[a–d]	Dose[c–e]	Blood THC[c,e,f]	Year	Ref.
Pursuit meter Delayed auditory feedback	Significant impairment 5/9 significant increased errors	5 mg SM	Not detectable (TLC)	1970	[269]
Pursuit meter Delayed auditory feedback	Impairment both doses, but poor dose-response Additive effect with ethanol	0, 2.5, 5 mg THC SM; 0, 0.13 g/Kg ethanol	N/A	1971, 1985	[267, 270]
Pursuit meter (hand-eye co-ordination) Delayed auditory feedback Stability, wobble board	Significant linear dose-dependent relationship 4/9 linear dose-dependent decrements, 5/9 no effect Decreased stability with dose	0, 12.5, 25, 50, 100 μg/Kg SM	N/A	1971	[237]
Recall of narrative material	Significant impairment; Addition of irrelevant material	25 μg/Kg SM	N/A	1972	[106]
Visual autokinetic phenomenon (motion of stationary light source)	Apparent movement increased with two high doses	0, 50, 100, 200 μg/Kg SM	N/A	1972	[395]
Information processing	Disrupted short-term memory	20, 40, 60 mg PO	N/A	1972	[438]
Information processing	Dose-related impaired peripheral vision detection	0, 50, 100, 200 μg/Kg SM	N/A	1972	[395]
Information processing Reaction time	Inconsistent effects in simple and complex tasks Slowed with high dose only	0, 10, 20 mg SM	N/A	1972	[386]
Divided attention, tracking errors Critical tracking breakpoint	Significant linear correlation 5–25 ng/mL for 2h Sigmoid relation with log THC (2–25 ng/mL for 7 h)	100, 200, 250 μg/Kg SM	Collected same conditions but different times	1972	[22]
Broad battery of psychomotor and cognitive tasks	Attention, concentration and motor function impairment; reduced adaptability in stressful situations; effects noticeable 8–10 h after smoking	0, 350, 400, 450 μg/Kg PO	N/A	1973	[230]
Pursuit meter Delayed auditory feedback Stability, wobble board	Significant impairment No consistent change Decreased stability with dose	0, 6, 12, 18 μg/Kg SM	N/A	1973	[117]
Pursuit meter; wobble board; delayed auditory feedback	Impaired performance after cannabis; no change in effects when amphetamine added	0, 25 mg THC SM; 0, 10 mg/70 Kg AM	N/A	1976	[131]
Psychomotor tracking	Dose-related errors in simple tracking; THC and ethanol additive effects on tracking; no effects on observer rated car-handling ability	0, 1.6, 6.8 mg SM; 0.3, 0.7% blood ethanol	N/A	1976	[163]
Standing steadiness; pursuit rotor; simple and complex reaction times;Vienna Determination Apparatus	Significant impairment by THC in all measures; ethanol and THC additive effects	215 μg/Kg PO; 0.54 g/Kg ethanol	N/A	1980	[31]
Information processing	Impaired speed of visual information processing	6 mg SM	N/A	1981	[42]
Roadside sobriety tests Coordination tests	Failures if THC >25 ng/mL 94% failed at 90 min and 60% at 150 min after SM	Ad lib SM	49.1% neg. THC (RIA) 150 min after smoking	1983	[364]
Memory	Dose-related decreases in immediate and delayed free recall; increase in intrusion errors; no reduction in recognition memory	0, 5, 10, 14 mg SM	N/A	1984	[302]
Concentrated attention Divided attention	Significant and prolonged drug impairment Significant impairment	0, 50, 100, 200 μg/Kg SM	N/A	1984	[309]
Pursuit meter	No significant difference between doses, decrement with both doses; impairment with THC > 5 ng/mL	37.5, 75 μg/Kg SM	RIA, 0–120 min THC/THCCOOH	1985	[279]
Body sway; pursuit rotor; simple and choice reaction time; addition and subtraction	At these dosages and with these tests, marijuana potency as follows: SM > PO > ethanol; 0.05% BAC ≈ 8.5 mg PO marijuana ≈ 1.5 mg SM marijuana	0, 5, 10, 15, 20 mg THC (PO and SM); 0, 0.75, 1.0 g/Kg ethanol	N/A	1985	[62]
Perceptuo-motor tasks Intelligence and memory	Heavy cannabis users reacted more slowly No differences	N/A	N/A	1988	[453]

