CANNABIS IN VETERINARY MEDICINE

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EXECUTIVE SUMMARY

The circumstances under which veterinary clinicians encounter cannabis-derived products are quite varied. A classic scenario is that of a patient exposed to marijuana plant material intended for the owner's recreational use; in recent years, products such as edibles, concentrates, or vaping devices may also be involved.[1] However, unintentional exposures of recreational products represent only one aspect of cannabis in veterinary medicine. As the potential therapeutic benefits of cannabis continue to be examined for people, veterinarians are encountering cannabis-derived products intended for use in companion animals. The scientific and regulatory landscapes continue to rapidly evolve, so this report represents a snapshot in time with the intention for regular updates.

Passage of the 2018 Agricultural Improvement Act (2018 Farm Bill) removed "hemp" from the definition of "marihuana" in the Controlled Substances Act (CSA), and descheduled it, although it left authority for scheduling hemp-derived products for therapeutic purposes intact.[2,3] Descheduling hemp removed significant barriers for medical research, so the body of knowledge regarding the chemical constituents of cannabis is now growing more rapidly.

Terms used when discussing cannabis and its derivatives are not uniformly applied. Depending on the subject matter, the intended use of the product, and historical conversational use, we note that the same term may be interpreted quite differently. Therefore, for this report, we define "cannabis," "marijuana," and "hemp," as follows:

> **"Cannabis"** refers to plants that are further defined as either "hemp" or "marijuana," depending on their Δ^9-tetrahydrocannabinol (THC) concentration. Cannabis is a genus of flowering plants in the family Cannabaceae, of which *Cannabis sativa* is a species, and *Cannabis indica* and *Cannabis ruderalis* are subspecies. Cannabis refers to any form of the plant for which the THC concentration on a dry weight basis has not yet been determined prior to further categorization as hemp or marijuana.[4]
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> **"Marijuana"** is defined as cannabis that has a THC concentration exceeding 0.3% so remains classified as a Schedule I controlled substance regulated by the DEA (as of the date of this publication).[3] The DEA additionally lists tetrahydrocannabinols as Schedule I controlled substances, including Δ^9-THC, Δ^8-THC, and others.
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> **"Hemp"** is defined in the 2018 Farm Bill as the plant species *Cannabis sativa* L. and any part of that plant, including the seeds and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a Δ^9-THC concentration of not more than 0.3% on a dry weight basis.[2]

Investigations of the therapeutic role of cannabis-derived products in modern medicine for humans and "other" animals are in their infancy, so many questions remain to be asked, much less answered. Although we recognize there is considerable interest in both hemp and marijuana for therapeutic purposes, the scope of this report is limited primarily to hemp and hemp-derived articles for dogs and cats.

We provide a bit of history, an introduction to the endogenous endocannabinoid system, a synopsis of manufacturing quality, a review of animal clinical studies exploring efficacy and safety, information about

potential adverse effects (including data around exposures and toxicoses from poison control centers), and a description of the current regulatory landscape.

Information is likely to evolve rapidly, so the AVMA will work to stay abreast of scientific and legal developments so that we can continue to keep veterinarians informed of the potential role of cannabis in veterinary medicine and responsibilities around its use.

SECTION 1

HISTORICAL PERSPECTIVE ON CANNABIS IN THE UNITED STATES

Understanding the historical role of cannabis-derived therapies facilitates understanding of their potential integration into current medical practice. This history also provides the context for different approaches to medicinal cannabis evident in various cultures. Cannabis has been part of recreational, religious, and medical activities for more than 5,000 years. Although the first evidence of cannabis cultivation for recreational and industrial use appears to be in China in 4000 BC, cannabis appears not to have been used for medicinal purposes until 2700 BC.[5] Reported in 1993, the first direct evidence of medicinal use is based on the presence of cannabis material in the remains of an Egyptian mother who died during childbirth in 400 AD.[6] Medical indications are recorded in the world's oldest pharmacopeia (0-100 AD) and Avicenna's *Canon of Medicine* (980-1037 AD), and cannabis is known to have been used in both Arabic (900-1400 AD) and South American medicine (1500s).[7,8,9] Analgesic, anticonvulsant, anti-inflammatory, and antibiotic effects were among its diverse medical indications. Cannabis first appeared in Western Europe in the 1830s as treatment for muscle spasms associated with tetanus and rabies. Its use rapidly spread among physicians in Europe and North America.

Common use of cannabis in the United States was evident by its inclusion in the 1850 United States Pharmacopeia.[10] In 1860, the Committee on Cannabis Indica of the Ohio State Medical Society reported on medical successes of cannabis for multiple indications.[7] By 1924, more than 100 papers describing therapeutic benefits had been published. Cannabis continued to be considered an acceptable intervention and was a common ingredient of over-the-counter pharmaceuticals used to treat a variety of diseases and conditions.

Efforts at regulatory control began emerging in the early 1900s. In 1906, the Pure Food and Drug Act regulated labeling of patent medicines containing *Cannabis indica*.[7] However, in the 1930s, other medical advances—including the development of the hypodermic needle, vaccines, analgesics such as aspirin, and synthetic drugs such as opioids—led to a general decline in attention paid to medicinal cannabis. Although local laws put some restrictions around the use of cannabis as early as 1860, the reduced importance of cannabis for medicinal use and a continued interest in its recreational use made medical cannabis vulnerable to political manipulation. While it is beyond the scope of this document to address the impacts of the politicization of cannabis, understanding the political path that led to its prohibition—despite efforts of the medical communities to retain medical access—is important in acknowledging the potentially important role cannabinoids could have had, and may still have, in medicine.

The efforts of the first commissioner of the Federal Bureau of Narcotics in the U.S. Treasury Department, Harry Anslinger, led to enactment of the Uniform State Narcotic Act (1925).[11] This act mandated that marijuana be regulated as a drug and granted states the authority to seize illicit drugs. The Marijuana Tax Act of 1937 was the first national regulation pertaining solely to cannabis products.[12] To deter the purchase of these products, which were assumed to be highly toxic despite suggestions to the contrary from the American Medical Association, the act criminalized the purchase of cannabis if a tax was not paid. Two committees, the Indian Hemp Drugs Commission of 1893-94 and the LaGuardia Committee of 1944, contradicted the U.S. Treasury Department's claims that marijuana use led to insanity and other adversities. Because payment of the tax required an admission of purchase, and because the tax targeted physicians and pharmacists, amongst others, this act effectively brought medical use of cannabis and much of the research related to

it to a halt. In 1941, medical cannabis was removed from the United States Pharmacopeia. The Marijuana Tax Act was struck down in 1969 because it violated the Fifth Amendment, and, by then, the increase in recreational cannabis use in the 1970s put marijuana back in the spotlight, leading to changes in regulation. The Marijuana Tax Act was almost immediately replaced with the Controlled Substances Act (CSA) of 1970, which established the Drug Enforcement Agency and the National Commission on Marijuana and Drug Abuse[3] (see Section 6: Regulatory overview of the use of cannabis-derived products in animals).

Despite the CSA, increased recreational use of marijuana in the 1960s and 70s reinvigorated interest in research on the use of cannabis in medical practice. Although several cannabinoids had been isolated, a pivotal event was the 1965 synthesis of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) by Raphel Mechoulam, the "Father of Cannabis."[13] Early research primarily focused on the neurologic or psychotropic effects of cannabinoids, particularly THC. Use of dogs in that research, which served the role of a bioassay in the 1970s and 80s, was followed by use of rodents. These bioassays were critical for describing adverse effects, including tolerance and physical dependence.

The second pivotal event that led to improved understanding of the mechanisms of cannabinoid action was the discovery of cannabinoid receptors in the 1980s. This discovery allowed investigators to relate the structure of cannabis-derived compounds to their potency and efficacy. Localization of the receptors using radioligand binding studies, identifying the receptors as membrane G-protein coupled, and cloning the receptors have markedly advanced medical knowledge. The final pivotal event, which occurred in the 1990s, was the discovery and description of endocannabinoids, the endogenous compounds that bind to cannabinoid receptors.

Subsequent to this work, medical access to marijuana was approved in several states. For example, in 1996, California passed the Compassionate Use Act, which was in opposition to the federally mandated prohibition of marijuana and provided for medical use of marijuana by humans.[14] Many other states have now followed suit. Laws and regulations, however, vary from state to state. Many states stipulate specific conditions under which medical marijuana is allowed.[10]

The science around medical use is not clear. Although insufficient evidence might exist for some indications, therapeutic benefits have been clearly demonstrated for others, such as the FDA-approved drugs for treatment of epilepsy, anorexia, and nausea.[15] Among phenomena associated with increases in medical marijuana use has been the emergence of medical marijuana dispensaries, or pharmacies, and the manufacture and marketing of products containing medical cannabinoids as dietary supplements. Many veterinary patients are being exposed to these products marketed as dietary supplements, despite that such a category for animal use does not exist under the Federal Food, Drug, and Cosmetic Act (FDCA)[16] (see Section 6: Regulatory overview of the use of cannabis-derived products in animals). Accompanying decriminalization of marijuana at the state level during the last two decades has been an increased exposure of both consumers and the medical communities to a plethora of information regarding the potential medical benefits of cannabinoids. However, discriminating science from testimony can be difficult.

For veterinarians and pet owners, results of recent investigations in companion animals emphasize the need for controlled clinical trials as contrasted to case studies and anecdotal reports. Such controlled studies provide much needed clarity for veterinary practitioners and shape the future of cannabis-derived products for veterinary use.

SECTION 2

CANNABIS PHARMACOLOGY AND THE ENDOCANNABINOID SYSTEM

Cannabis species (*Cannabis* spp.) are pharmacologically diverse plants with three cultivars: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. *Cannabis ruderalis* flowers independent of photoperiod and yields low cannabinoid content, making it a poor choice for commercial growth.[17]

Cannabis spp. contain at least 480 distinct compounds, the presence and concentration of which vary within and among species and subspecies (cultivars). *Cannabis* spp. contain approximately 90 different terpenophenolic compounds known as cannabinoids—with the remaining compounds being other terpenoids and phenylpropanoids.[18,19] Cannabinoids are lipophilic, low-weight (300 Da) molecules.[20] There are three types of cannabinoids, two of which are naturally-occurring: phytocannabinoids, derived from *Cannabis* spp. plants, and endocannabinoids, found in animals. The third type is synthetic cannabinoids designed for therapeutic or illicit recreational use.

Phytocannabinoids are derived from the carboxylated form of cannabigerol (CBG) or cannabigerovaric acid (CBGVA).[21] Determining the most medically important phytocannabinoids will take some time, but, currently, Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabichromene (CBC), and CBG are most commonly cited.[19] THC, CBD, and CBC are formed as the carboxylic acids tetrahydrocannabivarin carboxylic acid (THCVA), cannabidiolic acid (CBDA), and cannabichromene carboxylic acid (CBCA), respectively, when processing via drying, heating, or aging decarboxylate phytocannabinoids in the plant.[21]

Of these cannabinoids, THC is the most understood because its psychogenic effects have been of considerable interest. However, CBD is less psychotropic and has many therapeutic effects similar to THC, so it is also emerging as a commonly studied cannabinoid.[22] Cannabinol (CBN) is important as the primary product of the metabolism of THC, and it has been used to predict the age of marijuana plants. Because CBG is rapidly metabolized to THC, CBD, and CBC, very low concentrations of CBG exist in the plant.[23]

In addition to phytocannabinoids, cannabis contains approximately 140 different terpenoids or terpenes. Terpenes share a precursor molecule with phytocannabinoids and are not unique to *Cannabis* spp. They are responsible for a variety of pharmacologic effects, such as taste and scent, and are often targets for *Cannabis* spp. hybridization. Prominent cannabis-derived terpenes include limonene, myrcene, α-pinene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol, and phytol.[21] Other components in the cannabis plant include nitrogen-containing compounds; carbohydrates, such as common monosaccharides (e.g., fructose, glucose, mannose), selected disaccharides (e.g., sucrose, maltose), and several polysaccharides (e.g., cellulose, pectin); as well as several sugar alcohols (e.g., mannitol, sorbitol, glycerol). Flavonoids and fatty acids are also present. An advantage of having this number and variety of compounds in the cannabis plant is the potential for an "entourage effect" in which negative aspects of one cannabinoid (e.g., anxiousness induced by THC) is offset by the effects of another (e.g., anxiolytic effects of CBD).

The presence and concentration of compounds (cannabinoid and non-cannabinoid) in cannabis cultivars vary, and multiple strains have been genetically modified or hybridized to preferentially generate specific cannabinoid or other substance content.[24] This hybridization includes differences in the proportions of both cannabinoids and terpenes.

The cannabinoid constituents of cannabis or their synthetic analogs are available in approved drugs. These include the synthetic THC dronabinol (Marinol and Syndros, Schedules III and II, respectively) approved for use as an appetite stimulant in patients with AIDS or cancer; the synthetic THC nabilone (Cesamet, Schedule II) approved for use as an antiemetic in patients undergoing chemotherapy, but also used under extralabel guidelines as an analgesic; and the most recent approval of CBD (Epidiolex, descheduled in 2020) for treatment of refractory epilepsy in children.[25] The DEA indicates the descheduled status for Epidiolex is for that drug only because other CBD products have not been demonstrated to be safe. In the UK, nabiximol is a combination of THC and CBD (1:1) undergoing investigation for treatment of spasticity associated with multiple sclerosis, and a synthetic CBD analogue is undergoing phase one clinical trials for treatment of pediatric epilepsy. Synthetic forms of CBD are currently being investigated as cheaper and more effective alternatives to natural products.[26]

The products in the previous paragraph that are FDA-approved are available for legal use in humans and legal extralabel use in veterinary patients (see Section 6: Regulatory overview of use of cannabis-derived products in animals). However, far more publicly accessible are a plethora of cannabis-derived products that, due to their intended use, meet the definition of an unapproved drug. Such products are often marketed as supplements or food products to which cannabinoids have been added. Despite their prevalence, such products have not been evaluated or approved by the FDA, which has initiated enforcement action against many manufacturers (see Section 6: Regulatory overview of use of cannabis-derived products in animals).

The structural characterization of THC and CBD has informed synthesis of cannabinoids that vary in their agonist effect on cannabinoid or related receptors. While several pharmaceutical synthetic cannabinoids have been developed for medicinal use, as is the case for previously mentioned nabilone and dronabinol, most have been synthesized for illicit recreational use.[27,28]

For many illicit synthetic cannabinoids, the chemical structure has been modified to preserve the psychotropic effects while rendering the molecules more difficult to detect with standard assays. Because these synthetic analogues are structurally different from THC and CBD, some testing methods that might otherwise be used to determine cannabinoid exposure may not be effective (see Section 5: Cannabis toxicosis in companion animals).

Congress passed the Synthetic Drug Abuse Prevention Act of 2012 making these unapproved recreational synthetic cannabinoid products illegal and empowering the DEA to take enforcement action. However, these products continue to be both a human and animal safety risk.[1,29]

THE ENDOCANNABINOID SYSTEM

Pharmacodynamics

The presence of the endocannabinoid system has only been recognized for several decades, so new information continues to emerge. We currently understand that the endocannabinoid system comprises endocannabinoid receptors and endogenous cannabinoid ligands, with the latter referred to as endocannabinoids.[30,31] The discovery and description of the effects of THC on one of the primary endocannabinoid receptors paralleled that of the discovery of opioid receptors leading to the discovery of the endogenous cannabinoid system. The neuromodulatory function of the endocannabinoid system is widespread throughout the CNS, contributing to synaptic plasticity and response to both endogenous and nervous stimuli.[32] The system is frequently cited for its importance in neuroprotection.[33]

Receptors

Two major endocannabinoid receptors (CBR) have been described: CB_1R and CB_2R. Similar to opioid receptors, endocannabinoid receptors are G protein-coupled cell-membrane receptors (GPCR). They are distributed throughout the body, playing critical roles in most tissues.[31]

CB_1R are highly conserved in vertebrates. They are the most common metabotropic receptors (act through a second messenger) and are one of the most abundant GPCR in the brain. However, they are distributed in certain cell types in selected areas, specifically the basal ganglia nuclei, hippocampus, cortex, and cerebellum. CB_1R largely inhibit neurotransmitter release, neuronal excitability, and synaptic plasticity.[31,34]

Neurotransmitters reported to be modulated by CB_1R include glutamate, gamma-amino butyric acid (GABA), acetylcholine, noradrenaline, and serotonin.[34] Localization of CB_1R in the brain reflect their control of motor function, cognition, memory, and analgesia.[31] Classic CB_1R-mediated responses include hypolocomotion, analgesia, catalepsy, and hypothermia.[35] However, the dopaminergic reward pathway is also stimulated by CB_1R, contributing to overeating, smoking, and substance use disorders.

