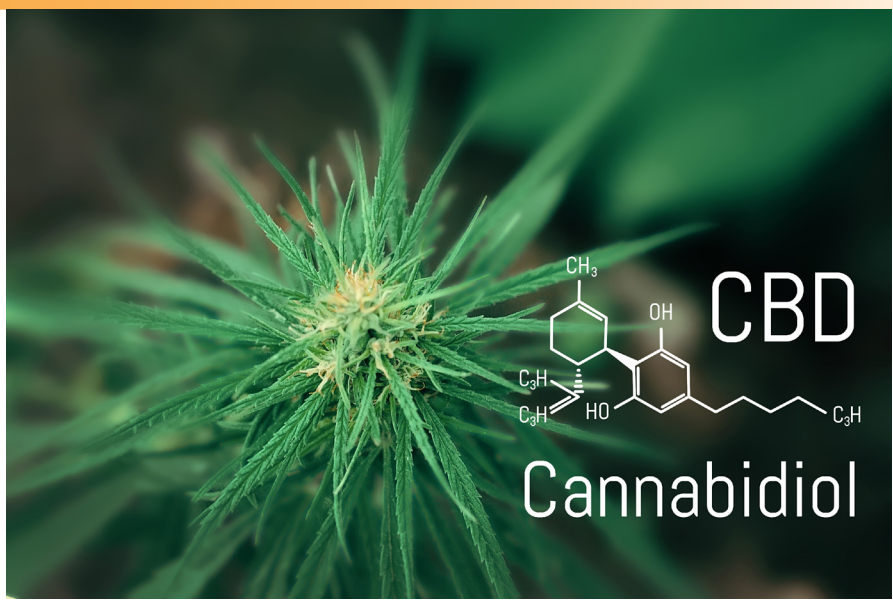
2020

Cannabis Use and Associated Risks

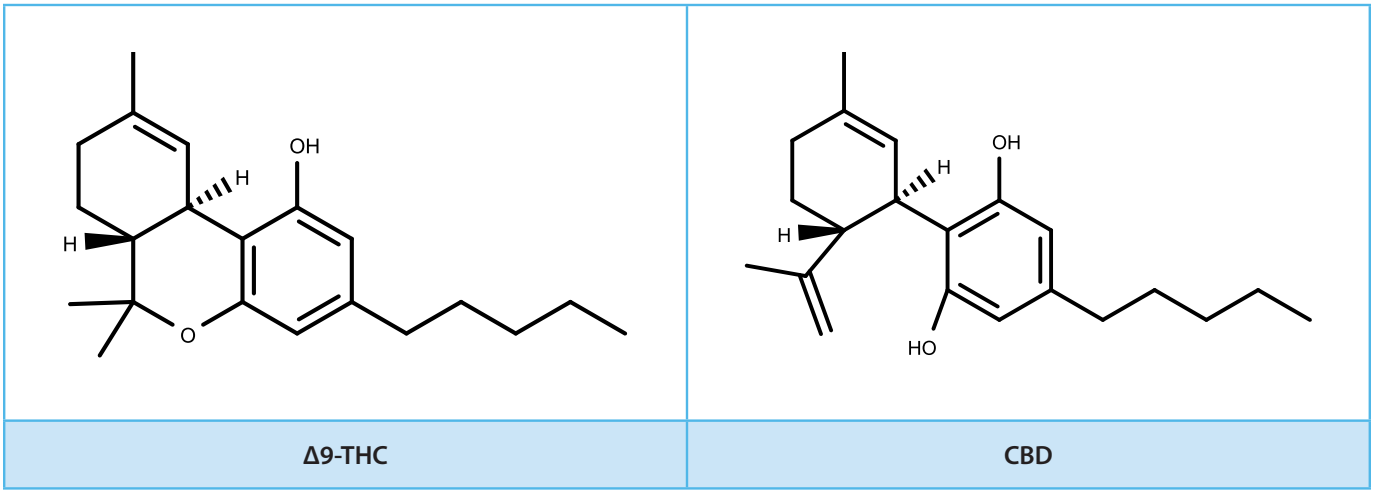


Cannabis (marijuana) has a long history of production and use as a food source, medicine, and textile fiber. Cannabis contains over 100 compounds known as phytocannabinoids that have molecular structures similar to that of delta-9-tetrahydocannabinol (Δ9-THC), the major psychoactive (mind-altering) compound in cannabis. Currently, cannabis is mainly used as a recreational drug and for medicinal purposes. Using cannabis recreationally produces a feeling of euphoria or a "high," along with behavioral and physiological effects. Some of marijuana's effects impart substantial risk to the individual and those around them, depending upon the individual circumstances of use. Marijuana use causes changes in perception, impaired short-term memory, altered sense of time, difficulty thinking and problem solving, impaired body movement, relaxation, increased appetite, and many other effects. High-dose use can lead to paranoia, delusions, and psychosis. Marijuana also affects brain development, especially in teens. A study from New Zealand by Meier et al.[1] found that people who started smoking marijuana heavily in their teens and had an ongoing marijuana use disorder exhibited broad neuropsychological decline across domains of function between ages 13 and 38. Lost mental abilities did not fully return in those who stopped using marijuana as adults.