Table 2. (Continued)

Task[a]	Findings[a–d]	Dose[c–e]	Blood THC[c,e,f]	Year	Ref.
Memory	Short-term memory deficits in cannabis-dependent adolescents for > 6 weeks	N/A	N/A	1989	[391]
Circular lights; DSST Automated tracking task	Low and high dose marijuana decreased response speed, but not accuracy on DSST High dose ethanol impaired all tasks	0, 1.3, 2.7% THC SM; 0, 0.6, 1.2 g/Kg ethanol	N/A	1989	[179]
Digit span (immediate recall) Divided attention DSST	Inconsistent results for two doses on digit span No effect on divided attention task Impairment on DSST with high dose only	0, 1.3, 2.7% THC SM	N/A	1989	[178]
Information processing	Long-term cannabis users decreased ability to filter out irrelevant material and in focusing attention	N/A	N/A	1991	[414]
Cognitive tasks: serial addition and subtraction, logical reasoning, mannikin Short term memory and attention: matrix and serial addition and subtraction Time estimation: time wall Psychomotor: DSST	No cannabis effects on serial addition and subtraction, matrix, mannikin, DSST, and time wall; decreased accuracy on the logical reasoning task	0. 1.75, 3.55% THC SM	Comprehensive GC/MS data during absorption to 7 days post drug	1992	[201]
Repeated acquisition task; simple and choice reaction times; DSST	Decreased error with combined high dose of cocaine and cannabis; prolonged subjective effects	0, 2.7% THC SM; 0, 16, 32 mg IV cocaine	N/A	1993	[126]
DSST, word recall, VAS, number recognition, time	Dose related changes in subjective measures; decreases in word recall with cannabis	0, 3.55% THC SM	THC 4, 8, or 16 puffs: 63, 150, and 188 ng/mL (RIA, plasma)	1997	[175]
Validity of drug evaluation and classification program to predict marijuana use	Best 7 variables for prediction of marijuana use, increased sum of 3 pulse readings, abnormal eyes, increased sum of pupil diameter, bloodshot eyes, increased errors on finger to nose test, slowed pupillary reactions to light and increased errors in the one leg stand; with these variables: sensitivity 61.4%, specificity 93.3%, false positives 6.7%, false negatives 38.6%, efficiency 82.7%	0, 3.58% THC SM	THC (0.5 ng/mL) THCCOOH (1.0 ng/mL by NCI GC/MS	1998	[177]
ARCI, VAS, EPS, circular lights, PAB	Decrement in smooth pursuit eye tracking, no effects day following dosing	0, 1.8%, 3.6% THC SM	N/A	1998	[119]
Neuropsychological battery: trail making test, efficiency test system, intelligence structure test, benton multiple choice form G, comprehensive psychiatric rating	Significantly impaired cognitive function after smoking	0, 290 μg/Kg THC SM; n = 60 between subject design		1999	[244]

[a] Task: DSST = Digit symbol substitution test; VAS = Visual analog scale; ARCI = Addiction Research Center inventory; EPS = Eye performance system; PAB = Performance assessment battery.
[b] BAC = Blood alcohol concentration.
[c] THC = Δ^9-Tetrahydrocannabinol; THCCOOH = 11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol; AM = Amphetamine.
[d] Route of administration: SM: Smoke; PO: Oral; IV: Intravenous.
[e] N/A = Not applicable.
[f] TLC = Thin layer chromatography; RIA = Radioimmunoassay; GC/MS = Gas chromatography/mass spectrometry.

a double-blind manner, what dose and route were employed for drug administration, whether multiple doses were used to demonstrate a dose-response effect, how difficult the performance task was, and whether subjects were well-trained to a stable level of performance prior to testing. Generally, the more complex the task, the more sensitive the measure to detect cannabis impairment. Also, tasks that are well practiced, such as driving, tend to be more resistant to drug effects. Therefore, laboratory tests that require divided attention and response to stress-

ful, demanding situations are more likely to demonstrate performance impairment. Another key factor in evaluating reported effects is the availability of simultaneously collected blood THC concentrations. Few performance studies have included measurement of drug concentrations in blood. Drug measurements are important due to the difficulty in delivering a specified THC dose by the smoking route. Clinical studies including strict controls on smoking dynamics, e.g., number of puffs, time between puffs, hold time, and inhalation time, have reported wide intra- and inter- subject variability in blood THC concentrations due to the subjects' ability to titrate drug dose [196].