CB_1R are also located within cells and in peripheral tissues. Mitochondria are one of the most common CB_1R-labeled organelles.[34] CB_1R are also expressed in lower concentrations in the periphery, primarily in circulating immune and hematopoietic cells, including microglia.[34] Organ and cell locations include the spleen, tonsils, thymus, lungs, testes, macrophages, and leucocytes.

Activation of CB_2R does not cause mentation effects typical of CB_1R activation. Along with CB_2R, CB_1R are up- or down-regulated during immune responses. Their expression increases in the CNS in selected disease states, particularly inflammation, immune suppression, and cancer.[31]

That CB_1R and CB_2R are GPCR indicates their importance in normal physiology. Interactions between ligand and GPCR can occur in a variety of ways, resulting in a variety of signals, thus allowing for complicated drug-dose-response relationships that interface with other physiologic signals.[36] The receptors have at least two sites at which ligands can bind: the site in which endogenous ligands bind (orthostatic) or at a site distant from the orthostatic site (allosteric). Allosteric binding allows modulation of the effects of endocannabinoids. Ligands can interact at the orthostatic site as agonists, partial or mixed agonists, inverse agonists, or antagonists. Interestingly, while many agonists demonstrate minimal selectivity for either CB_1R versus CB_2R, antagonists tend to be highly selective for one CBR compared with the other.[31]

The manner in which ligands interface with either cannabinoid receptor can also differentially modulate β-arrestin, which regulates the number of CBR on the membrane surface. These changes can lead to desensitization or a diminished response that might occur with repeated administration of an exogenous cannabinoid (e.g., phytocannabinoids or synthetic cannabinoids). Rapid desensitization results in tachyphylaxis, whereas a more gradual desensitization results in tolerance, physical dependence (and thus withdrawal signs) and, potentially, drug resistance.[37]

Cannabinoid tolerance may develop due to either biochemical or cellular changes.[31] Although mechanisms have not been fully elucidated, changes in CBR binding due to down-regulation and desensitization have been proposed. β-arrestin is likely to regulate CB_1R signaling and adaptation. In humans, the amount of CB_1R downregulation can be positively correlated with the number of years of (THC) smoking and is reversible when smoking is discontinued. CB_2R also down-regulate in response to agonists. The manner in which ligands bind to the receptor may influence the degree of down-regulation. For example, allosteric modulation of CB_1R provides analgesia but not tolerance or dependence.[38]

GPCR are capable of dimerization; i.e., monomers of GPCR can bind with one another. Dimerization of cannabinoid receptors has been demonstrated to allosterically modulate opioid receptor activity. As such, cannabinoids have the potential of influencing opioid and other GPCR.[39] An additional complicating factor is the existence of GPCR that are not CB_1R or CB_2R but nonetheless interface with cannabinoids.[40] The importance of these orphan (receptors with no identified endogenous ligand) GPCR is being investigated.

Endocannabinoids

Endogenous cannabinoids are lipophilic signaling molecules synthesized on demand from cell membrane phospholipids. Like neurotransmitters, they are released in response to increased calcium concentrations following post-synaptic depolarization of activation of metabotropic glutamate receptors.[41]

Although many endocannabinoids have been described, the most prevalent and most studied in mammals are 2-arachidonoyl glycerol (2-AG) and anandamide (AEA). These two endocannabinoids are particularly prevalent in the brain but also are distributed throughout the body. Interestingly, AEA concentrations are higher in plasma than serum.

Most endocannabinoid effects occur through CB_1R and CB_2R.[42] Although not yet totally clear, their binding affinities to CBR differ. 2-AG is currently thought to bind with moderate affinity to both CB_1R and CB_2R as a full agonist, whereas AEA is currently thought to bind with high affinity to CB_1R as a partial agonist.[41,43] AEA is about tenfold more potent than 2-AG, but concentrations are very low.[41] Binding of both AEA and 2-AG is competitive. The differential binding of the two major endocannabinoids allows for modulation of different functions.

The metabolism (formation and degradation) of these two endocannabinoids also varies, potentially paving the way for differential pharmacologic manipulations.[32] Arachidonic acid is contained in both AEA and 2-AG, but the pathway to AEA synthesis is complex compared to 2-AG. Four pathways of AEA formation have thus far been proposed.[32] The importance of understanding these pathways reflects the role AEA is suspected to have in disease.[32] The degradation of both 2-AG and AEA to arachidonic acid is rapid. The impact of COX-2 inhibitors, including certain non steroidal anti-inflammatory drugs, on AEA formation is still being investigated, but ultimately COX-2 inhibitors selective only for AEA or prostaglandins may be developed.

The basic physiologic effects of the endocannabinoid system have been substantially reviewed elsewhere.[35,42] Briefly, endocannabinoids appear to influence every major body system and have important roles in metabolism (e.g., food or energy intake, body adiposity, exercise, and energy expenditure), cell regulation (e.g., sleep and wakefulness), and systemic inflammation and stress. Interestingly, circulating AEA concentrations are inversely related to measures of anxiety and depression and are altered in human patients with post-traumatic stress disorder. Memory and cognition are also influenced by AEA through CB_1R.[42] The role of endocannabinoids in addictive behaviors and reward is less clear, but 2-AG, in particular, is associated with reward.

Endogenous cannabinoids increase in response to a variety of pathologic situations. The role of AEA and 2-AG in pain is also an area of research, with higher concentrations of AEA and 2-AG, for example, being associated with chronic pain syndromes.[42] It is beyond the scope of this report to describe the known and presumed physiologic effects of AEA and 2-AG; however, reviews are available focusing on energy metabolism;[44] epilepsy;[45] pain (including neuropathic);[46] inflammation;[46,47] cancer;[48] and the central nervous,[49] cardiovascular,[50] gastrointestinal,[51,52] immune,[53] skin,[54] lower urinary,[55] musculoskeletal,[56] and reproductive systems.[57,58]

Cannabinoid receptors and phytocannabinoids

The endocannabinoid system interacts differentially with phytocannabinoids; THC, CBD, CBC, and CBG are illustrative.[35] THC binds as a partial agonist at both CB_1R and CB_2R in nanomolar concentrations. As a partial agonist, THC either directly activates CB_1R or attenuates the tone of endogenous cannabinoids. Although most of the physiologic effects of THC can be attributed to CBR binding, it may also interface with orphan GPCR cannabinoid receptors.[35]

On the other hand, CBD has very low affinity for cannabinoid receptors, with weak antagonist activity at CB_1R and inverse agonist activity at CB_2R.[35,59] However, CBD may act indirectly as an agonist at both receptors by inhibiting AEA hydrolysis.[35] Interestingly, CBD exists naturally as the negatively charged enantiomer, which does not bind to CB_1R; however, the synthetic positively charged enantiomer has been shown to bind both CB_1R and CB_2R.[60] As early as the 1960s, CBD began to be used as an anticonvulsant, with effects similar to phenobarbital.[60]

CBC is another non-psychotropic cannabinoid. It exhibits strong anti-inflammatory effects by indirect activation of CB_1R, through inhibition of endocannabinoid inactivation.[61] Most recently, CBC was determined to normalize intestinal motility in a mouse experimental intestinal inflammation model, but not alter the rate of transit in control animals.[62]

Even though little CBG occurs in *Cannabis* spp., it has been studied nonetheless. It appears to be a partial agonist/antagonist at both CB_1R and CB_2R.[23] Interestingly, it is also an agonist at alpha-2 adrenoreceptors, and thus serotonin (5-hydroxytryptamine or 5HT) 1A receptors, interfaces with select transient receptor potential channels, and inhibits cyclooxygenases 1 and 2, although the clinical relevance of these *in vitro* studies, if any, is not clear. Theoretically, modulation of inflammation is anticipated.

Tolerance to phytocannabinoids has been described in humans.[31,37] Tolerance and rapidly diminishing clinical response have also been documented with chronic THC use (e.g., dronabinol [Marinol]).[63] Tolerance to cardiovascular and selective adverse CNS effects developed within 12 days of initiating therapy, but not to appetite stimulation, the approved indication. A withdrawal syndrome was reported when dronabinol was abruptly discontinued, indicating physical dependence had occurred.[63] In contrast, CBD did not induce physical dependence after 28 days of therapy.[64] Although tolerance is not described for CBD (Epidiolex), users are warned to gradually withdraw the drug to minimize the risk of status epilepticus (package insert).[64]

Pharmacokinetics of the major phytocannabinoids

The lipophilic nature of phytocannabinoids contributes to potentially complicated pharmacokinetics. Care must be taken to not assume the disposition of one cannabinoid can be used to predict others. Also, in humans, the pharmacokinetics of THC from inhaled marijuana is different from that from orally administered products. This review focuses on oral administration. The pharmacokinetics of other routes of administration for humans have been reviewed elsewhere.[65,66]

Because both THC (as a synthesized form, dronabinol [Marinol]) and CBD (Epidiolex) are available as FDA-approved human drugs, quite a bit of human pharmacokinetic information is available.

In humans, THC (Marinol—dosed at 2.5 mg every 12 hours, with gradual titration as needed up to a maximum dose of 10 mg divided every 12 hours)—is almost completely absorbed, but about 10% to 20% reaches systemic circulation.[63] However, at least one of the major metabolites, 11-OH-Δ-THC, is active and is present in plasma in concentrations equal to THC. Concentrations peak anywhere from 30 minutes to 4 hours after

oral administration. Pharmacokinetics are largely dose-dependent at 2.5 to 10 mg (total dose), although proportionality increases at higher doses (**Table 1**). Although food increases the area under the curve (AUC) by approximately threefold, it also delays the time to maximum concentration by 4 hours. Elimination follows two compartments with an initial half-life of 4 hours, then a longer one of 25 to 36 hours. First pass metabolism is extensive, with bile being the major route of elimination and only 10% to 15% of a dose being recovered in urine. Enterohepatic circulation may result in low but detectable concentrations in urine and feces for as long as 5 weeks or more. THC is metabolized primarily by CYP2C9 and CYP3A4. The impact of other drugs that induce or inhibit these enzymes has not been reported.[63]

The package insert for CBD as Epidiolex—dosed at 2.5 mg/kg every 12 hours, with titration up to 20 mg/kg/day total dosing—does not report bioavailability.[64] By 7 days of dosing, the AUC of the active metabolite is 38% of the parent and continues to contribute to bioactivity. Oral absorption is largely concentration-dependent at doses of 5 to 20 mg/kg but the proportionality declines with higher doses. Its maximum serum concentration and AUC are markedly impacted by a high fat meal, with both increasing five- and fourfold, respectively. The elimination half-life of CBD is 56 to 61 hours in humans. It is metabolized primarily in the liver, with some GI tract metabolism. Elimination occurs primarily through the bile and feces. The package insert indicates that neither CBD nor its active metabolite interact with most clinically relevant transporters.[64]

Drug interactions

Drug interactions involving cannabinoids might occur at the level of transporter proteins, including influx and efflux proteins (e.g., P-glycoprotein), blood albumin, or at the level of elimination. Of these three, elimination and, specifically, metabolism have been most studied. After understanding that phytocannabinoids are metabolized by cytochrome (CY) P450, concern for drug interactions involving these enzymes became a focus of research.[67]

Two areas of concern regarding interactions involving CYP450 include the impact of phytocannabinoids on other drugs by virtue of their ability to induce or inhibit metabolism, and the impact of other drugs known to be inducers or inhibitors of CYP450 on THC and CBD metabolism. Current drug interaction data have been systematically reviewed.[67] Although *in vitro* studies have demonstrated potential CYP450 drug interactions to date, clinically relevant reports have been limited to a case report of CBD-associated increase in the concentrations of a clobazam (see Section 5: Cannabis toxicosis in companion animals).[68]

Other sources of information regarding drug interactions come from the package inserts for Marinol (dronabinol) and Epidiolex (CBD).[63,64] According to the package inserts for Marinol (dronabinol) and Epidiolex (CBD), potential drug interactions involving CYP450 have not been established, but caution is recommended when using phytocannabinoids with drugs metabolized and known to inhibit CYP3A4 (e.g., imidazole antifungals, including ketoconazole, itraconazole) or CYP2C9 (e.g., amiodarone or imidazole antifungals, including fluconazole).[63] Pharmacodynamic interactions of concern listed for THC involve additive CNS or cardiac effects. Although competition for protein binding sites may be of concern for THC, displacement has not been confirmed *in vitro*.

The package insert for Epidiolex (CBD) indicates it has the potential to inhibit CYP2C8, CYP2C9, and CYP2C19 and induce CYP1A2 and CYP2B6 at clinically relevant concentrations.[64] Although, as previously indicated, drug interactions at the level of transporters are not of concern for either CBD or its active metabolite, the inactive 7-COOH metabolite does interact with P-glycoprotein. Because this metabolite (in humans) achieves an AUC 40-fold higher than THC, a potential risk of competition for P-glycoprotein may exist.[64]

Table 1. A summary of pharmacokinetics for two major cannabinoids (THC and CBD) reported for humans, dogs and cats.

Species	Units	Human		Dog							Cat
		CBD	THC	THC	CBD	CBD	CBD	CBD	CBD	CBD	CBD
Author		Epidiolex PI; Taylor 2018	Marinol PI; Taylor 2018	*Garrett 1977	Samara 1988	Barner 2018	Gamble 2018	Boothe		Deabold 2020	Deabold 2020
Preparation		Synthetic, Pure	Pure	Pure	CB in 70% EtOH	Oil	Oil	Oil	Soft Chew	Soft Chew	CBD Fish Oil
Dose	mg/kg (or TD)	1500 mg TD	2.4-10 TD	0.1 to 2	45 / 90 (1.9 to 5.6 mg/kg)	10 to 20	2 to 8	2	2	2	2
Route		PO	PO	IV	IV	PO	PO	PO	PO	PO	PO
N				3 (Mongrel)	6 (Mongrel)	5 (Beagles)	4 (Beagles)	8 (Beagles)	8 (Beagles)	(Beagles)	8 (DSH)
Parameter											
Cmax	ng/mL	334±81.3	1.32±0.62 to 7.9±4.54	NA	NA	625±164 to 845±262	102 (61-132) to 591 (389-905)	110±61 (*289±127)	*272±130	301±63 (SEM)	43±9 (SEM)
Tmax	hr	2.5 to 5	0.5 to 4	NA	NA		1-5 to 2.0	2.0±4.0 (*2.3±0.7)	*0.7±2.0	1.4±0.2 (SEM)	2.0±0.6 (SEM)
AUC	ng/mL/ hr	1987	2.88±1.47 to 15.2±5.52		2706+519 /6095+1741	135±46 to 297±112 ug/mL/ min	367(183-437) to 2568 (1753-3048)	1672±2535 (*1292±579)	*1100+379	1297±210 (SEM)	1647±29 (SEM)
Clearance	L/hr/kg	1111	0.2	0.53±0.16; 17±2.95	0.85±0.17 /0.795±0.2						
Half-life	hr	56 to 61	25 to 36	1.2 DAYS 8.2+ 0.23 DAYS	6.8±2.7/9.3±3.3	3.3±0.9 to 2.1±0.5	4.2 (3.6-6.8) to 4.2 (3.8-4.8)	6.4±3.3 (*6.3±1.7)	8.1+2.0	1.0±0.2 (SEM)	1.5±0.2 (SEM)
MRT	hr				7.0±3.5 / 7.5±2.7	217±46 to 298±43	5.6(4.2-9.1) to 5.6 (5.1-7.0)	39±76 (*7.0±0.8)	*8.1+2.0	1.4±0.3 (SEM)	3.5±1.4 (SEM)
Protein binding	%	94	97								
Volume of distribution	L/kg	20963 to 42849	10 L/kg	0.064	8.4±2.3/ 10.5±4	NA	NA			NA	NA
Bioavailability			10-20%		15	108±10					
Comments		1,6,14,21	2-5,13,21	16,18-20	12, 15,17		7	10,11,19	10,11,19		

AUC = Area under the curve. DSH = Domestic shorthair cat. MRT = Mean residence time. PI = Package insert. TD = Total dose. SEM = Standard error of the mean

1 Cmax increased by 5 fold and AUC by over 4 fold when administered with high fat/high calorie meal
2 THC is 90-95% absorbed but first pass metabolism reduces oral bioavailability
3 THC is metabolized to an active metabolite (11-hydroxy-delta 9 THC)
4 AUC is 0 to 12 hrs
5 Cmax not significantly increased but AUC increased by 3 fold when administered with high fat/high calorie meal
6 2.5 to 20 mg/kg/day is recommended dose
7 Median and range
10 Unpublished data
11 *Fed
12 AUC is in μg/h/L
13, 14 Volume of distribution reported out as ratio to bioavailability
15 74% hepatic extraction
16 Based on average weight of 14 kg
17 Based on average weight of 20 kg
18 *Based on radioactive labeling, thus reflects THC and metabolites
19 The shorter half-life is the "best" estimate for THC; the longer half-life reflects THC and radiolabeled metabolites
20 Clearance of bound (124+38 mL/min) versus unbound (4131+ 690 mL/min) drug
21 Clearance is based on total body weight, not per kg

CANNABINOIDS IN ANIMALS

Currently, the most information regarding cannabinoids' actions in domestic animals is available for dogs, but even that is limited. Initial studies in the 1970s and 80s that used dogs as a model focused on the impacts of THC and, to a lesser degree, CBD on humans. Early studies provide some evidence that dogs may respond to cannabinoids in unique ways.