An important type of harm related to the use of cannabis is the increased risk of injury and death caused by driving impairment. Cannabis use while driving has been shown to increase risk substantially because of impaired motor and cognitive functions needed for safe driving.[2,3] Obviously, impairment in the workplace and many other settings imparts great risk to all associated with those using marijuana and the users themselves. Other broadly identified risks associated with cannabis use include the increased potency of cannabis, prenatal exposure, unintentional childhood exposure, and adult "cannabis use disorder" (see below).

Cannabis use disorder (CUD) is defined in the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders[4] as the continued use of cannabis despite clinically significant impairment. CUD is characterized by a pattern of cannabis use that can cause clinically significant psychiatric distress (e.g., somatization, depression, irritability, phobia anxiety, paranoid ideation, psychoticism), social impairment (e.g., family member complaints, lost friends, financial difficulty, impaired work or school performance, legal problems), and other adverse consequences (e.g., inability to stop using, loss of self-confidence, memory loss, withdrawal symptoms).[4] The public health burden of CUD is substantial. An estimated 1.5% of US citizens 12 years or older (four million individuals) have a current (past year) CUD.[5] No medications are currently available to treat CUD, but therapy and motivational treatments can be effective in some cases.[6]

In addition to Δ9-THC, the cannabis plant also produces a non-psychoactive isomer (same molecular formula) of Δ9-THC called cannabidiol (CBD). As shown in **Figure 1**, CBD is structurally similar to Δ9-THC but lacks the additional carbon-oxygen ring. The medicinal properties of CBD have been widely acclaimed, and it is marketed as a broad cure-all. Many manufacturers claim it helps alleviate virtually all bodily ailments—from relieving anxiety to stopping the spread of cancer. Despite these claims, the risks and benefits of CBD have not been proven by adequate and well-controlled clinical studies, and there are both real and suspected risks associated with the use of CBD products. Legitimate prescription use of CBD is restricted to Epidiolex®, an oral CBD solution approved in 2018 by the US Food and Drug Administration (FDA) for treatment of seizures associated with certain forms of childhood epilepsy. Another pharmaceutical product, Sativex®, contains both CBD and Δ9-THC in equal proportions. Sativex® has been approved by other countries (e.g., Canada in 2005) for adjunctive treatment of spasticity in patients with multiple sclerosis but has not been approved for use in the United States.



Δ9-THC	CBD

Figure 1. Molecular structures of Δ9-THC and CBD

The availability of CBD received an immediate boost from the passage of the Agriculture Improvement Act of 2018 (the 2018 Farm Bill), which legalized hemp and defined it as cannabis that contains no more than 0.3% Δ9-THC (based on dry plant weight). Thus, hemp products containing CBD with ≤0.3% Δ9-THC can be produced for commercial sale and can be legally consumed. In contrast, marijuana with higher levels of Δ9-THC remains a Schedule I drug and is illegal. Thousands of CBD products are currently available for sale over the counter, by mail order, and online. These products come in many types, including lotions, creams, topicals, and formulations for ingestion, smoking, and vaping administration. Based upon the types of commercial CBD products available and marketed to the public, oral ingestion of CBD appears to be the most common route of administration.

There are a number of issues with the 2018 Farm Bill's allowance of up to 0.3% Δ9-THC in CBD products. The first issue relates to the difficulty of producing hemp with more than 10% CBD, the level needed to maintain profitability, while adhering to the 0.3% Δ9-THC limit. Many factors affect Δ9-THC levels (e.g., soil nutrients and other growing conditions), and as CBD levels rise in the plant during maturation, so do Δ9-THC levels.[7]

Although the FDA has regulatory authority over foods, dietary supplements, and cosmetics, no regulatory attempts have been made to control CBD products for Δ9-THC content and other potential contaminants, such as pesticides, mold, and heavy metals.[7] Consequently, CBD labels may not accurately reflect the content of CBD or its "contamination" with Δ9-THC. A 2016 study found a wide range of CBD and Δ9-THC concentrations in 84 CBD products purchased online.[8] This uncertainty about CBD and Δ9-THC content in products has resulted in a "buyer beware" situation for the consumer. Most consumers are not aware of these issues and have no way to independently verify product content.