In general, laboratory performance studies (Table 2) indicate that sensory functions are not highly impaired, but perceptual functions are significantly affected. The user's ability to concentrate and maintain attention may be decreased during cannabis intoxication. Perceptual errors are the most frequently cited errors leading to driving accidents when under the influence of ethanol, and could be significant factors in cannabis impairment [309]. Moskowitz et al. reported a prolonged impairment in concentrated and divided attention tasks [309]. Kurzthaler et al. studied the effect of cannabis on cognitive functions and driving ability [244]. They suggested that the decrease in learning noted after cannabis use could be due to a disinhibition of overlearned response and/or an increased susceptibility of recently acquired information to intrusions. This learning effect could signify that a driver under acute cannabis influence would be unable to use acquired knowledge from earlier experiences adequately to ensure road safety. Additionally, higher scores of concentration difficulties and thought disorders indicated disturbances of perceptual motor speed and accuracy as well as a reduction in the driver's ability to organize or retrieve new information immediately after cannabis consumption. The authors concluded that perceptual motor speed and accuracy, important parameters of driving ability, were impaired immediately after cannabis consumption, but had fully resolved within 24 h. Also, cannabis's effects appeared to be almost exclusively neurological, with much less psychomotor impairment than that noted after ethanol. This indicates that the standard physical examination used to evaluate individuals suspected of driving under the influence may be much less effective in evaluating driver impairment following cannabis.

Cannabis's effects on visual processes involved in driving have been the subject of several investigations. Cannabis smoking was shown to affect the phasic response to a light flash, but to have little effect on pupil diameter [119,434]. A dose-related impairment of peripheral vision and an increase in the visual autokinetic phenomenon were observed after cannabis [42,238,395]. Fant et al. reported that smoking a single 3.6% THC cigarette acutely produced decrements in smooth pursuit eye tracking, especially in peripheral visual fields [119]. This performance impairment was observed 0.25–5.5 h (peak at 1.75 h) after smoking. Binocular depth inversion for different natural and artificial objects was assessed in 17 healthy volunteers before and after administration of 120 μg/Kg dronabinol (synthetic THC) [254]. A dose-dependent effect of THC on binocular depth inversion was noted with maximal effects at 140–250 min. An impairment of top-down processing of visual sensory data by THC was suggested, further supporting the hypothesis that the endogenous cannabinoid system is involved in perceptual processes on a higher level of information processing.

Perceptual motor skills, decision-making, and car-handling skills may also be reduced. Overall, impairment was noted in studies utilizing the pursuit meter or other tracking devices; impairment increased with dose except under very low-dose conditions [237,269]. However, Heishman [178] did not report impairment in an automated tracking task following smoking of a single 2.7% THC cigarette. The author indicated that the tracking task might have been less difficult than tasks in other tracking studies and therefore, less sensitive to cannabis effects. Barnett et al. [21] found a sigmoid relation between the critical tracking breakpoint and the log of the THC concentration over the range of 2–25 ng/mL THC was observed, with effects noted for up to 7 h. The brain's centers for coordination of movement are the cerebellum and basal ganglia, two areas rich in cannabinoid receptors. Impairment of hand-eye coordination is dose-related over a wide range of cannabis dosages and has been shown to be additive with cannabis and ethanol exposure [31]. Coordination and body sway decrements have been documented. Stability of stance was decreased in a dose-related manner following cannabis use [62,117]. Reeve [364] found that following ad-lib smoking of marijuana, 94% of subjects failed roadside sobriety and coordination tests 90 min after smoking; there was a 60% failure rate after 60 min.