Pharmacodynamics

Receptors

In 1975, tritium-labeled Δ^9-THC (0.5 mg/kg IV) radioactivity was demonstrated to be distributed throughout the canine cerebellum and cerebral cortex, with increased concentrations in grey matter as compared with white matter, and up to 50% of the signal reflected metabolites.[69] Peripherally, radioactivity occurred in all organs except vitreous humor. Peripheral tissues with the highest relative concentrations included bile, adrenal glands, liver, heart, renal cortex, and pancreas. Lowest concentrations were found in fat, trachea, and testes. More recent studies in dogs have demonstrated CB_1R in the cells of parotid and mandibular salivary glands.[70] Dogs have high concentrations of CBD receptors in the cerebellum, where they appear to control motor movement, contributing to a static ataxia that may be unique to dogs.[71] Using radiolabeled studies, THC (-) and, to a lesser degree, THC (+) are much more potent in the dog compared to cannabidiol. More recently, Freundt-Reveille et al confirmed the unique cerebellar distribution of the CB_1R in dogs, and distribution similar to other species in the central and peripheral nervous system.[72] In other studies, both CB_1R and CB_2R were demonstrated in the canine epidermis and dermis; both receptors appear to increase in atopic dogs.[73] Finally, the recently cloned and characterized canine CB_2R reveal 76% homology with that of other species.[74]

Endocannabinoids

Information regarding endocannabinoids in dogs is limited. Freundt-Reville et al measured anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) in the CSF of normal dogs and dogs with spontaneous steroid-responsive meningitis-arteritis following natural spirocercosis infection.[75] These authors demonstrated higher concentrations of AEA and 2-AG in both CSF and serum prior to glucocorticoid treatment and a decrease in both after treatment.

Tolerance to CBD has been reported for dogs. Dogs developed tolerance to the static ataxia associated with intravenous CBD administration as soon as 3 days after intravenous administration of 0.5 mg/kg THC, which was no longer evident by 7 days after administration.[69] In a related study, the intravenous dose of THC necessary to induce ataxia in dogs increased from 0.5 mg/kg to 161 mg/kg after 80 days of dosing every 8 days. Tolerance was still present 23 days after the last dose.[76] Tolerance has also been demonstrated to the analgesic effects within 8 days in dogs subjected to tooth pain.[77]

Pharmacokinetics

Limited THC and CBD pharmacokinetic data are available for dogs. For THC, although it has been administered intravenously to dogs in several studies, pharmacokinetics on the parent compound are not available. Although tissue disposition of radiolabeled THC and its metabolites has been described for dogs, separating parent compound from metabolites is difficult.[78,79] A best terminal half-life of 1.24 days was reported for THC, as compared with 8.2 ± 0.23 days for all radiolabeled activity.[79] The longer half-life reflects the parent compound and the many metabolites, whose pharmacologic activity is not known. THC undergoes enterohepatic circulation in dogs, prolonging its half-life (**Table 1**).

Several recent studies have provided limited tissue disposition information for CBD-based products in dogs. Very early studies provide limited data on intravenous administration (**Table 1**). Single-dose CBD disposition (n=six dogs) after 2 to 5 mg/kg IV (prepared in 1.5 mL of 70% alcohol) revealed a large volume of distribution and a mean half-life of 7 to 9 hours, indicating the compound does not appear to accumulate over time.[80] The elimination half-life reported after intravenous administration is similar to that reported for orally administered CBD in oil or soft chews.[81,82,83,84] Research also indicates that feeding enhances absorption, although not as substantially as in humans[85] (see Section 3: Clinical research investigating therapeutic potential and pharmacokinetics in companion animals).

One study describes the pharmacokinetics and potential adverse effects of CBD administered orally in fish oil to eight cats for 3 months.[81] The pharmacokinetics reported are similar to those reported for dogs with respect to timing and half-life. Monthly CBC and serum biochemical analyses were performed, and one cat did have an elevated alanine aminotransferase activity, with no changes in any other parameters. However, the study provides limited information because CBD was not readily bioavailable (see Section 3: Clinical research investigating therapeutic potential and pharmacokinetics in companion animals). An unpublished pilot study using soft chews indicates improved oral absorption in cats using an emulsified preparation. Dogs metabolize cannabinoids differently than humans, and it is not known which metabolites are, and are not, active. Differences in metabolites contribute in part to the unknown relevance of human test kits for detecting cannabinoids in animals. One study has demonstrated that kits that detect cannabis exposure in people were not effective detecting exposure in dogs[86] (see Section 5: Cannabis toxicosis in companion animals).

A report in abstract form reveals marked variability in the serum concentrations of CBD and THC in dogs (n=183) receiving CBD products marketed as dietary supplements[85] (see Section 6: Regulatory overview of the use of cannabis-derived products in animals). CBD concentrations ranged from non-detectable to greater than 1,000 ng/mL, with a median of 13.7 ng/mL, while THC concentrations ranged from nondetectable to 87.4 ng/mL (median of 0.6 ng/mL). More than 40 different oil- or capsule-based products were represented. This variability suggests that therapeutic drug monitoring of phytocannabinoids might be prudent in clinical patients.

A recent study in dogs explored the dose-concentration relationship of THC and its active metabolite 11-OH-Δ-THC and CBD and its metabolite 7-COOH-CBD (which, in humans, is inactive, according to the Epidiolex package insert). The dose escalation was tenfold, resulting in approximately 49 mg/kg THC and 62 mg/kg CBD).[87] Notably, the incidence of significant adverse events was rare, but when they did occur they occurred primarily with THC administration alone or with CBD administered alone (serum concentrations of THC associated with adverse events were 785 ng/mL or 133-296 CBD and 99-361 ng/mL THC combined; see Section 3: Clinical research investigating therapeutic potential and pharmacokinetics in companion animals).[87]

SECTION 3

CLINICAL RESEARCH INVESTIGATING THERAPEUTIC POTENTIAL AND PHARMOCOKINETICS IN COMPANION ANIMALS

This section provides an overview of the clinical evaluations of cannabidiol (CBD), including preclinical pharmacokinetic data, efficacy data for several therapeutic indications, and potential adverse effects of CBD products reported in limited peer-reviewed literature. When appropriate, this review also addresses cannabinoid derivatives that may have biological value. *Cannabis sativa*-derived products low in Δ^9-tetrahydrocannabinol (THC, < 0.3%) content are referred to as CBD-rich hemp products throughout this section. Data derived from dogs, cats, and horses are summarized. The cutoff date for inclusion of studies was October 31, 2024.

PHARMACOKINETIC STUDIES INVOLVING ADMINISTRATION OF CBD PRODUCTS TO DOGS

Prior to embarking on clinical investigations to determine the therapeutic potential of cannabinoids, researchers engaged in preclinical pharmacokinetic studies examining the bioavailability of cannabinoids in dogs. Several such studies are described below.

One pharmacokinetic examination was conducted by Bartner et al in 2018.[83] This study examined 30 dogs in six cohorts (five dogs/experimental group) that received either 10 mg/kg/day or 20 mg/kg/day of CBD from a hemp extract containing small amounts of other cannabinoids and terpenes, corresponding to a 75-mg dose of CBD every 12 hours or a 150 mg dose of CBD every 12 hours, respectively. During the 12 hours following the first dose, plasma CBD concentrations were measured eight times to determine the relative half-life of three different formulations: an oral CBD-rich infused oil, oral microencapsulated beads, and a transdermal cream. Briefly, plasma concentrations during the first 12 hours as well as at 2, 4, and 6 weeks showed greater absorption and retention from CBD-rich infused oil than from microencapsulated beads or transdermal cream. For dogs given doses of 10 mg/kg/day of CBD-infused oil and 20 mg/kg/day of CBD-infused oil, mean plasma maximal concentrations were 649 and 903 ng/mL, respectively[83] (see Section 2: Cannabis pharmacology and the endocannabinoid system).

The most prevalent adverse effect regardless of CBD dose was diarrhea.[88] Erythematous pinnae also were observed exclusively in the groups receiving transdermal applications. Urinalyses and CBCs revealed no differences over time, while serum biochemical analyses indicated increased activity of alkaline phosphatase (ALP) in 36% of dogs (11 of 30). A significant rise of twofold or more in ALP activity was noted, with higher elevations in the microencapsulated bead group than the infused oil group. Elevations in ALP activity were not observed in dogs given the transdermal formulation.[88]

As part of a clinical osteoarthritis study (which is also discussed in the next subsection, Clinical investigations of canine pain management), 24-hour pharmacokinetic analyses were also performed in four Beagles receiving two different doses 1 week apart of an orally administered CBD/cannabidiolic acid (CBDA) formulation.[82] This study determined serum maximal concentrations (Cmax) of CBD after an intended total oral CBD dose of 2 mg/kg (CBD dose of 1 mg/kg and CBDA dose of 1 mg/kg) and 8 mg/kg (CBD dose of 4 mg/kg and CBDA dose of 4 mg/kg). Cmax values were approximately 100 ng/mL and 600 ng/mL, respectively, with half-lives of approximately 4 hours in fasted dogs fed 2 hours after oral dosing. However,

we now know that CBDA was not converted to CBD in the body. Hence, in hindsight, the CBD measured in the blood was actually from a total CBD dose of 1 and 4 mg/kg.

A subsequent CBD/CBDA study with similar dosing (1 mg/kg each of CBD and CBDA) using a soft chew evaluated eight Beagles in a contract research laboratory setting.[81] Twenty-four-hour pharmacokinetics in fasted dogs revealed a Cmax of approximately 300 ng/mL at 1 to 2 hours and a half-life of 2 to 3 hours. More importantly, this study included twice daily dosing of dogs over a 3-month period to determine whether there were any abnormalities on physical examination or changes in blood work parameters. Significant changes in blood counts, serum chemistry values, and physical examination abnormalities were not detected, implying the relative safety of this product in these younger, healthy Beagles for that duration of administration.[81]

Differences in absorption between the soft chew formulation and oil tincture with and without feeding were further elucidated for eight dogs receiving three sequential treatments with a 7-day washout period between treatments. In this study,[89] administration of 2 mg/kg of CBD in an oral oil formulation resulted in a similar Cmax and a slightly longer half-life (about 4 hours), compared with results of the soft chew study using CBD/CBDA.[81] These data support that administering CBD with food likely enhances its absorption by approximately threefold[81,89] (see Section 2: Cannabis pharmacology and the endocannabinoid system).

Two additional investigations involved the use of three different oral formulations and one transdermal product.[90,91] The first looked at CBD, its native acidic form CBDA, THC, and THC's acidic form THCA. Each dose was designed to deliver 1 mg/kg of CBD and 1 mg/kg of CBDA, and less than 0.04 mg of THC and 0.04 mg of THCA every 12 hours. Products were formulated as a sesame oil base with either 25% medium chain triglycerides or 25% sunflower lecithin, or as a soft chew. All dogs were fed 100 grams of wet food during dosing to promote absorption. Twenty-four-hour pharmacokinetics and 1- and 2-week steady state evaluations, with blood samples collected 6 hours after a morning dose, were reported.

Results of 24-hour pharmacokinetics evaluation revealed that CBD and CBDA were absorbed equally, and 1- and 2-week serum concentrations indicated equal absorption and retention of CBD and CBDA (75 to 100 ng/mL of each), except for the 25% lecithin base product, for which CBDA concentrations were higher (125 to 200 ng/mL).[90,91] THC retention (less than 10 ng/mL) appeared to be lower than THCA retention (15 to 30 ng/mL) across all oral forms. Conclusions regarding 11-OH-THC could not be made due to low levels of detection. Finally, the retention of CBDA (15 to 30 ng/mL) resulting from aural administration of the transdermal formulation was approximately twofold higher than that of CBD at weeks 1 and 2 of a 4 mg/kg twice-a-day application (see Section 2: Cannabis pharmacology and the endocannabinoid system).

A similar 24-hour and 1-week steady state study was conducted to compare a soft gel versus sesame oil formulation of a CBD/CBDA rich extract given orally at 2 mg/kg.[92] During the 24-hour pharmacokinetic evaluation, when a single dose was administered, Cmax was higher for all measurable components (CBD, CBDA, THC, and THCA) for the soft gel formulation, compared with the sesame oil formulation. However, steady state data after 1 week of twice daily dosing showed a higher serum CBDA concentration and a lower serum CBD concentration for the soft gel formulation, compared with the sesame oil formulation, indicating that the differences between formulations noted following a single dose may not predict results achieved with chronic dosing.

A further investigation of pharmacokinetic data for dogs receiving 1, 2, 4, and 12 mg/kg doses of purified CBD once daily for 28 days found that total systemic exposure to CBD increased in a dose-dependent manner following acute and chronic administration.[93] The 24-hour trough plasma CBD concentrations were

dose dependent, with a steady state reached after 2 weeks of administration. Dogs receiving 12 mg/kg/day exhibited more gastrointestinal adverse events and higher ALP activities than controls dogs. Within each CBD dosage, repeated administration increased total exposure (area under the curve [AUC]) 1.6- to 3.3-fold. Mean half-life ranged from 5.4 to 9.3 hours after the first dose and, following chronic administration, ranged from 13.8 to 24.6 hours.

Chicoine et al conducted single-dose pharmacokinetic studies comparing oral administration of 2 mg/kg of CBD/0.1 mg of THC (low dose), 5 mg of CBD/0.25 mg of THC (medium dose), and 10 mg of CBD/0.5 mg of THC (high dose).[94] Plasma CBD and THC concentrations increased in a dose-dependent, nonlinear manner with disproportionally greater serum cannabinoid concentrations relative to the dose increase. CBD and THC were rapidly absorbed (time to Cmax [Tmax] of 1.9 to 2.3 hours) and initially depleted rapidly; however, a prolonged elimination phase for CBD was observed (terminal elimination half-life of 13.3 to 24.4 hours) after low, medium, and high doses.

Dose-adjusted AUC between 0 and 12 hours for CBD was 346, 487, and 588 ng*h/mL per mg/kg for the low, medium, and high doses, respectively, and for THC was 434.7, 815.5, and 903 ng*h/mL per mg/kg, respectively.[94] Dose-adjusted Cmax for CBD was 107, 168, and 187 ng/mL per mg/kg for the low, medium, and high doses, respectively, and THC Cmax was 175, 270.2, and 276.6 ng/mL per mg/kg for the same doses, respectively.

While receiving the high dose, five of six dogs displayed neurologic signs, one dog receiving the medium dose coughed, and one receiving the medium dose vomited.[94] Therefore, the high dose was eliminated from subsequent study phases, with investigators choosing to evaluate adverse events for the medium and low doses only. Neurologic changes could be detected at 2 hours after a single 5 mg/kg dose but were diminished or absent within 6 hours. Substantially fewer neurologic signs were observed after dogs had received five of the 5 mg/kg doses (with 12 hours between doses) than after a single 5 mg/kg dose, indicating the potential for tolerance to neurologic effects to develop.

A study by Corsato Alvarenga et al compared oral administration of CBD at dosages of 5 or 10 mg/kg/day for 26 weeks, including pharmacokinetic analysis at 13 and 26 weeks.[95] This study also found dose-responsive changes in plasma CBD concentrations. Preprandial plasma concentrations for the 5 and 10 mg/ kg dosages were 97.3 ng/mL and 236 ng/mL, respectively, and postprandial concentrations were 341 ng/mL and 1,068 ng/mL, respectively. Cmax and AUC both increased from 0 to 18 weeks and 18 to 36 weeks, indicating continuous exposure over the 36-week period. Plasma CBD concentrations dropped 3.8 to 4.9 times that of peak concentrations within 24 hours, indicating that twice daily dosing may be considered. Adverse events for dogs in the 10 mg/kg group included a greater frequency of soft feces and higher ALP activity than those receiving a placebo.[96] One dog in the 10 mg/kg had high alanine aminotransferase (ALT) activity at 32 weeks, which returned to normal 2 weeks after the study ended.[96]

Mills et al found that dogs orally administered 2 mg/kg or 4 mg/kg of a CBD/CBDA-rich product every 12 hours for 2 weeks, with a 1-week washout between treatments, had CBD concentrations that reached 30 to 100 ng/mL and CBDA concentrations that reached 100 to 200 ng/mL.[97] No adverse events or adverse behavioral changes were noted. However, ALP activity exceeded the reference range in three of 16 dogs administered the 4 mg/kg dose. An improvement in handling scores was noted between the 4 mg/kg and 2 mg/kg treatment groups, with dogs in the 4 mg/kg group being easier to handle.