CBD consumers may be at risk of testing positive for marijuana in an employment or other required drug test because of the presence of Δ9-THC in CBD products. It is feasible that consuming legitimate CBD products that meet the Δ9-THC limit in the 2018 Farm Bill may lead to a positive test. Some laboratory-based employment test results (including all federally regulated tests) are reviewed by Medical Review Officers (MROs) prior to reporting to employers. If the donor has a legitimate excuse (i.e., a valid prescription), the MRO will typically change a laboratory positive drug report into a negative report. However, when reviewing a positive marijuana result that arose because the donor legally consumed a hemp product, MROs face a dilemma. That is, MROs cannot determine if a positive test for marijuana is from legitimate CBD use or illicit marijuana use. If an MRO reports a positive marijuana result for a donor who used a legal CBD product, the donor may face adverse consequences from their employer. Conversely, if the MRO accepts the donor's explanation of legal CBD use and reports the test as negative, illicit marijuana users may be able to claim CBD use as an excuse for a positive test for marijuana.

There are other concerns regarding the use of CBD products. One is the potential for adverse drug reactions between CBD and other drugs metabolized by the same hepatic enzyme system. An adverse interaction could result from either inhibition or activation of enzyme systems, leading to higher or lower blood levels of drugs. Furthermore, there is a known interaction between high doses of CBD, as prescribed in Epidiolex®, and valproic acid, which may result in liver damage when these two substances are co-prescribed.[9] Another concern is the widespread health claims advertised for CBD. Individuals may turn to CBD use rather than seeking out legitimate treatments established by clinical studies.

The rapidly changing cannabis landscape (e.g., new routes of administration, new illicit and licit products) undoubtedly has implications for the federal workplace drug testing program. The Substance Abuse and Mental Health Services Administration (SAMHSA) has conducted a number of scientific studies to understand the effects of illicit cannabis use and legitimate hemp use. For example, SAMHSA sponsored a study to determine whether exposure to the smoke of higher potency cannabis increased the risk of testing positive among non-smokers.[10-12] An extreme exposure study of six non-smokers sitting alongside six smokers in a small sealed room without ventilation resulted in a single positive urine test for the marijuana metabolite, delta-9-tetrahydocannabinol-9-carboxylic acid (THCA), and transient amounts of Δ9-THC detected in oral fluid for 1 to 3 hours, but this occurred only under extreme conditions. This and related studies indicate that exposure to second-hand marijuana smoke under normal ventilation conditions poses no risk that an individual will have a passive exposure-related positive urine or oral fluid test result under the standards used in the Mandatory Guidelines for Federal Workplace Drug Testing Programs.[13,14]

Another SAMHSA focus has been the broadening popularity of cannabis products produced for oral consumption. A SAMHSA-sponsored study detailed the pharmacokinetic and pharmacodynamic profiles in six healthy adults of acute oral doses of 10, 25, and 50 mg of Δ9-THC in a food product (brownies).[15,16] Following oral administration, blood concentrations of Δ9-THC never exceeded 5 ng/mL, and time-to-peak concentration was 2–3 hours; in contrast, inhaled concentrations are typically >10 times higher and peak within 10 minutes of use. Despite the low blood concentrations, those receiving oral Δ9-THC doses reported significant drug effects at all three doses and also showed evidence of significant cognitive/psychomotor impairment after the 25 and 50 mg doses. These findings have major implications in areas such as driving under the influence of drugs (DUID) programs.

The growing use of vaporization as a means of drug administration prompted SAMHSA to sponsor a study comparing smoked versus vaped marijuana.[17-19] Seventeen adults self-administered vaped or smoked cannabis in doses of 0, 10, and 25 mg of Δ9-THC in a double-blind cross-over design study. Although the pharmacokinetic patterns of Δ9-THC and metabolites in blood were similar in terms of their time courses, the vaped route led to higher blood concentrations. Additionally, while vaporized and smoked cannabis produced dose-orderly drug effects, vaped drug effects were stronger than those resulting from the smoked route.

The first SAMHSA-sponsored study of CBD use was published recently.[20] Pure CBD and CBD containing 0.39% Δ9-THC (by dry weight) were administered by vaping, and pure CBD was administered orally to six drug-free participants. Acute ingestion or vaping a 100 mg dose of pure CBD did not result in a positive urine test for THCA when using the Mandatory Guidelines for Federal Workplace Drug Testing Programs criteria for initial and confirmatory testing. In contrast, inhalation of cannabis containing 100 mg of CBD contaminated with 3.7 mg of Δ9-THC (0.39% of the plant material) produced positive test results. Two of six individuals produced positive initial and confirmed test results with THCA C_{max} values of 29.9 and 23.2 ng/mL. The lack of positive tests for THCA in urine after ingestion of pure CBD indicated that CBD is not converted in the body to Δ9-THC.

Additional publications under preparation detail the pharmacokinetics of CBD and metabolites in blood and oral fluid and the pharmacodynamics of CBD by the vaped and oral routes of administration.

Although significant inroads have been made in understanding the risks and benefits of cannabinoids, much research remains to be conducted. SAMHSA stands at the interface between the changing landscape of licit and illicit drug culture and how these changes impact federal workplace drug testing programs.

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