Deficits in information processing have been documented following cannabis exposure [302,438]. Impairment was observed in immediate and delayed free recall, but not in recognition memory. Impairment was not demonstrated in the digit span immediate recall and divided attention tasks following marijuana smoking in a study by Heishman [179]. The most consistently reported cognitive effect following marijuana use is a disruption of short-term memory [105]. Huestis [201] demonstrated significant impairment in only one of six performance tasks after

marijuana smoking; decreased accuracy in the logical reasoning task was observed after smoking a single 1.75% or 3.55% THC cigarette. Significant effects were noticeable 8–10 h after smoking in a battery of psychomotor and cognitive tasks following ingestion of cannabis [230]. Barnett et al. [21] found a linear correlation between THC concentration and divided attention performance over the range of 5–25 ng/mL THC. A prolonged impairment in concentrated and divided attention tasks was reported by Moskowitz [309].

A study of perceptuomotor tasks with heavy cannabis users found a slower reaction time in these tasks; however, no differences were found in intelligence or memory functions [453]. Long-term cannabis users also were reported to possess a decreased ability to filter out irrelevant material and to focus attention on the required task [414]. Forney [131] observed marijuana impairment on psychomotor tests; the combination of amphetamine and cannabis did not reduce the observed psychomotor impairment. In a study of cannabis and cocaine effects on performance of a repeated acquisition task that included simple and choice reaction time tests and the digit symbol substitution test (DSST), high-dose cocaine and cannabis exposure increased the number of errors compared to either drug alone [126].

Epidemiological studies indicate that cannabis is usually combined with ethanol, and sometimes with other licit or illicit drugs. In the few studies where cannabis and ethanol were both administered, effects have been found to be additive [31,163,270]. This accentuates the need for laboratory performance studies evaluating the effects of cannabis in conjunction with ethanol and other drugs.

C. Driving and Flying Simulator and Open/Closed-Course Driving Studies

Results of driving simulator and closed- and open-course driving studies are found in **Table 3**. The degree of performance impairment observed in driving simulator tasks and open and closed driving courses following cannabis is not consistent between studies. Early studies by Hansteen, Attwood, Perez-Reyes, Rafaelsen, and coworkers documented decreased car-handling performance [14,163] and reduced reaction times [345,359] following cannabis. Smoked cannabis impaired time and distance estimation in a dose-related manner and affected decision-making that relied upon these skills [240,406]. Smiley et al. evaluated the effects of 0, 100, and 200 μg/Kg THC alone and in combination with 0, 0.425, or 0.68 g/Kg ethanol in a driving simulator [406]. Interestingly, blood ethanol concentrations were found to be lower when ethanol was combined with cannabis, suggesting that alcohol metabolism may be altered by cannabinoids. Within the simulator, crashes during presentations of emergencies, and lane, speed, and headway variability were increased following cannabis smoking, primarily with the higher dose. As previously described, the more difficult the task, the more apparent the impairment. Sutton [427] described no significant effects in a closed-course task when only ethanol or cannabis was used; however, significant effects were noted following combined ethanol and cannabis exposure. The authors suggested that driving is a well-practiced task, and the course did not significantly challenge subjects' ability to perform. It should be remembered that prescription medications, including benzodiazepines and antihistamines, might impair driving performance as significantly as illicit drugs, especially during the first weeks of chronic treatment [1,93,286,326,327,452].

In a 1998 study, Liguori et al. described smoked cannabis effects on equilibrium, psychomotor performance, and simulated driving [255]. Ten subjects smoked placebo, 1.77% and 3.95% THC cigarettes on three separate occasions followed by critical flicker fusion (CFF, a measure of central nervous system excitability), choice reaction time (CRT), and computerized body sway tasks, and rapid judgment and brake latency evaluation in a driving simulator. There were no significant changes in CFF, CRT, somatosensory, visual, and visual preference scores; however, the high dose significantly increased body sway and tended to increase brake latency. The dynamic posturography-CFF-CRT composite equilibrium scores decreased after both doses. The authors concluded that cannabis impaired several key aspects of driving, including reaction time and maintenance of stable upright posture. The need to include unexpected sudden appearances of cues, as occurs in challenging real-life driving situations, was stressed in order to capture performance impairment following cannabis use. Lamers et al. attempted to address this issue in a study of visual search performance during urban city driving following low alcohol (BAC 0.05%), low THC (100 μg/Kg), and combination low alcohol and THC conditions [245]. Minimal effects were noted after either low dose, with a small reduction of 3% in visual search performance in the combination condition.