Limsuwan et al compared the pharmacokinetics of orally administered CBD in natural virgin coconut oil base, nanoemulsion, and water-soluble formulations (all liquids) and a semisolid formulation (50 mg of CBD mixed in a treat).[98] Liquid forms were dosed at 5 mg/kg, while semisolid dosage forms were dosed as one treat/dog. Significant differences in pharmacokinetic profiles were not observed among the three liquid formulations. Significant differences were observed between the one semisolid and the three liquid formulations, with the AUC and Cmax for liquid formulations being significantly greater than for the semisolid formulation. AUC to the last quantifiable time point ranged from 853.29 μg/L*h to 1,432.06 for the liquid formulations, and was 296.05 μg/L*h for the semisolid form. Cmax ranged from 175.35 μg/L to 314.3 μg/L for the liquid formulations, and was 92.29 μg/L for the semisolid formulation. Additionally, a secondary peak was noted for one dog in each group except the nanoemulsion group. This peak was postulated to have occurred due to enterohepatic recycling or intestinal lymphatic absorption.

Hepatic first-pass effect: Another pharmacokinetic study sought to investigate whether an administration route other than oral could be utilized to bypass the hepatic first-pass effect.[99] Pharmacokinetic data following intranasal and intrarectal administration of CBD were compared with data following oral administration. Although oral administration was reported to yield a numerically higher Cmax normalized for dose, compared with the intranasal and intrarectal routes, this difference was not statistically significant. Similarly, Della Rocca et al reported no significant difference in pharmacokinetics between oral transmucosal and oral administration of CBD.[100]

PHARMACOKINETIC AND SAFETY STUDIES OF CBD OR CBD-RICH HEMP PRODUCTS IN CATS

Several studies have investigated CBD administration in cats. Jukier et al examined the bioavailability of Epidiolex (the only FDA-approved CBD product) with or without food.[101] Cats were administered 5 mg/kg of Epidiolex. Results demonstrated a near 11-fold increase in bioavailability for the fed group versus the fasted group. Results also showed a mean ± SD Cmax of 269 ± 334 ng/mL for the fasted group and 465.3 ± 220 ng/mL for the fed group. Terminal half-lives were 4.1 ± 4.4 hours and 5.9 ± 2 hours for the fasted and fed group, respectively. The authors indicated that twice or thrice daily dosing regimens may maintain circulating CBD concentrations better than once daily regimens.

Lyons et al conducted single-dose pharmacokinetic evaluations for 2 mg/kg of CBD plus 1.0 mg/kg of THC (group A) and 5 mg/kg of CBD plus 0.25 mg/kg of THC (group B), administered orally.[102] Blood samples were drawn up to 48 hours after administration, and plasma was analyzed for CBD, THC, 6-OH-CBD, 7-OH-CBD, 11-OH-THC, and THC-COOH. CBD and THC had mean Tmax values of 2.4 to 2.9 hours. Cmax ranged from 36 to 511 ng/mL for CBD and 6.8 to 61 ng/mL for THC. Dose-adjusted Cmax and AUC values were significantly higher for THC than CBD. Of the metabolites measured, only 6-OH-CBD could be quantified, with the highest single concentration observed of 16.8 ng/mL.

Significant variation in measures of CBD and THC were noted, with coefficients of variation (CVs) for CBD exceeding 50% for six of the 10 time points where CBD was above the limit of quantification for group A and nine of the 12 time points where CBD was above the limit of quantification for group B.[102] Similarly, CVs for measures of THC exceeded 50% for four of the seven time points where THC was above the limit of quantification for group A and eight of the nine time points where THC was above the limit of quantification for group B. Salivation was noted in two cats with substantially lower plasma CBD concentrations than other cats. The authors concluded that the study demonstrated marked variability of absorption in cats. No adverse effects were noted, which was interpreted as indicating tolerability in cats.

Rozental et al investigated escalating single-dose oral administration of purified CBD at 2.5, 5, 10, 20, 40, and 80 mg/kg, with a 2-week washout period between doses.[103] Cmax and AUC increased in a dose-dependent manner for all dosing groups. Reported Cmax values for the 2.5, 5, 10, 20, 40, and 80 mg/kg groups were 17.8, 61.1, 132.6, 281.0, 251.7, and 963.9 ng/mL, respectively. Tmax was 2 hours after administration for all groups except the 80 mg/kg group, which had a Tmax of 3 hours. No nonbehavioral adverse effects were observed. Behavioral changes included head shaking, lip smacking, and hypersalivation immediately after dosing. Terminal half-life ranged from 6.7 to 13.2 hours across all groups. Both creatinine and BUN concentrations significantly decreased by 24 hours, compared with values at the study start. Also noteworthy was that 42% of the time, creatinine values were greater than or equal to 1.6 μg/dL, which is the cut off for chronic kidney disease in cats by the International Renal Interest Society standards. The investigators did not provide an explanation for the reported BUN and creatinine changes.

A similar safety study of escalating oral cannabinoid doses in cats was conducted by Kulpa et al.[104] The investigators titrated up to 30.5 mg/kg of CBD alone, up to 41.5 mg/kg of THC alone, and a combination dose of 13.0 mg/kg of CBD and 8.4 mg/kg of THC over a 6-to-7-week period. Pharmacokinetic data for CBD, THC, and metabolites 7-COOH-CBD and 11-OH-THC were reported. Following CBD oil administration, CBD and 7-COOH CBD reached mean ± SD peak plasma concentrations of 236 ± 193 ng/mL and 49 ± 21.1 ng/mL, respectively. Following THC oil administration, THC and 11-OH-THC reached peak plasma concentrations of 518 ± 428 ng/mL and 6.8 ± 5 ng/mL, respectively. Data collected after the 10th and 11th doses (the final of the escalating doses) indicated that higher plasma concentrations of parent and metabolite cannabinoids were achieved after administration of CBD and THC in combination versus separately. Adverse effects were reported as mild and transient, and resolved without medical intervention. Gastrointestinal signs were most commonly observed after medium-chain triglyceride vehicle administration. Lethargy, hypothermia, ataxia, and protruding nictitating membranes were more commonly observed after administration of oils containing THC. No changes in biochemical parameters were observed.

Wang et al investigated the pharmacokinetic behavior of CBD in cats after oral administration of a paste containing near equal parts of CBD and CBDA and minimal amounts of THC, tetrahydrocannabinol acid (THCA), cannabigerol (CBG), and cannabigerolic acid (CBGA).[105] 24-hour and 1-week steady state pharmacokinetic data were reported. An average Cmax for CBD of 282 ± 149.4 ng/mL was observed, with an elimination half-life of 2.1 ± 1.1 hours, while for CBDA the Cmax was 1,011.3 ± 495.4 ng/mL, with a half-life of 2.7 ± 1.4 hours. After twice daily dosing for 1 week, serum concentrations 6 hours after a morning dose showed that acid CBD molecules were approximately double the concentration of the nonacid molecules. The investigators indicated a potential bioavailability benefit to administering acidic cannabinoids. No changes in biochemical parameters or adverse effects were noted.

A study investigating tolerability of orally administered CBD in cats at 4 mg/kg daily for 4 weeks did find increased ALT activity in the treatment group, but found no difference between treatment and control groups when cats were administered the same dose daily during a second, longer-term study lasting 26 weeks.[106] No other biochemical differences were noted between groups. Pharmacokinetic values were evaluated on days 0 and 14 of the 4-week study, with a peak occurring within 2 hours on both days and a Cmax of 251 and 431 ng/mL for days 0 and 14, respectively.

CLINICAL INVESTIGATIONS OF CANINE PAIN MANAGEMENT

An owner survey of CBD-rich hemp product use in dogs and cats revealed pain management, seizures, neoplasia, quality of life, and anxiety or other behavioral issues as the top reasons that owners opted to use these products.[107] A review follows of reported studies in which clinical effects were evaluated.

Multiple publications report on the clinical effects of CBD-rich hemp on osteoarthritis. The first was a placebo-blinded, randomized crossover clinical trial involving osteoarthritic dogs.[82] The study looked at CBD-rich hemp in an olive oil base that contained less than 0.3% THC/THCA and an equal mix of CBD and CBDA. The CBD/THC ratio in the study was approximately 25:1. The reported dosage was 2 mg/kg of total cannabinoids (approximately 1 mg/kg of CBD and 1 mg/kg of CBDA) administered every 12 hours with food. The working solution of the oil contained approximately 50 mg/mL of CBD and CBDA combined. Sixteen dogs randomized into groups completed the crossover study of 1 month's treatment with a 2-week washout period between treatments. Dogs could concurrently receive fish oil, glucosamine supplements, nonsteroidal anti-inflammatory drugs (NSAIDs), or a combination thereof for minimum of 4 weeks prior to enrollment. No changes in treatment were allowed during the trial. Twenty-two dogs were originally enrolled, but six were ultimately excluded.

All owners completed the Canine Brief Pain Inventory (CBPI) and Hudson activity scale to assess pain and activity at 0, 2, and 4 weeks.[82] Veterinarians assessed pain, lameness, and weight bearing every 2 weeks during the study. CBC and serum biochemical analyses were also performed every 2 weeks. Assessments performed by owners indicated a significant reduction in pain scores and increase in activity scores when the dogs received CBD-rich hemp oil, compared with placebo oil. In addition, the two veterinarians evaluating these dogs reported reductions in pain indices at weeks 2 and 4 for dogs receiving CBD-rich hemp treatment versus placebo oil. However, there were no significant changes in veterinarians' physical examination findings for gait and weight bearing. CBC results did not differ, but serum biochemical analyses revealed an increase in ALP activity at week 4 for dogs in the treatment group, compared with the placebo group (nine of 16 dogs had an increase over their initial measurements). Dogs were allowed to remain on NSAIDs during the trial. No association with increased ALP activity was observed when using CBD in combination with NSAIDs. Overall, assessments of pain relief by owners and veterinarians were positive.

Another study of osteoarthritis involved 37 enrolled dogs, 32 of which completed the 90-day trial with no placebo-treated control group.[108] This was a dose escalation study starting at 0.25 mg/kg of a CBD oil product (13:1 CBD/THC in hemp seed oil containing 30 mg/mL CBD) with food once a day for 3 days, and then approximately every 12 hours. Pain assessments of each dog were performed every 2 weeks. CBD dose escalations of 0.5 to 0.75 mg/kg approximately every 12 hours were prescribed at each reassessment until the patient's pain score on palpation was 0 to 1 of 10 (0 = no pain and 10 = greatest pain).

In that study,[108] dogs could receive concurrent gabapentin, but not NSAIDs, and concurrent acupuncture or electroacupuncture, nutraceuticals, polysulfated glycosaminoglycan, or a combination thereof. Physical examination by veterinarians and owner assessments were done every 2 weeks using the Cincinnati Orthopedic Disability Index (CODI). Changes in supplements, physical therapy, or other integrative modalities were not allowed, but owners were allowed to lower the gabapentin dose based on owner comfort. CBC and serum biochemical analyses were assessed prior to and 3 months after the study began. A veterinarian performed a gait speed assessment, pain palpation scoring, and physical examination, which occurred every 2 weeks. If the veterinarian's palpation pain index score did not show improvement, the dose of CBD-rich hemp

seed oil was increased from 0.5 to 0.75 mg/kg until a palpation score of 0 to 1 was achieved. If palpation pain scores decreased, an attempt was made to reduce the gabapentin dose.

Two of the 32 dogs did not respond during the 90-day study, with their overall pain scores remaining at 1/10.[108] The final dose for these two non-responding dogs was 2 mg/kg. CBD-rich hemp treatment appeared to be effective within the CBD dosing range of 0.3 to 4.12 mg/kg every 12 hours. Most of the patients required 1 to 2 mg/kg of CBD-rich hemp product to achieve a palpation score of 0 to 1. The initial mean ± SD pain palpation score was 3.2 ± 2.2, which then significantly decreased to 1.0 ± 0.8 by the end of the study. Unfortunately, data for the owner's assessment using the CODI were not reported other than to indicate that 94% of owners felt the treatment positively impacted the dog's quality of life. Of the 23 dogs that also received gabapentin for pain mitigation, 10 had its use completely discontinued and 11 had the daily dose reduced. The average initial dose of gabapentin was 1,846 ± 1,756 mg/day, which decreased to 710 ± 1,112 mg/day by the end of the study.

With respect to CBC and serum biochemical analyses prior to and after the trial, only serum ALP activity showed a significant increase; no changes in serum ALT activity were observed.[108] Neither the owners nor the veterinarians reported evidence of adverse effects from the treatment. Owners felt their dogs slept less and interacted more with family while on the CBD-rich hemp product.

A different study by Verrico et al investigated the therapeutic potential of CBD for osteoarthritis, using both CBD in fractionated coconut oil and lecithin-liposomally encapsulated CBD in a 4-week, randomized, placebo-controlled, double-blinded study.[109] This pilot study included 20 dogs with an average weight of 41 ± 15 kg divided into four groups (n = 5/group). They were orally administered fractionated coconut oil (placebo), 20 mg or 50 mg/day of CBD in fractionated coconut oil, or 20 mg of sunflower lecithin liposomally prepared CBD daily, with no information on whether the treatment was provided with a meal or not. Before study initiation and at day 30, a veterinarian used a 5-point scale to assess the dogs while walking, running, and assuming a standing position from both a sitting and lying down position. Owners also evaluated their dogs before treatment, at week 4 of treatment, and then again at week 6 (2 weeks after discontinuing the treatment) using the Helsinki Chronic Pain Index. Veterinary examinations and owner evaluations indicated no significant difference in response between dogs given a placebo or 20 mg/day of coconut oil-based CBD, but significant improvement was noted for all sitting to standing and lying to standing transitions for dogs that received 50 mg/day of CBD in coconut oil and 20 mg/day of liposomal CBD. Dogs receiving 50 mg/day of CBD in coconut oil also showed improvement in walking when pre- and posttreatment assessments were compared.

In a study by Brioschi et al, dogs orally receiving 2 mg/kg of CBD twice daily with concurrent use of an anti-inflammatory drug (either prednisone or firocoxib), gabapentin, and amitriptyline showed meaningful improvement in CBPI scores, compared with a placebo group also receiving an anti-inflammatory drug, gabapentin, and amitriptyline.[110] CBPI scores were lower at 1, 2, and 4 weeks after starting CBD medication, and pain interference scores were lower at 1, 2, and 12 weeks. Quality-of-life index values also improved 1 week after starting CBD. No relevant changes in CBC or serum biochemical parameters were observed, and only mild gastrointestinal side effects were noted.

However, in an efficacy study of a CBD- and CBDA-rich hemp extract in dogs following tibial plateau leveling osteotomy, ALP activity was reported to be higher and, interestingly, eosinophil counts lower in the treatment group.[111] The study found no difference in pain indicators following 2 to 2.5 mg/kg twice daily oral dosing for 4 weeks. At 2 weeks after surgery, four patients in the control group and no patients in treatment group needed trazodone for activity restriction. The investigators indicated that a reduction in postoperative anxiety

associated with CBD administration may have occurred. Similarly, a study by Mejia found no difference in osteoarthritis-associated pain indicators between patients orally administered CBD, compared with a control group.[112] Nevertheless, elevations in liver enzyme activities and vomiting were noted in the CBD treatment group.

Talsma et al conducted a double-blinded, placebo-controlled crossover study where 42 dogs with mobility impairment were orally administered 5 mg/kg of CBD twice daily for 45 days, with a 30-day washout period between treatment and control phases.[113] Compared with the control group, dogs receiving CBD showed improved outcomes on blinded veterinary assessments, CBPI scores, and client subjective outcome measures, but not on objective measurements (accelerometry and objective gait analysis using a pressure sensitive walkway). Also noteworthy: Patients receiving CBD alone and CBD combined with NSAIDs showed elevations in ALP activity. However, ALP elevations were greater for those receiving CBD and NSAIDs combined versus CBD alone. Only patients receiving CBD and NSAID had an elevation in ALT activity. Two dogs vomited on CBD alone and one dog on CBD and placebo, and one dog had diarrhea on CBD alone.

Two studies were conducted investigating the effect of CBD in dogs under anesthesia. Casas-Alvarado et al found no difference in pain scores for dogs undergoing ovariohysterectomy between groups receiving meloxicam, CBD, or meloxicam and CBD combined.[114] However, Hasckel Gewehr et al found that oral premedication with 6 mg/kg of a total cannabinoid dose of a 1:21 THC:CBD and 1.6:1 CBD:CBDA in a CBD-rich extract was able to decrease the propofol dose necessary for induction by 23%, compared with a control group, with no effect on sedation.[115]

CLINICAL INVESTIGATIONS OF CANINE NEUROLOGIC AND BEHAVIORAL DISEASE

In addition to the aforementioned studies investigating analgesic and anesthetic indications, the application of CBD to seizure management has also been explored. McGrath et al conducted a randomized, blinded, placebo-controlled trial in a small cohort of dogs with idiopathic epilepsy refractory to traditional management.[84] This study included dogs receiving the antiepileptics potassium bromide, phenobarbital, levetiracetam, zonisamide, or a combination thereof, without other comorbidities. Dogs were randomized to orally receive either chicken-flavored placebo hemp oil or CBD-rich hemp oil containing 100 mg/mL of CBD with other trace cannabinoids. Dogs were given doses of 2.5 mg/kg every 12 hours and continued on their existing antiepileptics throughout the 12-week trial. Blood work was performed every 4 weeks to assess CBC and serum biochemical parameters, serum bromide and phenobarbital concentrations, and plasma CBD concentrations. Owners recorded in diaries the number, type, and length of seizures on a monthly basis. The mean monthly frequency of seizures for 16 weeks prior to initiating the study provided the reference for determining a significant response. A significant response was defined as a 50% or greater reduction in seizures. Behavioral assessments were conducted at weeks 0 and 12.

Twenty-six dogs met the criteria for enrollment; 12 were allocated to the CBD-rich hemp oil group and 14 to the placebo oil group.[84] Seventeen of the 26 dogs completed the study: nine in the CBD-rich hemp oil group and eight in the placebo oil group. Dogs were withdrawn from the study due to antiepileptic drug alterations during the protocol (three in the placebo group), euthanasia due to status epilepticus (one in the CBD group), and ataxia (two in the CBD group). After data were collected, one dog in the placebo oil group was found to have been given CBD oil by its owner during the protocol period, resulting in nine dogs in the CBD-rich hemp oil group and seven dogs in the placebo oil group that continued to meet the study criteria. The median number of seizures per month prior to study initiation averaged four and decreased to 2.7 for dogs in the CBD rich hemp oil group, while dogs in the placebo group remained at two per month prior to and after study

initiation. Two dogs in each group met the 50% or more reduction in seizures objective during the 3-month trial. The only change in blood work was a significant rise in serum ALP activity of approximately 400 U/L, with one dog having a value as high as 1,450 U/L.

Plasma CBD concentrations were measured at each of the 4-week visits so the mean concentrations for each patient could be assessed against the percentage seizure reduction.[84] Plasma concentrations ranged between 150 and 975 ng/mL for the nine patients given CBD-rich oil. Regression analysis suggested a significant association between plasma CBD concentration and seizure reduction. Additionally, serum assessments did not detect alterations in phenobarbital concentration for the seven such patients in the CBD rich oil group. Significant differences in aggression, fear, anxiety, trainability, excitability, or energy were not reported for dogs in the treatment group. The authors concluded that this study suggests promise for this CBD-rich hemp oil product.

Rozenthal et al conducted a crossover study in which 29 dogs were orally administered 9 mg/kg/day of CBD for 3 months, with a 1-month washout period between treatment and placebo phases.[116] A 24.1% decrease in seizure days was reported for dogs receiving CBD and a 5.8% increase for those receiving a placebo. During the CBD phase, dogs had a 3.3% increase in total seizures, compared with a significantly different 30.7% increase during the placebo phase. A significant reduction of seizures or seizure days was not found using a 50% reduction cut off. Dogs receiving CBD had significantly higher ALP values, as has been noted in previous studies. Additionally, a significant difference in mean ALT activity was found between the CBD and placebo phases. Vomiting and reduced appetite were more common in the CBD phase. However, drug interactions between CBD and phenobarbital, potassium bromide, zonisamide, and levetiracetam had no effect on change in seizure days or total seizures. Post hoc analysis indicated that the number of dogs included in the study provided sufficient power to detect a percentage change from baseline in seizure days, but not in total seizures.

Garcia et al investigated seizure occurrence in dogs with refractory epileptic seizures that orally received a CBD- and CBDA-rich hemp extract at 2 mg/kg twice daily for 12 weeks in a 24-week placebo-controlled crossover study.[117] Mean ± SD seizure frequency during the placebo phase was 8.0 ± 4.8 over 12 weeks, compared with 5.0 ± 3.6 over 12 weeks during CBD-CBDA phase. Mean number of epileptic seizure days was 5.8 ± 3.1 and 4.1 ± 3.4 for the placebo and treatment phases, respectively. Both differences were significant. Six of 14 dogs had a greater than 50% reduction in epileptic activity while on treatment, whereas none had such a reduction while receiving the placebo. No differences were noted in serum zonisamide, phenobarbital, or potassium bromide concentrations during treatment. According to owner-reported data, three of 13 dogs had lethargy/somnolence and four of 13 had transient ataxia increases during the CBD-CBDA phase; however, these proportions did not differ significantly from those observed during the placebo phase (1/13 dogs each).

Preliminary investigations of behavior modification in dogs receiving CBD have been reported. Several studies found no difference between treatment and control groups when investigating therapeutic potential for treatment of behavioral indications.[118–121] However, in a study by Flint et al investigating the impact of CBD on stress associated with car travel, multiple parameters—including cortisol levels, whining, lip licking, and other qualitative behavioral ratings—improved with once daily oral CBD administration at 4 mg/kg.[122] Masataka also found a significant decrease in vocal activity between treatment and control groups when evaluating the effect of CBD on temporary separation from caregivers in healthy dogs orally administered 4 mg/kg/day.[123]

CLINICAL INVESTIGATIONS OF CANINE ATOPIC DERMATITIS

Loewinger et al investigated the effect of a mixed CBD- and CBDA-based oil on dogs with atopic dermatitis by orally administering a 2 mg/kg dose of the product or placebo twice daily for 4 weeks.[124] Although no differences were observed in the Canine Atopic Dermatitis and Extent and Severity Index, improvements in the Pruritus Visual Analogue Scale were noted at days 14 and 28 versus day 0. No differences were found between groups in serum levels of interleukin (IL)-6, IL-8, monocyte chemoattractant protein-1, IL-31, or IL-34. Four of the 17 dogs in the treatment group had increased ALP activity at day 28, but the overall increase was not significant. Lethargy, regurgitation, increased flatulence, and inconsistent appetite were also noted in the treatment group. Behavioral changes included somnolence, sleepiness, decreased aggression, and increased calmness. Two dogs in the treatment group had increased energy/mobility. In the placebo group, one dog experienced diarrhea and regurgitation.

Mogi et al similarly found that CBD decreased the occurrence of pruritus in dogs with canine atopic dermatitis when CBD was orally administered twice daily.[125] However, the study was a retrospective case series with no control group, no analysis of the product reported to inform the reader of the product's chemical constituents, and unclear timing of assessments.

FELINE CLINICAL INVESTIGATIONS

Efficacy studies of CBD in cats are limited. A crossover study investigating the potential for pain improvement following dental extractions was performed by Coelho et al and involved 22 cats that each received 4 mg of CBD orally, twice daily for 15 days.[126] The Composite Oral Pain Scale and the Stomatitis Disease Activity Index (SDAI) were measured at days 0 and 15. Improvement in SDAI scores was noted, compared with the placebo group. No changes in biochemical parameters were observed. The tested CBD formulation contained vitamin B3, vitamin B6, and omega-3, -6, and -9 fatty acids, which may have anti-inflammatory properties, and the investigators were unable to say whether these substances impacted their findings. No severe adverse effects were noted. Behavioral effects included occurrence of vomiting hairballs, salivation, licking, head shaking, diarrhea, and vomiting. However, other medications including an anti-inflammatory, an antibiotic, and another analgesic were used in the study, which could have influenced the observed gastrointestinal signs.

An additional efficacy study evaluating analgesic effects in cats undergoing ovariohysterectomy found fewer cats treated with CBD at 2 mg/kg required fentanyl, compared with the control group.[127] However, pain scores did not differ between groups except at 0.5 hours after extubation, when lower scores were detected in the CBD group. The authors noted that it was possible that a higher number of analgesic interventions in the first 2 hours of surgery may have contributed to lower pain scores in the placebo group. No adverse events were noted. Also of note were the higher sedation scores observed for cats administered CBD, compared with the control group.

A study by Weller et al investigating the effect of CBD on stress in cats when being transported in a carrier and meeting a novel person in an unfamiliar environment found no effect in all measured parameters.[128]

PRECLINICAL SAFETY STUDIES OF CBD IN DOGS

Several of the previously mentioned pharmacokinetic and clinical studies have described the profile of adverse effects noted in their study participants. However, the following studies aimed to address the potential toxicity resulting from long-term use of CBD or CBD-rich hemp products for dogs (see Section 5:

Cannabis toxicosis in companion animals). Preclinical safety studies performed prior to FDA approval of two CBD products, Sativex and Epidiolex, indicated no observable adverse effects at a level of 100 mg/ kg of CBD.[129,130] Reported side effects associated with 10, 50, or 100 mg/kg daily oral administrations included hepatocellular hypertrophy and weight loss, which were most common in dogs dosed at 100 mg/kg.[129]

An additional safety study involving 20 purpose-bred Beagles examined CBD, THC, and an equal mix of CBD and THC in a dose escalation trial with at least 3 days between escalating doses.[87] Oral administration of THC and CBD/THC oils resulted in obvious neurologic effects for one dog in the THC group when the dose of THC reached 254 mg. Two dogs given the equal mix of THC and CBD also showed neurologic effects when CBD and THC doses reached 105 mg and 72 mg, respectively. CBD-rich hemp oil treatment (18.3 mg/mL CBD oil) given at an escalating dose every 3 days resulted in no apparent adverse events that were different from the occasional gastrointestinal adverse effects that occurred at a similar frequency in the placebo group when CBD was given at approximately 62 mg/kg (see Section 5: Cannabis toxicosis in companion animals).

A study by Bradley et al involved 40 healthy dogs, with half orally administered a 4 mg/kg dose of CBD for 6 months and the other half receiving a placebo.[131] A transient elevation in plasma ALP activity was found in 11 of 20 dogs receiving CBD at four of the six points that biochemical markers were assessed, but all of these dogs returned to normal 4 weeks after CBD administration ceased. Additionally, mean plasma protein and calcium concentrations were below reference range at certain time points for dogs receiving CBD, with significant differences noted between treated and control groups at various points in the study. All other biochemical markers did not show differences between treated and control groups. An interesting aspect of this study was that investigators also measured bone-specific ALP (BALP) and found a strong correlation between ALP and BALP activities, indicating that the consistent increases in ALP noted in dogs when administered CBD may not have been completely attributable to hepatic-specific ALP, as previously suspected.

Corsato Alvarenga et al found that for dogs orally administered 0, 5, or 10 mg/kg/day of CBD for 36 weeks (6 dogs/group), the 10 mg/kg group had a higher frequency of soft feces than the other groups and ALP activity was higher in dogs receiving CBD than in the control group.[132]

Concerns also have been raised that CBD may affect tear production or intraocular pressure when used long term. However, Jost et al found no effect of daily oral dosing of CBD for 36 weeks on intraocular pressure or tear production in healthy dogs.[133]

CLINICAL INVESTIGATIONS OF CBD IN HORSES

Pharmacokinetic and efficacy studies in equids are limited. However, a single case report suggests CBD-rich hemp helped alleviate a mechanical allodynia problem.[134]

Jones et al report that oral administration of a hemp-infused pellet providing approximately 250 mg of CBD per horse (typical 400- to 500-kg horses) results in similar pharmacokinetics as found in dogs.[135] However, peak serum CBD concentrations ranged between 1 and 6 ng/mL at 2 hours after administration.

An additional pharmacokinetic study with 8 horses orally administered 2 mg/kg or 8 mg/kg of CBD/CBDA or placebo in a crossover design yielded a median Cmax of CBD and CBDA of 5.2 and 36.95 ng/mL, respectively, for the 2 mg/kg group and 40.35 and 353.56 ng/mL, respectively, for the 8 mg/kg group.[136] Median elimination half-life was not calculated for the 2 mg/kg CBD group due to lack of time points above the lower quantifiable limit beyond Cmax, while it was 7.75 hours for the 8 mg/kg group. CBDA absorption was noted

to be biphasic. Tolerability was also evaluated by assessment of vital parameters, pedometry data, blinded mentation, gait, manure production, and gastrointestinal transit time. No differences in measured tolerability parameters were demonstrated between treatment and control groups.

Finally, a study by Eichler et al investigated the therapeutic potential of CBD for treatment of stress and anxiety in horses.[137] Results indicated no difference from the control group for healthy horses orally administered a CBD paste (total CBD dose, 3 mg/kg) twice daily for 15 days in terms of behavioral parameters, facial expression, cortisol levels, heart rate, and heart rate variability.

SECTION 4

ANALYTICAL TESTING AND QUALITY CONTROL IN THE CANNABIS INDUSTRY

In recent years manufacturers of cannabis-derived products have marketed an increasing variety of new cannabidiol (CBD) products, despite a lack of regulatory evaluation and approval of their safety or efficacy. In a study reported in 2019, 13 commercially available CBD oils intended for use in animals were analyzed and determined to have inaccurate label information compared to the actual chemical contents of the products.[138] This study also revealed that 12 of the 13 products had greater than Canada's acceptable level of Δ^9-tetrahydrocannabinol (THC) in hemp (<10 ppm). Similarly, analyses by ConsumerLab and a report in the *Journal of the American Medical Association* (*JAMA*) revealed that many available CBD products contain different amounts of cannabinoids than indicated on their labels.[139,140]

The purpose of this section is to briefly identify the substances evaluated in cannabis and cannabis-derived products to help ensure their safety and to describe the quality control (QC) measures that should be in place for laboratories that conduct analytical testing of cannabis-derived products. Reliable testing procedures will help ensure label accuracy.

Current areas of interest in testing the quality of cannabis are the concentration of intended chemical constituents, such as cannabinoids, flavonoids, and terpenes; as well as the concentration of undesirable contaminants, such as residual solvents, pesticides, herbicides, heavy metals, bacteria, and mycotoxins. When veterinarians are presented with cannabis-derived products it is valuable to inquire with manufacturers regarding which of these chemical constituents they test for and the analytical methods used to quantify them. **See Table 2** for a list of examples of the chemical constituents that may be found on the product label for which veterinarians should inquire with manufacturers.

QUALITY CONTROL OF ORGANIC COMPOUNDS IN CANNABIS

Hundreds or perhaps thousands of organic compounds can be found in cannabis plants. In this report, we describe the intended and unintended chemical constituents of cannabis-derived products and consider the relative merits of various analytical techniques in meeting the needs of potential consumers, including veterinary clinicians and pet owners who desire products of known safety and efficacy. Several contract testing laboratories across the United States serve a growing need for chemical analysis of cannabis-derived products. Considerable interstate inconsistency has emerged with respect to analytical processes as each state has adopted unique regulations, so we also consider which modern analytical technologies are preferred for the chemical analysis of the different constituents of cannabis and its many derived products.

Mass spectrometry

Mass spectrometry is the technique of choice for quality control within the pharmaceutical, food safety, and environmental industries. Mass spectrometry can play a critical role as both a sensitive and selective analytical technique for the accurate determination of intended and unintended compounds in cannabis. Although liquid chromatography-mass spectrometry (LC/MS) and gas chromatograph-mass spectrometry (GC/MS) techniques are used in some cannabis applications (*vide infra*), other less definitive techniques, such as liquid chromatography-photometric diode array (LC/PDA), gas chromatography-flame ionization detector (GC/FID), and near infrared spectroscopy are popular techniques in some laboratories.[141,142] The following chemical

Certificate of analysis: Substances of interest		
Cannabis constituents	Cannabinoids	Δ^9-tetrahydrocannabinol (THC) cannabidiol (CBD), cannabichromene (CBC), cannabigerol (CBG) and cannabinol (CBN) tetrahydrocannabinolic acid (THCA) cannabidiolic acid (CBDA)
	Terpenes	limonene, myrcene, α-pinene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol, and phytol.
Cannabis contaminants	Residual solvents	hexane, ethanol, butane, propane, chlorinated solvents
	Pesticides	azoxystrobin, bifenazate, etoxazole, imazalid and imidacloprid
	Heavy metals	lead, cadmium, mercury, arsenic, magnesium, copper, chromium, and cobalt
	Bacteria	Salmonella, Shiga toxin producing E. Coli,
	Fungi	*Aspergillus flavus, Aspergillus parasiticus.*
	Mycotoxin	Aflatoxins B1, G1, G2, G21, OA

** This list is not meant to be exhaustive of all possible substances that may be found on a CoA of a cannabis derived product.*

Table 2

constituents should be evaluated by reliable analytical techniques to help veterinarians interpret a product's certificate of analysis (CoA).