In a 1986 review of seven driving simulator performance studies and six on-road driving performance studies, Smiley concluded that after cannabis, drivers tended to reduce speed, were less likely to pass, and increased their following distance in an attempt to compensate for their perceived impairment [405]. Their comprehension of potential impairment and added concentration could have accounted for the improvement in driving perfor-

Table 3. Driving and simulator studies

Task[a]	Findings[a–c]	Dose	Year	Ref.
Driving simulator	Brake and start time increased by cannabis and ethanol; gear changes decreased by cannabis and ethanol; time and distance estimation impaired by cannabis in dose-related manner	8, 12, 16 mg THC PO 70 g ethanol	1973	[359]
Closed courses and city streets	Impaired judgment, concentration on closed courses; amplified on city streets; improved performance in some subjects	0, 4.9, 8.4 mg THC SM	1974	[240]
Driving and psychomotor tracking studies	Car-handling performance impaired after ethanol and high dose marijuana (measured with analytical instruments; observers in the vehicle unable to document impairment following marijuana)	0, 1.4, 5.9 mg THC SM; ethanol 0.07%	1976	[163]
Closed course	Car-handling performance impaired; THC plasma levels ranged from 8.5–21.2 ng/mL (75 μg/Kg) and 12.9–31.2 ng/mL (150 μg/Kg); drivers did not weave on road or brake or accelerate erratically	75, 150 ug/Kg THC SM; 0.63, 1.25 g/L ethanol	1981	[14]
Closed course	Significant effects under combination condition; no significant effects on a simple task when THC or ethanol alone; serum THC, BAC provided	0, 2% THC smoke; 0, 0.06% BAC	1983	[427]
Perceptual-motor tasks Perceptual tasks Decision-making, passing Decision-making, rapid stop	Impaired at highest dose Inconsistent results, simplified task Reduced number of attempts by marijuana Reduced by marijuana, significantly impaired by combination	0, 100, 200 ug/Kg THC SM; 0.425, 0.68 g/Kg ethanol	1985	[406]
Driving simulator	Accuracy reduced and reaction time prolonged by marijuana; ethanol impairment enhanced by marijuana in additive or synergistic manner	One 2.4% THC cigarette; 0, 0.42, 0.85 g/Kg ethanol	1988	[345]
Closed course	Driving affected by both marijuana and alcohol, especially in combination; effects (slower driving) of marijuana less than alcohol; no impairment by marijuana alone on critical tracking task	1.9% THC SM; 3 alcoholic drinks (10 min apart)	1989	[339]
Closed course	SDLP significantly increased by all cannabis doses for 2 h (equivalent to alcohol at 0.03 to 0.07 g%); speed not affected; no correlation between THC or THCCOOH concentration and impairment, tracking, hand steadiness, or body sway; minimal effect on visual search	0, 100, 200, 300 ug/Kg THC SM	1993	[373]
Driving in heavy traffic	No impairment in vehicle handling or traffic maneuvers (with either alcohol or cannabis) by expert observer, but impairment following alcohol (only) observed by instructor in car; hand steadiness and time interval estimation impaired by cannabis; no correlation with THC concentration	0, 100 ug/Kg THC SM; BAC 0.04%	1993	[373]
Driving; road tracking and car following	SDLP and distance variability (during deceleration) affected by cannabis; all tasks affected by ethanol; SDLP increases: 100 μg/Kg THC + 0.04% BAC similar to 0.09% BAC and 200 μg/Kg THC + 0.04% BAC similar to 0.14% BAC; THC effects dose-related and persisted at least 2.5 h; degree of impairment not correlated with THC and THCCOOH concentrations	0, 100, 200 μg/Kg THC SM; BAC 0.04%	1998, 2000	[372, 360]
Equilibrium, psychomotor performance and driving simulator, CFF, CRT	Significant increase in body sway and trend toward increased brake latency observed at high doses; similar to 0.05% alcohol; no CFF or CRT effect	0, 1.77, and 3.95% THC SM	1998	[203]

[a] SDLP = Standard deviation of lateral placement; CFF = Critical flicker fusion; CRT = Choice reaction time task.
[b] THC = Δ^9-Tetrahydrocannabinol; THCCOOH = 11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol.
[c] BAC = Blood alcohol concentration.

mance observed in some subjects in low-dose cannabis studies. Cannabis reduced the number of attempts at passing other cars or risk-behavior, in contrast to ethanol that increased risk-taking. Reaction time and initial incorrect responses were increased along with impaired emergency response behavior. A driver's ability to respond to unexpected events or when continuous attention is required could be impaired by cannabis.

Logistical difficulties of testing impairing effects of drugs on city streets and highways severely limit the number of such studies. Klonoff et al. tested the effect of low THC concentrations (approximately 5–8.5 mg THC) on driving ability on the streets of Vancouver and reported impairment primarily of driver judgment and concentration [240]. In 1993, Robbe and O'Hanlon examined driving performance 40 and 100 min after smoking a placebo,

100, 200, or 300 μg/Kg THC cigarette on a closed section of highway [373]. All active THC doses significantly affected the standard deviation of lateral position (SDLP) as compared to placebo for 2 h, approximately equivalent to the impairment produced by 0.03–0.07 g% ethanol. Mean speed, standard deviation of speed, and steering wheel angle were not affected. No correlations were found between plasma THC or THCCOOH concentration and impairment on laboratory tests similar to roadside sobriety tests of tracking ability and hand and posture stability. These findings were substantiated in additional studies conducted in the presence of other vehicles on the highway and in heavy traffic, although only the lower dose was tested in the latter study for safety reasons. Cannabis users appear to be aware of drug effects on their driving performance and attempt to compensate by driving slower, taking fewer risks, and maintaining greater concentration. Robbe et al. suggest that lateral tracking is dependent on the automatic information processing system that operates outside of conscious control and is less subject to drivers' conscious efforts to compensate [373]. The performance effects of cannabis were not different than the effects of many medicinal drugs. Driving impairment after cannabis could be greater following higher doses, on prolonged monotonous drives, with distractions by other passengers, or when unexpected emergency situations occur. In these cases, cannabis effects on attention, reaction time, informational processing, and judgment could play a role. In addition, the authors stressed the need to measure impairment at time points beyond measurable THC concentrations to ensure that epidemiological studies are not underestimating the number of individuals driving under the influence of cannabis and hence, its contribution to accident causation.

A 1983 California Department of Justice study had indicated that THC was present in a significant proportion of blood samples from drivers detained for impaired driving performance. Ad lib smoked marijuana was found to impair field sobriety tests for up to 3 h, although placebo controls were not included for comparison [363]. Peck et al. conducted a controlled drug administration study of the effects of marijuana and alcohol on actual driving performance of 80 volunteers on a closed test course that included real-world driving conditions [339]. This study was a placebo-controlled, repeated-measures, within-subject design, evaluating the effects of three alcoholic drinks (estimated to produce a peak blood ethanol of 0.08%), a single 1.9% THC cigarette, and ethanol and cannabis in combination. Dependent variables included ratings of vehicle handling and skill, speed, accelerator reversals, brake presses, steering control, lateral placement, field sobriety tests, self-assessment ratings, risk assessment task, critical tracking task, and a time estimation task. Both cannabis and alcohol affected driving performance with approximately additive effects when both drugs were administered. Interestingly, cannabis alone did not affect critical tracking, in contrast to other studies. The authors concluded that although it was clear that cannabis impaired psychomotor abilities functionally related to skillful driving, particularly at high doses and among naïve subjects, the extent to which cannabis-impaired driving caused accidents could not be deduced from currently available driving studies.