POTENCY: CANNABINOIDS

Eleven different phytocannabinoids (cannabinoids derived from plants) can be measured in cannabis plant material, including THC, CBD, cannabichromene (CBC), cannabigerol (CBG), and cannabinol (CBN), and the list grows constantly (see Section 2: Cannabis pharmacology and the endocannabinoid system).[143] Potency generally refers to the percentage of THC, CBD, or both in the plant material. However, tetra-hydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), and CBN are also measured routinely. **Figure 1** shows the structures of these and several related cannabinoid compounds.

Cannabis strains, or cultivars, may have varying compositions. Each cultivar contains a wide variety of chemical constituents present in different relative ratios.[144] At least 480 compounds have been identified in *Cannabis sativa* plants, including 90 phytocannabinoids and 120 terpenes.[20]

A key component of accurate and precise analyses is specificity, or the selectivity of the detector used. Unfortunately, most current analytical methods used for phytocannabinoid potency testing involve high-performance liquid chromatography-photometric diode array (HPLC/PDA) and a calibration curve approach that is contrary to modern accepted regulated bioanalytical techniques in the pharmaceutical

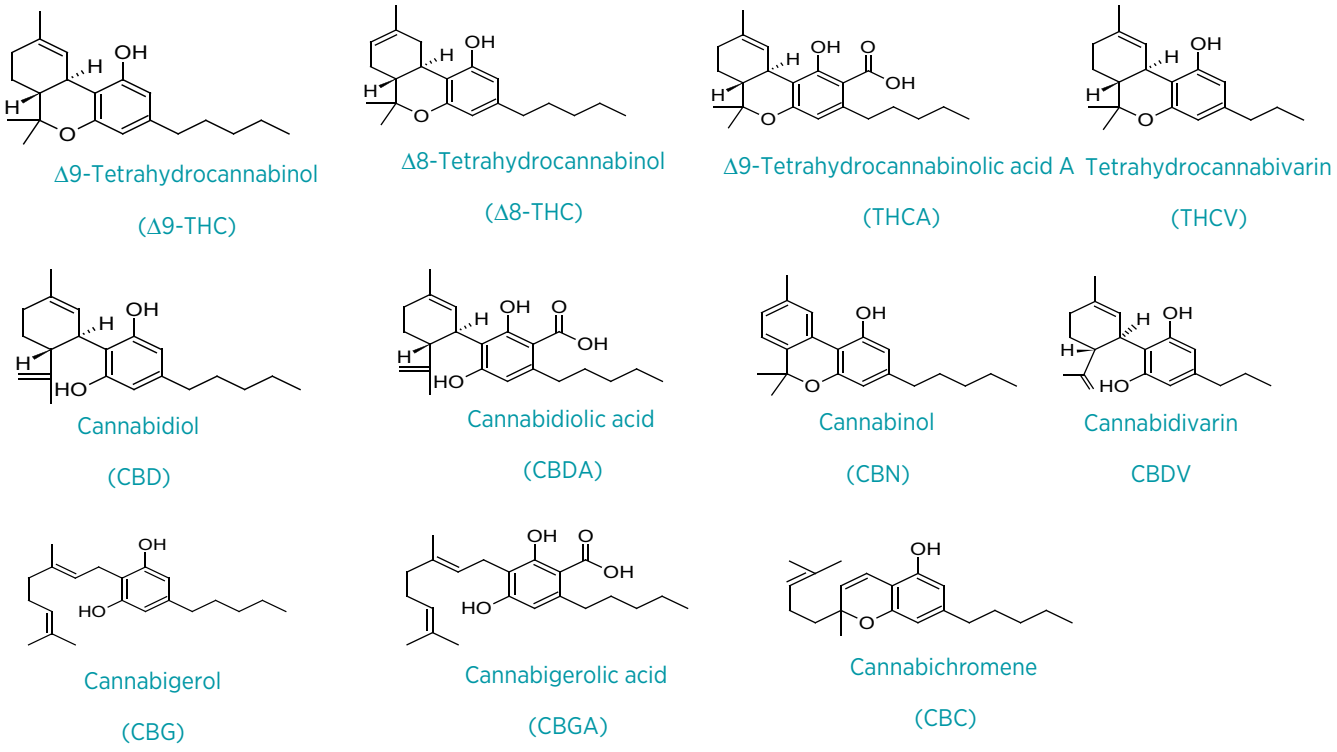


Figure 1. Chemical structures for 11 common cannabinoids found in cannabis plant materials.

and environmental industries. Use of HPLC/PDA for potency determination has the potential for a variety of errors.[145]

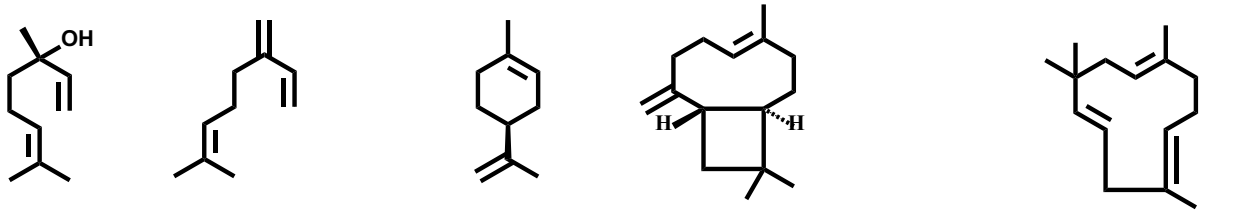
TRICHOMES AND TERPENES

Trichomes are plant hairs that have glands that can secrete terpenes. Trichomes are important for the biosynthesis of botanical chemicals and are important in cannabinoid synthesis.[146] Fresh cannabis plants owe their familiar smell in part to terpene-related compounds.[146] Although terpenoids are not unique to cannabis, cannabis plants produce unique terpene profiles that, in combination with unique cannabinoid ratios, may determine some of their physiological (including medicinal) effects.[147] The quantitative analysis of terpenes is perhaps best done by either GC/MS or LC/MS/MS.

Terpenes commonly found in cannabis plants include limonene, myrcene, α-pinene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol, and phytol. See **Figure 2** for representative terpene structures. (See Section 2: Pharmacology and the endocannabinoid system.)

PESTICIDES

Pesticide residues rank high on the list of quality concerns in cannabis and cannabis-derived products, and can be challenging for manufacturers to control because cannabis growers often feel they need to use pesticides to mitigate damage by insects, mold, etc.[148] Cannabis samples from retail facilities in various states



Linalool | Beta-Myrcene | Limonene | Beta-Caryophyllene | Alpha-Humulene

Figure 2. Representative terpene structures

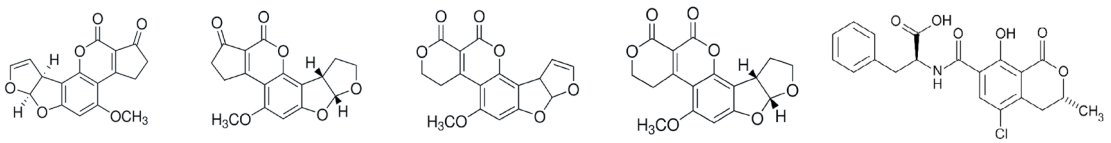
where the sale of recreational marijuana has been legalized have reported contamination with insecticides, fungicides, rodenticides, and other pesticide compounds.[149] Even though some cannabis is grown indoors with careful light, humidity, and temperature control, a variety of insect and bacterial pests can adversely affect the growth and quality of the plant before harvest. As a result, growers are tempted to use pesticides to control these problems; however, very few pesticide products are registered for use on hemp.[150] Extralabel use of pesticide products is not lawful under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA), so if the pesticide is not approved for cannabis its use is likely illegal. Recalls of cannabis products in multiple states and Canada highlight the need for regulatory control.[150-152]

Pesticide levels and cannabis product quality, in general, are particularly important if cannabis products are to be used for patients with already compromised health. Pesticides of interest include azoxystrobin, bifenazate, etoxazole, imazalid, and imidacloprid.[153] However, many pesticides are in use, and states have their own lists of those pesticides that must be monitored in cannabis samples. California, for example, currently has a list approaching 100 pesticides which must be monitored with "action levels" that reflect low part-per-billion lower limits of quantitation (LLOQ).[154] This large number of pesticides, coupled with the need to quantify them at part-per-billion levels, may pose challenges to some cannabis testing laboratories. Different states may require testing for different pesticides, perhaps at different action levels.

In general, most state laboratories suggest use of LC/MS/MS techniques for the quantitative determination of trace levels of pesticides in cannabis and cannabis-derived products.[155] This technology, coupled with recommended sample preparation techniques, may provide broad coverage with high sensitivity and selectivity for the quantitative determination of more than 100 pesticides.

MICROBIOLOGY

Cannabis is often grown in greenhouses under carefully controlled conditions, including warm temperatures with relatively high humidity. These are excellent conditions for the growth of a wide variety of bacteria, such as *Salmonella* and Shiga toxin-producing *E. coli*, and fungi, such as *Aspergillus flavus* and *Aspergillus parasiticus*. Accordingly, most states now require analysis for both microbial growth and byproducts of such growth. Microbiological contamination of cannabis plants and products is typically detected using either culture growth or quantitative polymerase chain reaction (qPCR) techniques.[156]



B1 B2 G1 G2 OTA

Figure 3A

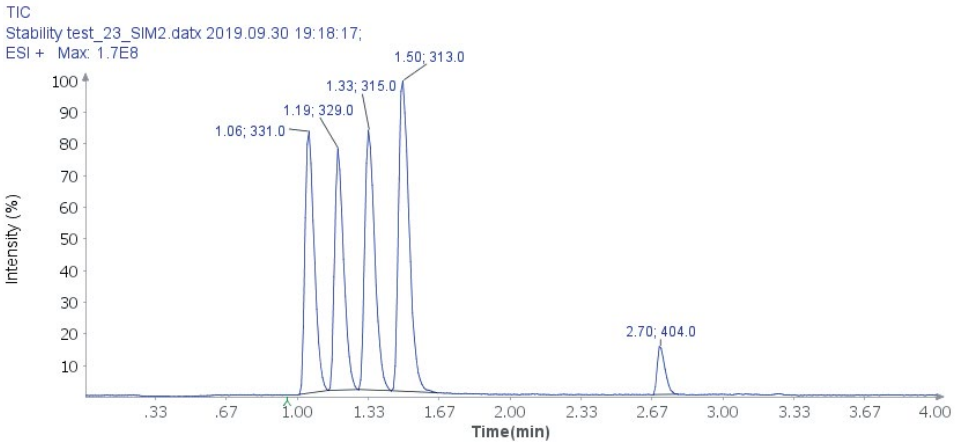


Figure 3B

Figure 3AB. Chemical structures for five targeted aflatoxins (A) and the SIM LC/MS total ion chromatogram obtained from the LC/MS analysis of a synthetic mixture of these five aflatoxins (B)

MYCOTOXINS

Mycotoxins, which are toxic secondary metabolites of mold, are a concern in cannabis plants because carcinogenic mycotoxins may also cause acute, chronic, or both types of toxicosis.[147] Aflatoxins are a subset of mycotoxins produced by *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxin B_1 is considered the most toxic, but the presence of B_2, G_1, and G_2 must also be considered. **Figure 3** shows the structures for aflatoxins B_1, B_2, G_1, G_2, and OTA (ochratoxin A), which are often targeted in the chemical analysis of cannabis and its associated products. Although capillary GC/MS may be used, it is generally preferred that LC separations coupled with mass spectrometry be used for the quantitative determination of mycotoxins.

RESIDUAL SOLVENTS

When cannabinoids are extracted from the cannabis plant, particular solvents are used for the extraction process, and residual solvents often remain in the cannabis product. Some of these solvents include hexane, ethanol, butane, propane, and, in some cases, chlorinated solvents.[147] Many states require testing for solvent residuals via analysis of headspace (solvent that is evaporated from the sample and into the air) samples, using GC/FID. Although an alternative analytical technique for analysis of such headspace samples could be electron ionization gas chromatography/mass spectrometry (EI GC/MS), the lower equipment costs of GC/

FID may cause that approach to prevail for the foreseeable future. The difference in cost may be justified given the positive selectivity of MS detection in the event of any potential GC retention time deviations.

HEAVY METALS AND ICP-MS

Cannabis plants, both marijuana and hemp, are hyperaccumulators of inorganic heavy metals from the soil in which they grow. Among those heavy metals most commonly evaluated are lead, cadmium, mercury, and arsenic, although, depending which U.S. states are involved, this list may also include magnesium, copper, chromium, and cobalt. These latter metals are often found if the plant is grown near mining, smelting, sewage sludge, or automobile emission sites.[157]

Cannabis testing laboratories are adding a growing list of heavy metals to the analysis of cannabis and cannabis-derived products. Cannabis plant materials can be tested for heavy metals in many ways, including various forms of atomic spectrometry, among them: atomic absorption, inductively coupled plasma optical emission spectroscopy (ICP-OES), and inductively coupled plasma mass spectrometry (ICP-MS). Experienced analytical chemists generally report that ICP-MS offers the best sensitivity and is the method of choice in many modern laboratories. For some important organometallic compounds, it can be useful to employ liquid chromatography inductively coupled plasma mass spectrometry (LC/ICP-MS) techniques that can allow detection and quantitation of individual organometallic compounds.[158] The FDA and United States Pharmacopeia (USP) have standardized methods for heavy-metal analysis, which are very useful resources for the fledgling cannabis testing industry.[159]

QUALITY CONTROL SAMPLING AND SAMPLE PREPARATION PROTOCOL FOR CANNABIS IN THE FIELD

A detailed analysis of sampling and sample preparation is beyond the scope of this resource. However, veterinarians should note that variation in sampling and sample preparation can contribute to inconsistent chemical profiles from samples from the same harvest. Regulatory employees, as well as laboratory employees, should follow local guidance or consider recent USDA guidance for sampling and sample preparation until further updates are published.[160] In the end, sampling protocols are not yet well defined or consistent, and each state tends to use their own interpretation of best practices. All this can reflect forward to the CoA of a cannabis-derived product that is intended for safe and efficacious use in a veterinary patient.

SUMMARY THOUGHTS

There is an urgent need for accurate and precise chemical analysis of both cannabis plant materials and final consumer products. The financial incentives in the cannabis industry are sufficiently great that both existing laboratories and startup laboratories are seeking new business opportunities. Some of these efforts do not include the rigor and professionalism practiced in the recent past by Good Laboratory Practices (GLP) laboratories meeting pharmaceutical industry and FDA requirements. In most cases the turnaround times for sample results are quite long because testing requires considerable manual intervention. Limited automation currently exists because of a lack of widespread focus on improving the workflow of cannabis analyses in laboratories. As a result, some growers and producers have submitted the same sample to two different laboratories and received different results. Rigorous, high-quality chemical analyses can reduce the risk of such inter-laboratory inconsistencies. Good examples to follow are those recommended by GLP procedures as well as approved methods and guidance provided by well-established organizations such as the International Organization for Standardization/International Electrotechnical Commission (ISO/IEC)

17025,[161] AOAC (Association of Official Agricultural Chemists), A2LA (American Association of Laboratory Accreditation), and individual state departments of health, agriculture, or both. In other rigorous laboratory testing arenas, such as the regulation of the use of performance-enhancing substances in athletes, an independent organization will submit blind samples to the laboratory for chemical analysis. This is called proficiency testing and assures the industry that the laboratory is competent. This also would be one way for a veterinarian evaluating a cannabis product to be comfortable that the potency of the product is as indicated on the label and contaminants are unlikely.

Although mass spectrometry techniques are currently used to some extent in the cannabis industry, some suggest they should be more widely adopted to achieve the superior selectivity and sensitivity demanded by the chemical complexity and diversity of the plant, its many products, and many potential contaminants. Quality testing is necessary for the production and sale of consistently safe products needed to earn consumer confidence. When well-qualified analytical service laboratories are in place and used for monitoring the chemical safety and integrity of cannabis and cannabis-derived products, wider acceptance, use of approved products, and more success in their use to treat medical ailments in humans and animals is likely.

SECTION 5

CANNABIS TOXICOSIS IN COMPANION ANIMALS

Reported cases of cannabis toxicosis in companion animals are primarily associated with exposure to Δ^9-tetrahydrocannabinol (THC). Such cases have become more common as recreational and medical marijuana products have become legal to some degree for human use in most states.[162] Most cases of cannabis exposure to date have affected companion animals and horses. This review, however, focuses on exposures in companion animals because there are limited data regarding cannabis exposure and subsequent potential toxicoses in horses.

Historically, cannabis toxicoses have been associated with exposure to marijuana plant material. However, a wide variety of edible products are also now readily available. Edible products often are made by extracting lipid-soluble THC from cannabis plant material and adding it to butter or oil. These edible products are now the most common source of companion-animal exposures to THC, due to both high palatability and very high concentrations of THC.[1] Veterinarians have been seeing an increase in companion animal toxicoses resulting from exposures to vaping devices containing THC or cannabidiol (CBD).[1] In addition, the concentration of THC in marijuana plants raised for recreational products has increased significantly over time.[1]

Dogs account for most exposures reported to animal poison control centers, but cats and other companion animal species also have been affected.[163] Toxicoses have been documented for dogs of all ages, although younger dogs are most likely to be affected.[164] The clinical presentation, exposure types, diagnosis, therapy, and prognosis of cannabis toxicosis in companion animals follows.

CLINICAL PRESENTATION

Dogs may be more sensitive to the psychoactive properties of THC than humans due to a larger number of cannabinoid receptors in the canine brain.[165] However, the minimum lethal dose of THC is high (greater than 3 to 9 grams of plant material per kilogram), and an LD_{50} has not yet been established.[163] Although such dosages are calculated based on measurements of plant materials, veterinarians should note the THC content of plant material can vary considerably (see Section 4: Analytical testing and quality control in the cannabis industry). Depending on the route of exposure, clinical signs may become evident within minutes (if inhaled) to hours (if ingested).[1] Clinical signs are most commonly seen within 1 to 3 hours after ingestion, although delays of up to 12 hours are reported.[145] THC is primarily eliminated in the feces via the biliary system and therefore undergoes enterohepatic recirculation, which can prolong elimination. Recovery from toxicosis normally occurs within 24 hours in most cases, but clinical signs may persist up to 96 hours depending on the exact THC exposure (longer periods of clinical effect tend to be associated with edibles).[1,164]

THC toxicosis in companion animals has high morbidity, but low mortality. The most common clinical signs in dogs are ataxia/incoordination and lethargy/depression. Other common clinical signs are vomiting, urinary incontinence/dribbling, increased sensitivity to motion or sound (often manifested as flinching), head bobbing, mydriasis, hyperesthesia, ptyalism, and bradycardia. Other, less common clinical signs include agitation, aggression, bradypnea, hypotension, tachycardia, and nystagmus. Hypothermia is more common, but hyperthermia can occur.

Cats are less often affected. A single case report in the literature describes disorientation, alternate periods of agitation/aggression and apathy, polyuria, polydipsia, and periods of polyphagia mixed with periods of inappetence.[166]

SYNTHETIC CANNABINOID EXPOSURE

"Synthetic cannabinoids" typically are designer recreational drugs that became popular in the 2000s and have a higher affinity for cannabinoid receptors in the brain than THC. These compounds either are sprayed on dried plant material to be smoked, or are sold as liquids to be vaporized and inhaled in e-cigarettes and other inhalant devices. Synthetic cannabinoids are more likely than marijuana-derived THC products to cause serious toxicosis in both people and animals.[167,168] In dogs, signs may include hyperesthesia, aggression, inappropriate mentation, tremors, and seizures.[167,168] In one case, signs progressed to a comatose condition with apnea, tremors, and opisthotonos.[167] Also of concern is that these products may be laced with other chemicals or drugs, including caffeine or other stimulants. Recently, synthetic cannabinoids contaminated with rodenticides led to a multistate outbreak of severe coagulopathy in humans. Fortunately, no animal patients were affected during the outbreak, but pesticide contamination should be considered in cases of synthetic cannabinoid exposure.[169]

CBD PRODUCT EXPOSURE AND CONSIDERATION OF DRUG INTERACTIONS

CBD is currently the cannabinoid of greatest therapeutic interest in veterinary medicine. CBD products recently have become widely available, and a multitude of products are marketed for companion animals. These products have become more accessible with the recent removal of hemp (defined as *Cannabis sativa* and derivatives of cannabis with less than 0.3% Δ^9-tetrahydrocannabinol [THC] on a dry weight basis) from the Controlled Substances Act (see Section 6: Regulatory overview of use of cannabis-derived products in animals).[2] However, quality control and evaluation of such products has been limited (see Section 4: Analytical testing and quality control in the cannabis industry). Pet Poison Helpline reports that up to 47% of CBD exposures reported to that organization were symptomatic.[170] Clinical signs included those associated with THC exposure such as lethargy, ataxia, and vomiting. Current thinking is that these signs may reflect contamination of the products with THC or other substances—or that the animals had consumed such large doses that the allowable level of THC became significant—rather than the signs being due to the CBD itself.[170] With respect to toxicity associated with CBD, elevations in liver enzymes have consistently been reported, although preliminary pharmacokinetic studies of relatively small numbers of dogs have indicated a general tolerance to CBD over a 6-week period with oral, transdermal, and transmucosal administration.[82,84] (See Section 2 and Section 3.)

Research into the short- and long-term effects of CBD on animals is needed. One issue of concern to veterinary practitioners is any potential interaction between CBD and FDA-approved drugs used in practice. The human literature reports both inhibition and potentiation of metabolizing enzymes by CBD and THC, which can impact blood concentrations of FDA-approved drugs. Potential interactions with FDA-approved drugs used in people that are also used in an extralabel manner by veterinarians include warfarin, tacrolimus, theophylline, ketoconazole, and zonisamide.[171,172] Investigations of similar or additional drug interactions with THC, CBD, or both are needed for companion animal species.

DIAGNOSIS

Diagnosis of THC toxicosis is most often made based on clinical signs and a history of possible exposure. With regard to the latter, thorough and tactful history-taking is important to get accurate information from animal owners. In states where recreational marijuana use is legal, clients may be more willing to admit to the possibility of such exposure. However, there have been cases where the clients were unaware of potential exposure (e.g., dogs that had ingested cannabis while playing in a park or while on a walk through an apartment complex), and it also is important to rule out other possible toxins that may mimic the signs of THC toxicity. Urine dribbling is uncommon after exposure to most other toxins, so the presence of this sign should increase suspicion of THC toxicosis.

Over-the-counter human urine drug tests are generally unreliable for the diagnosis of THC exposure in companion animals.[1] For dogs, while a positive urine drug test is typically supportive of THC exposure, false positives are possible (e.g., in humans, the presence of NSAIDs such as ibuprofen and naproxen may cause false positives on the THC test). In addition, false negatives are very common. Dogs excrete different urine metabolites than humans, which may account for the latter finding. False negatives can also occur if the test is run too soon following exposure, as a result of errors in sample collection and storage (THC binds to glass and rubber stoppers), or due to dilute urine secondary to increased water consumption by the patient. Additionally, it is important to keep in mind that synthetic cannabinoids are not detected by urine THC tests.[1]

Other toxins that may cause signs similar to THC include alcohols, ethylene glycol, benzodiazepines, muscle relaxants, opiates, tranquilizers, ivermectin or other macrocyclic lactones, bromethalin, and other hallucinogenic substances. In some patients, other diseases can cause similar CNS signs and a thorough diagnostic workup is indicated in cases where clinical signs are progressively worsening or do not resolve after 24 to 48 hours of symptomatic/supportive care.[1]

TREATMENT

Treatment is largely symptomatic and supportive, and depends on the severity of clinical signs. Emesis can be considered in companion animals with a history of recent cannabis ingestion that are not showing clinical signs. Emesis should not be induced in companion animals exhibiting clinical signs due to the risk of aspiration.[1,144] For companion animals with significant clinical signs where there is concern about a large amount of cannabis-containing material remaining in the stomach (e.g., wads of buds, large quantity of brownies containing marijuana butter), gastric lavage is a safer, and thus preferred, option. Gastric lavage should be performed under sedation with an inflated endotracheal tube to prevent liquid from entering the airway. Activated charcoal can be given through the orogastric tube following lavage.

Activated charcoal can be given to companion animals that are still alert and that have an intact gag reflex. An anti-emetic (e.g., maropitant or ondansetron) should be administered to prevent vomiting of the charcoal provided there is not concern for a foreign body obstruction. Due to enterohepatic recirculation, multiple doses of activated charcoal (two to three) given every 8 hours may be beneficial if clinical signs persist.[144] If multiple doses of activated charcoal are given, companion animals should be hospitalized with administration of intravenous fluids and evaluation of electrolyte concentrations prior to administering each dose of charcoal to prevent development of hypernatremia. Use of activated charcoal may not be necessary in all cases, and the benefits of its use should be weighed against potential risks (e.g., vomiting and aspiration, hypernatremia, dehydration).[1]

In mild cases of toxicosis, where patients remain alert, ambulatory, normotensive, normothermic, and with no cardiovascular effects, outpatient monitoring and supportive care may be appropriate. Patients that are more severely affected should be hospitalized. Anti-emetics should be considered to prevent vomiting and aspiration, especially in patients that are recumbent or non-responsive. Balanced crystalloid therapy is used to maintain hydration and perfusion, although intravenous fluid therapy has not been shown to hasten recovery. Anxiolytics (e.g., diazepam, butorphanol, or acepromazine) can be used for patients who are agitated, tachycardic, and/or hypertensive.[1,144] Acepromazine should not be used in hypotensive patients.[1] Good supportive care, including thermoregulation, is necessary. Monitoring should include assessing temperature, heart rate, blood pressure, and rate and quality of respiration. Patients that are comatose and/or hypoventilating may need to be intubated and mechanically ventilated. Atropine may be used in bradycardic patients (heart rate 40 to 50 beats/minute).[1]

Although intralipids have been used in more severe cases of toxicosis, especially if edibles or oils are involved, clinical results have been mixed, especially without prior emptying of the gastrointestinal tract.[162,167] At this time, the clinical efficacy of intralipids has not been demonstrated via controlled studies. Intralipids may also bind other drugs that may be indicated to treat clinical signs (e.g., diazepam).[1] Dosing for the use of intralipids in veterinary medicine has been extrapolated from human use. Protocols include administration of a 20% solution, 1.5 to 4 mL/kg intravenously over 1 minute, followed by 0.25 mg/kg/min, over 30 to 60 minutes, or re-dosing of aliquots of 1.5 mL/kg every 4 to 6 hours for up to 24 hours.[173]

PROGNOSIS

Prognosis for recovery from THC toxicosis is generally good. However, life-threatening toxicosis is possible, and fatalities have occurred.[1] Causes of fatality have included secondary complications, such as combined toxicities (e.g., THC and chocolate toxicosis from ingestion of edibles, multiple medications, or illicit drugs) or aspiration, and insufficient financial resources to support necessary therapy (e.g., comatose patients that require mechanical ventilation).

SECTION 6

REGULATORY OVERVIEW OF THE USE OF CANNABIS-DERIVED PRODUCTS IN ANIMALS

Regulation of cannabis and cannabis-derived products at the state, federal, and international levels continues to evolve. At the federal level, this document focuses on the roles of the U.S. Department of Agriculture (USDA), Food and Drug Administration (FDA), and Drug Enforcement Agency (DEA), although other agencies may have authority to regulate the promotion, manufacturing, distribution, and use of cannabis products. The regulatory approach at the state level is highly variable.

We first present a reminder of the regulatory definitions of cannabis, hemp, and marijuana, and follow with an overview of the federal regulatory landscape, as well as information about state and international regulatory activities.

DEFINITIONS

"Cannabis" is the name of a group of plants that, depending on their Δ^9-tetrahydrocannabinol (THC) concentration, are further defined as either "hemp" or "marijuana." Cannabis is a genus of flowering plants in the family Cannabaceae, of which *Cannabis sativa* is a species, and *Cannabis indica* and *Cannabis ruderalis* are subspecies. Cannabis refers to any form of the plant where the THC on a dry weight basis has not yet been determined to allow categorization of cannabis as hemp or marijuana. "Cannabis" is important in describing regulations that apply to plant production, sampling or handling prior to determining its THC content.[4]

"Marijuana" is cannabis that has a THC concentration exceeding 0.3%. Marijuana remains classified as a Schedule I controlled substance regulated by the DEA under the Controlled Substances Act (CSA).[3] The DEA additionaly lists tetrahydrocannibinols as Schedule I controlled substances, including Δ^9-THC, Δ^8-THC, and others.

"Hemp" is defined in the Agricultural Improvement Act of 2018 (2018 Farm Bill) as the plant species *Cannabis sativa* and any part of that plant, including the seeds and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a Δ^9-THC concentration of not more than 0.3% on a dry weight basis.[2]

CANNABIS REGULATION AT THE FEDERAL LEVEL

On January 15, 2021, the USDA announced the final rule regulating the production of hemp in the United States.[174] The final rule describes the process for USDA approval of plans submitted by states and indigenous tribes for the domestic production of hemp, including provisions for maintaining information on the land where hemp is produced, testing the concentrations of THC, disposing of plants not meeting necessary requirements, licensing requirements, and ensuring compliance with new requirements.

Hemp cultivated under state and tribal plans will serve as the starting material for hemp-derived consumer products that are regulated by the FDA. The Federal Food, Drug, and Cosmetic Act (FDCA) authorizes the FDA to obtain evidence of safety for new drugs, issue standards for food, and conduct factory inspections.[175]

On July 22, 2020, the FDA released draft guidance Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research; Draft Guidance for Industry.[176] This guidance addresses quality considerations such as sourcing compounds for clinical research and calculation of percentage of THC in botanical raw materials, extracts, and finished products. However, this draft pertains to the development of cannabis derived products intended for human use only and does not pertain to products intended for animals.[176]

Questions often arise as to whether cannabis-derived products are regulated as drugs, food, food additives, or dietary supplements. Here we discuss these terms in the context of their application to veterinary patients, as well as the current approach to enforcement for products available in the marketplace.

Cannabis-derived products regulated as drugs

"Drugs" are defined in the FDCA as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, and articles (other than food) intended to affect the structure or any function of the body of man or animals.[177] "New animal drug" means any drug intended for use for animals other than people, including any drug intended for use in animal feed that is not generally recognized as safe and effective.[178,179]

"Intended use" is an important concept. FDA defines intended use as "... the objective intent of the persons legally responsible for the labeling of drugs"—most often the pharmaceutical sponsor. FDA indicates "the intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article."[179]

When a pharmaceutical sponsor begins drug development and investigates a substance for therapeutic potential and safety in animals, the new animal drugs for investigational use regulations apply.[180] Following successful demonstration that the technical requirements have been met (e.g., chemistry, manufacturing and controls, target animal safety, human food safety [if applicable], environmental impact, effectiveness, labeling, freedom of information summary), the drug sponsor normally submits a new animal drug application.[181,182] After the application has been approved by the Center for Veterinary Medicine (CVM) at FDA, the pharmaceutical sponsor may then legally market the drug. It is illegal to market a drug for use in non-human animals prior to FDA approval, conditional approval, or indexing.[i]

With respect to cannabidiol (CBD), the FDA states "...any product intended to treat a disease or otherwise have a therapeutic or medical use, and any product (other than a food) that is intended to affect the structure or function of the body of humans or animals" is a drug. The FDA has not approved any CBD products other than one prescription human drug product to treat rare, severe forms of epilepsy.[64,183] There is very limited information for other marketed CBD products, which likely differ in composition from the FDA-approved product and have not been evaluated for potential adverse effects on the body.[64]

[i] Articles meeting the definition of a new animal drug that also meet the definition of an animal biologic or pesticide, after inter-agency jurisdiction discussions, may be legally marketed after appropriate regulatory review by the USDA Center for Veterinary Biologics (CVB), or U.S. Environmental Protection Agency (EPA), respectively.