In later studies (1998 and 2000) of the effects of alcohol and cannabis on driving performance by Robbe et al, cannabis alone was found to affect SDLP and distance variability during deceleration maneuvers in the car-following task, while reaction time was unaffected [360,372]. Ethanol (0.04%) alone impaired all driving tasks, while 100 and 200 μg/Kg THC in combination with 0.04% ethanol produced SDLP impairments equivalent to 0.09% and 0.14% ethanol, respectively. Reaction time was also increased significantly after the higher dose combination. THC effects were dose-related and persisted at least 2.5 h after dosing. Despite consistent findings of impairment on tracking, divided attention and vigilance in laboratory studies following cannabis, driving simulator, and closed- and open-course tests have shown minor performance effects with cannabis doses up to 250 μg/Kg [372]. Cannabis effects at 200 or 300 μg/Kg were described as moderate; however, when combined with low doses of alcohol they were found to be severe. Plasma THC and THCCOOH concentrations were not related to the degree of impairment.

In the past, police officers have relied on standard field sobriety tests (SFSTs) and breath tests for alcohol to assess driving impairment at the roadside. These tests may not be useful in identifying impairment from other licit and illicit drugs. Useful information has been provided when cases of failed roadside sobriety checks [483] and police stops for erratic driving [353] can be linked to blood THC concentration data. It has been difficult to collate these data from different jurisdictions, although this could be very helpful in the interpretation of blood THC data. The Drug Recognition Examination program in the United States, and similar programs in other countries, have improved upon the identification of drug-intoxicated drivers by employing specially trained officers that evaluate an individual for drug consumption based on a series of behavioral tests. If the examination appears to indicate drug intoxication, a specimen is sent for toxicological examination and scientific confirmation. Currently, these results are not available at the roadside at the time of the stop, but extensive efforts are under way to develop a

sensitive and accurate testing scheme that would provide immediate information.

Results of flying simulator studies are found in **Table 4**. Impairment for up to 24 h has been reported in flying simulator studies following marijuana smoking [208,478]. Short-term memory, attention, and concentration were affected. Impairment was also found to relate to the difficulty of the task and the age of the pilot [249]. One of the most important aspects of the studies was the lack of pilot awareness of decreased performance or impairment [250]. The study designs of some of these studies have been criticized due to the lack of placebo controls, double-blind conditions, and concurrent THC blood concentrations.

D. Summary

It is clear from prevalence studies that cannabis is frequently used before and during driving, so one would expect that THC and its metabolites would be detected frequently in drivers' specimens [114]. The most serious limitations of prevalence studies is the lack of adequate control groups, but other important problems include the difficulty of collecting specimens quickly enough to capture rapidly decreasing active THC concentrations after cannabis smoking and the difficulty of accurately quantitating low concentrations of THC, 11-OH-THC, and THC-COOH in blood or plasma. In addition, the number of cases of cannabinoid only positive samples and drug negative samples must be large enough to adequately assess cannabis's effects on safe driving practices. It is not possible to distinguish the impairing effects of cannabis in a single case, when multiple drugs, including ethanol, are present. Studies examining cannabis's causal effect through responsibility analysis have more frequently indicated that THC alone did not increase accident risk, although the use of THC and alcohol have a greater effect than alcohol alone. Notwithstanding these results, the World Health Organization (WHO) issued a report in 1997 stating that cannabis acutely impairs cognitive development and psychomotor performance, increasing the risk of motor vehicle accidents in the intoxicated driver [477].

There is strong evidence from performance studies that THC has significant effects on the cognitive and psychomotor tasks associated with driving. Debate continues as to whether or not these effects increase accident risk. Simulator and closed- and open-road driving studies have given equivocal results. From performance studies, it would be expected that the more difficult and unpredictable the task, the more likely that THC will have an impairing effect. Controlled drug administration studies that test driving skills on open courses and in traffic most closely mirror real-life driving, although they incompletely assess drug impairment during unexpected events, during prolonged, monotonous driving situations, following high drug doses, and with distractions by drug- or non-drug-using friends. In a real driving situation involving multi-tasking and unexpected presentation of hazardous conditions, responses to external stimuli may be impaired while under the influence of THC.