As of the date of this report, Epidiolex, containing CBD, is the only cannabis-derived product approved by the FDA.[ii] Epidiolex is approved for use in people under Section 505 of the FDCA; however, under the Animal Medicinal Drug Use Clarification Act (AMDUCA) it may be prescribed by veterinarians for use in animals (extralabel use) as long as the Extralabel Drug Use regulations in 21 CFR Part 530 are met.[184] Therefore, under AMDUCA, Epidiolex remains the only cannabis-derived drug available for extralabel use by veterinarians. For completeness, there are also some FDA-approved THC-related drugs that may be used for veterinary patients under AMDUCA, including Marinol and Syndros, which contain dronabinol, a synthetic THC, and Cesamet, which contains nabilone, another synthetic THC. Unapproved CBD drug products have been recalled.[185]

However, it is possible that additional cannabis-derived products intended for use in animals may become available under a future regulatory pathway. On January 26, 2023, in a statement primarily pertaining to the use of CBD products in humans, the FDA concluded that a new regulatory pathway for CBD is needed that balances individuals' desire for access to CBD products with the regulatory oversight needed to manage risks.[186] Specifically, with respect to the use of CBD in animals, the FDA did convey that "a new pathway could provide access and oversight for certain CBD-containing products for animals."

In the meantime, the FDA continues to take enforcement actions on cannabis and cannabis-derived products. For example, on July 5, 2023, the FDA and the Federal Trade Commission warned six companies for illegally selling food products containing Δ^8-THC.[187]

CANNABIS-DERIVED INGREDIENTS IN ANIMAL FOOD OR FEED

"Food" under the FDCA means "articles used for food or drink for man or other animals, chewing gum, and articles used for components of any such article."[188] "Animal feed" means "an article which is intended for use for food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal."[189] The FDA has indicated that CBD or THC cannot be an ingredient of a food product because:

> "...it is prohibited to introduce or deliver for introduction into interstate commerce any food (including any animal food or feed) to which has been added a substance which is an active ingredient in a drug product that has been approved under section 505 of the FD&C Act [21 U.S.C. § 355], or a drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public.[190,191]
>
> "There are exceptions, including when the drug was marketed in food before the drug was approved or before the substantial clinical investigations involving the drug had been instituted or, specifically in the case of animal feed, that the drug is a new animal drug approved for use in feed and used according to the approved labeling. However, based on available evidence, FDA has concluded that none of these is the case for THC or CBD. FDA has therefore concluded that it is a prohibited act to introduce or deliver for introduction into interstate commerce any food (including any animal food or feed) to which THC or CBD has been added."

It is possible for FDA to make an exemption to this rule, but thus far, the agency has not done so.[191]

[ii] Dronabinol is a synthetic cannabinoid reported as not derived from cannabis, so it was not included here.

The Association of American Feed Control Officials[iii] (AAFCO) maintains an official publication (OP) that includes the most comprehensive list of ingredients approved by AAFCO for use in pet food or animal feed. The AAFCO does not maintain a forbidden list of ingredients because if an ingredient is not approved for use it is forbidden. The AAFCO has indicated that it has received no applications for cannabis-derived substances to be included in its OP as feed ingredients.[191] Therefore, as of the date of this report, there are no cannabis-derived substances approved at the federal level for use in pet food or animal feed.

FDA has responded with "no questions" to petitions for three hemp seed-derived products: hemp seed oil, hemp seed protein, and dehulled hemp seed. However, the response for these food additives was specific for human food only, not animal feed or food.[192]

Additionally, as previously mentioned, the FDA recently indicated that a new regulatory pathway for CBD is needed that balances individuals' desire for access to CBD products with the regulatory oversight needed to manage risks.[186] Specifically, with respect to the use of CBD in animals, the FDA did convey that "a new pathway could provide access and oversight for certain CBD-containing products for animals."

However, regarding the inclusion of CBD in food for animals, the FDA stated that "because it is not apparent how CBD products could meet the safety standard for substances in animal food, we also do not intend to pursue rulemaking allowing the use of CBD in animal food."

Cannabis-derived substances as food additives

"Food additive" means "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food … if such substance is not generally recognized … to be safe under the conditions of its intended use … ."[193] Analogous to a new animal drug application, an approved food additive petition is needed for the food additive to legally enter the marketplace. A food additive petition describes target animal safety, environmental impact, utility, and labeling.[194]

Included in its list of permissible food ingredients in pet food or animal feed, the AAFCO maintains a list of FDA-approved food additives for use in animal feed within the AAFCO OP. As is the case for food ingredients, AAFCO has indicated that no applications for cannabis-derived substances to be approved in pet food or animal feed as food additives have been submitted. Although the scope of this resource is limited to the use of cannabis products in companion animals, it is worth noting that to achieve approval for use in feed for food-producing animals, scientific evidence of appropriate withdrawal periods to limit consumer exposure to drug residues is also required.[191]

Cannabis marketed as dietary supplements for animals

The Dietary Supplement and Health Education Act of 1994 (DSHEA) provided a pathway to legally market vitamins, minerals, herbs or other botanicals, amino acids, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of these substances that do not meet the definition of a drug.[195] Manufacturers of such products

[iii] The Association of American Feed Control Officials (AAFCO) is a voluntary membership association of local, state and federal agencies. Members are charged by local, state or federal laws to regulate the sale and distribution of animal feeds and animal drug remedies. FDA and local and state agencies all play a role in regulating pet food and participate in the AAFCO.

must ensure that the product is safe, that the label claim is accurate, and that the products comply with all regulations including good-manufacturing-practice regulations of the FDCA. FDA indicates that DSHEA only applies to products for use in humans.[196] Therefore, if a product is marketed as a dietary supplement intended for animals, it is regulated by the FDA as either a drug or a food; there is no statutory language that defines "dietary supplements" for animals. The regulatory pathway for a particular product is determined by FDA CVM on a case-by-case basis.

"Dietary supplement" means a product other than tobacco that is intended to supplement the diet and bears or contains one or more of the following dietary ingredients: a vitamin or mineral, an herb or other botanical, an amino acid, or a dietary substance for use by man to supplement the diet by increasing the total dietary intake. Regarding the use of CBD products marketed as dietary supplements, FDA has stated in association with cannabis warning letters: "Some of the products are marketed as dietary supplements. However, CBD products cannot be dietary supplements because they do not meet the definition of a dietary supplement under the FD&C Act."[182]

Similar to the FDA's analysis of CBD or THC in animal food or feed, the agency has concluded that THC and CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FDCA.[197] Under that provision, if a substance (such as THC or CBD) is an active ingredient in a drug product that has been approved under section 505 of the FDCA (21 U.S.C. § 355), then products containing that substance are excluded from the definition of a dietary supplement. There is an exception to section 201(ff)(3)(B) if the substance was marketed as a dietary supplement or as a conventional food before the drug was approved or before the new drug investigations were authorized, as applicable. However, based on available evidence, FDA has concluded that this is not the case for THC or CBD.[191]

Reiterating this point, on January 26, 2023, the FDA denied the requests in three citizen petitions from the Consumer Healthcare Products Association (CHPA), the Council for Responsible Nutrition (CRN), and the Natural Products Association (NPA), that the FDA issue a regulation that would allow CBD products to be marketed as dietary supplements.[198] Such a regulation would be needed in order to provide a potential pathway for CBD products to be lawfully marketed as dietary supplements, because a provision in the law prohibits the marketing of certain drug ingredients as dietary supplements. The FDA's responses explain that they "do not intend to initiate such a rulemaking, because in light of the available scientific evidence, it is not apparent how CBD products could meet the applicable safety standard for dietary supplements." Such statements reference products intended for humans since, as previously stated, technically there is no such thing as a "dietary supplement" for animals, because the DSHEA does not apply to products intended for use in animals.

Cannabis products and the Controlled Substances Act

Some FDA-approved drugs are also categorized or scheduled as controlled substances under the Controlled Substances Act (CSA).[3] The scheduling of a controlled substance is based on its medical use, potential for abuse, and safety or dependence liability.[3] Scheduled products are subject to enforcement by the DEA, along with the FDA's enforcement based on the intended use of the product as a drug. Controlled substances are scheduled into one of five schedules. Under the CSA, Schedule I drugs have no currently accepted medical use and are at the highest level of abuse potential, and Schedule V drugs carry the least abuse potential. The CSA prohibits the prescription, administration, or dispensing of any Schedule I substance, and at present marijuana is a Schedule I substance. As previously indicated, marijuana is defined within the CSA as all parts of the plant *Cannabis sativa*, the seeds, resin extracted from any part of the plant, and every compound,

manufacture, salt, derivative or preparation of its seeds with several exemptions that has a THC concentration exceeding 0.3%.[3]

Hemp-derived products marketed for use in animals no longer fall under the oversight of the DEA unless the THC concentration exceeds 0.3% because the 2018 Farm Bill removed hemp from the definition of marijuana. Hemp-derived products, however, remain subject to oversight by FDA under the FDCA with respect to the FDA's evaluation of their intended use as either food or a drug.

Federal approach to enforcement of statute and regulations concerning cannabis products

On December 22, 2020, the FDA issued five warning letters to companies for selling products containing CBD in ways that violate the FDCA.[199] All five warning letters addressed the illegal marketing of unapproved CBD products claiming to treat medical conditions. The letters included CBD products that are especially concerning from a public health perspective due to the route of administration, including nasal, ophthalmic, and inhalation. In addition, the letters address violations relating to the addition of CBD to food, and the impermissible marketing of CBD products as dietary supplements. Two of the letters also addressed CBD products illegally marketed for pets, including a product for use in the eye.

On November 21, 2022, the FDA posted warning letters to five companies for illegally selling food and beverage products containing CBD.[200] The warning letters also outlined additional violations of the FDCA, including that several of the companies were illegally selling unapproved CBD products that claim to cure, mitigate, treat, or prevent various diseases, and adding CBD to animal foods, such as pet treats.

The FDA indicates that, when deciding to take action, it considers multiple factors, including agency resources and threats to public and animal health. The egregiousness of the label claim and any safety concerns associated with the product are key in determining those products for which it allocates enforcement resources.[191] Examples of what FDA considers to be therapeutic claims associated with the marketing of CBD products for animals include language such as:

> "...CBD and other chemicals found in cannabis have antitumor effects and could be used to improve standard treatments..."
>
> "...Due to its anti-inflammatory effect, cannabinoids may provide relief of joint pain and swelling, and decrease joint destruction and disease progression..."

FDA also communicates with federal and state agencies when making decisions about whether to initiate federal enforcement actions.[191,201] The long-term availability of unapproved cannabis products (including CBD and other hemp-derived compounds) in the marketplace will ultimately be determined by FDA enforcement actions targeting such products.

CANNABIS REGULATION AT THE STATE LEVEL

Various states have legalized medical marijuana, recreational marijuana, or both for human use only. Currently, these laws do not authorize veterinarians to prescribe or recommend medical marijuana for dogs or cats in any state. However, there are bills that have been signed into law that impact the use of cannabis-derived products in companion animals. Some states have adopted laws defining "hemp" and "marijuana" similarly to the federal definitions and, in some instances, including language indicating products derived from hemp may be intended for human or animal consumption.[202] Some states also have passed legislation regarding manufacturing and labelling requirements for such products.[203]

In certain states veterinary medicine has received greater legislative attention, such as in California's adoption of Assembly Bill (AB) 2215, which indicates that the state's Veterinary Medical Board (VMB) is prohibited from disciplining or revoking a veterinarian's license solely for discussing the use of cannabis in an animal for medicinal purposes but also prohibits a licensed veterinarian from dispensing or administering cannabis or cannabis products to an animal patient.[204] This legislation also required the VMB to adopt guidelines for such discussions including conveying the risks associated with such products and, in many cases, their lack of regulatory evaluation for safety and efficacy.[205] In 2022, California additionally passed AB 1885, which prohibits the VMB from disciplining a veterinarian who recommends the use of cannabis on an animal for potential therapeutic effect or health supplementation purposes, unless the veterinarian is employed by or has an agreement with a cannabis licensee.[206]

Nevada has also passed AB 101, which allows a veterinarian to administer a product containing hemp or CBD that contains not more than 0.3% THC or to recommend to the owner the use of such a product to treat a condition of the animal; and prohibits the Nevada State Board of Veterinary Medical Examiners from taking disciplinary action against a licensed veterinarian—or the facility in which a licensed veterinarian engages in the practice of veterinary medicine—based on the administration or recommendation of such a product.[207] Additionally, Nevada law (AB 533 [2019]) requires the development and adoption of quality standards for packaging and labeling of "hemp" products intended for human or animal consumption.[208]

Furthermore, Michigan passed House Bill (HB) 5085, which states that a veterinarian may consult with an animal owner on the use of marijuana or industrial hemp on their animal.[209] Florida rule 5E-3.004 states that pet food, pet treats, specialty pet food, and specialty pet treat products may contain hemp extract as defined by Florida Statutes Section 581.217(3), provided the product is not a drug as defined in Section 580.031(9).[210] South Carolina (Bill H3449),[211] Vermont (Bill S.58),[212] New Jersey (Bill A5322),[213] New York (Assembly Bill A7680),[214] and Ohio (Senate Bill 57)[215] now define hemp products in accordance with the federal definition and include food intended for animal or human consumption. Finally, New York (Assembly Bill A5172)[216] provides access to medical marijuana for an animal when a veterinarian determines such animal has any medical condition that may benefit from treatment with medical marijuana.

For information on a specific state's approach to regulating cannabis-derived products for veterinary patients, veterinarians should consult their state's veterinary practice act and pharmacy act, and also should inquire with their state board of veterinary medicine.

CANNABIS REGULATION AT THE INTERNATIONAL LEVEL

The World Health Organization (WHO), which sits within the United Nations (UN), is responsible for, among other human-health-related activities, promoting global access to safe and effective medicines for people while preventing or mitigating substance abuse risks and illicit drug trafficking. The WHO Expert Committee on Drug Dependence (ECDD) is tasked with reviewing psychoactive substances, including cannabis and cannabis-related substances, and making recommendations to the UN Commission on Narcotic Drugs (CND), the drug policy making body of the UN, regarding appropriate controls needed to address potential risks.[217,218] The CND is then charged with making final decisions on whether to place narcotic drugs and psychotropic substances under international control in compliance with three ratified drug control conventions.

Cannabis and cannabis-related products are regulated internationally by the CND in compliance with two of the three ratified drug control conventions: the UN 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances.[219,220] In accordance with these conventions, however, UN member

states, including the United States, must pass their own laws giving federal agencies enforcement authority. The U.S. Controlled Substances Act does so and largely complies with the obligations set forth in these international drug control conventions. Over the past several years, international scheduling of cannabis and cannabis-related products has undergone an extensive review by both the WHO ECDD and UN CND.

During its 40th meeting in June 2018, the ECDD concluded that cannabidiol (CBD) does not have psychoactive properties and, therefore, has no potential for abuse or development of dependency.[221] As such, the ECDD recommended that pure CBD not be placed under international control. In November 2018 during its 41st meeting, the ECDD recommended deleting cannabis and cannabis resin from Schedule IV of the Single Convention on Narcotic Drugs (1961), which would not impact their continued inclusion in the less restrictive Schedule I list.[222] Additional ECDD recommendations from that meeting effectively lessened restrictions on cannabis extracts and tinctures, as well as THC (either naturally derived or man-made) and its isomers. The WHO recommendations derived from the 40th and 41st ECDD meetings in 2018 were forwarded to the CND for consideration at its 62nd session in March 2019.[223] However, the CND did not take definitive action on these recommendations at that time, citing the need for further review and to provide UN member states the opportunity to comment. On December 2, 2020, the UN CND, reclassified cannabis and cannabis resin under an international listing that recognizes its medical value.

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ADDITIONAL RESOURCES

FDA

Cannabis-related webpages

FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)

FDA Regulation of Dietary Supplements & Conventional Food Products Containing Cannabis and Cannabis Derived Compounds

FDA warns 15 companies for illegally selling various products containing cannabidiol as agency details safety concerns

FDA Warns Companies Illegally Selling CBD Products to Treat Medical Conditions, Opioid Addiction

Warning Letters and Test Results for Cannabidiol-Related Products

Links to regulations

Human food

Substances Generally Recognized as Safe

Direct Food Substances Affirmed as Generally Recognized as Safe

Indirect Food Substances Affirmed as Generally Recognized as Safe

Animal food

Food Additives Permitted in Feed and Drinking Water of Animals

Substances Generally Recognized as Safe

Food Substances Affirmed as Generally Recognized as Safe in Feed and Drinking Water of Animals

Animal drugs

Extralabel Drug use in Animals

DEA

DEA announces steps necessary to improve access to marijuana research

Clarification of the New Drug Code (7350) for Marijuana Extract

List of Controlled Substances

Marijuana

USDA

Establishment of a Domestic Hemp Production Program

USDA National Institute of Food and Agriculture – Industrial Hemp

AAFCO

Questions and Answers Concerning Pet Food Regulations

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