Despite these limitations, a number of conclusions can be drawn. More than 300,000 people are killed and 10 million injured throughout the world each year in traffic accidents [123]. Cannabinoids are the number one illicit drug detected in motor vehicle injuries, fatalities, and DUID cases, and frequently are found in combination with ethanol or other drugs. Critical skills needed for the safe operation of motor vehicles and other forms of transport can be impaired following cannabis use. Impaired functioning of psychomotor activities including measures of coordination, tracking, and vigilance, and cognitive behavior including memory, learning, attention, information processing, decision-making, and perception have been reported following cannabis use. Most effects returned to baseline within 3–4 h, although some complex, divided attention tasks have indicated decrements in performance up to 24 h after cannabis use [176,250]. Current scientific evidence does not consistently support that these laboratory findings translate into increased accident risk, although clearly, driving under the influence of

Table 4. Flight simulator studies

Findings	THC levels[a,b]	Dose[a]	Year	Ref.
Impairment short term memory, attention, and concentration up to 4 h	N/A	0, 0.9 mg/Kg THC SM	1976	[208]
Performance decrements up to 24 h; pilots no awareness of impairment	N/A	19 mg THC SM	1985	[479]
Impairment with turbulent flight after high dose; impairment increased as task difficulty/complexity and pilot age increased	Serum THC 7 ng/mL at 1 h after high dose SM	0, 10, 20 mg THC SM	1989	[249]
24 h impairment; pilots no awareness of decreased performance	N/A	0, 20 mg THC SM	1991	[250]

[a] THC = Δ^9-Tetrahydrocannabinol.
[b] N/A = Not applicable; SM = Smoke.

cannabis and ethanol is a major safety issue. Moskowitz [310] summarized the difficult question of cannabis use and driving impairment by stating that "any situation in which safety both for self and others depends upon alertness and capability of control of man-machine interaction precludes the use of marijuana."

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Marilyn A. Huestis received a bachelor's degree in biochemistry from Mount Holyoke College (South Hadley, MA), a master's degree in clinical chemistry from the University of New Mexico (Albuquerque, NM), and a doctoral degree in toxicology from the University of Maryland in Baltimore (Baltimore, MD). Dr. Huestis is the acting chief, Chemistry and Drug Metabolism Section, Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program, National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH) in Baltimore, MD.

Dr. Huestis works in the fields of forensic toxicology, analytical toxicology, and clinical chemistry. She has published important papers in the areas of cannabis pharmacokinetics and pharmacodynamics, antagonism of Δ^9-tetrahydrocannabinol by the first CB1-cannabinoid receptor antagonist, novel immunoassay development, and on the use of alternate testing matrices for drug analysis including hair, saliva and sweat. Her research interests include the pharmacokinetics and behavioral effects of drugs of abuse in humans including correlations of blood levels of drugs and concurrent changes in performance; evaluation and validation of analytical techniques for detection of drugs of abuse in different biological fluids; as well as medication development projects including the use of buprenorphine as a pharmacotherapeutic agent in opioid dependence. Dr. Huestis is interested in evaluating diverse routes of drug administration and determining the effect of different routes on the abuse liability of drugs; effects on performance; and on the onset, peak, and duration of action of the resultant effects. Dr. Huestis was the principal investigator on a phase I clinical study evaluating the effects of the first cannabinoid receptor antagonist, SR 141716, in marijuana users. She currently is working on characterizing the pharmacokinetics and pharmacodynamics of oral tetrahydrocannabinol and hemp oil products and studying in-utero drug exposure of neonates whose mothers are participating in buprenorphine and methadone opioid treatment programs. Dr. Huestis hopes to develop a better understanding of drug abuse in women and the consequent drug exposure of neonates and children.

Dr. Huestis has presented her findings at numerous international meetings, conferences, and workshops, and contributes significantly to many federal agencies' efforts in the drug abuse field, as well as to chemistry and toxicology professional organizations. Dr. Huestis is recognized nationally and internationally for her contributions and has been awarded the American Academy of Forensic Sciences Irving Sunshine Award for "Outstanding Research in Forensic Toxicology" in 1992 for her work on cannabis.