TOX/2019/32

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Scoping paper on the potential adverse effects of CBD products

Background

1. Cannabidiol (CBD) has been investigated and researched in the medicinal sector for a number of years including clinical trials for treatment of epilepsy and seizure.

2. CBD has now entered the food sector and is present in several products available for consumption.

3. These consumable products range include beverages (beer, spirits, wine, coffee and soda style drinks), topicals (tinctures, drops, syrup, oils) chewables (gum drops) and chocolate. In addition, it is in pet food in various formats.

4. Future products proposed by industry include CBD infused olive oils, CBD infused honey, and medium-chain triglycerides which are easy to digest and easily metabolized, therefore marketing them as quickly accessible energy.

5. CBD products are becoming increasing popular. According to Forbes magazine the market could grow 700% by 2020[1]. The CBD market could pull in $16 billion by 2025 (Cowen Survey[2]). The Cowen survey found that CBD use is highest among consumers aged 18 to 34. Liquid extracts accounted for the biggest chunk of the market at 44 percent, followed by other topicals at 26%, capsules at 22% and beverages at 19%.

6. The amount of CBD present in these products varied from 2-200 mg in total. However, if used in tinctures this can vary further as the consumer controls the dosage, therefore the dosing range can be somewhat higher. In addition, foreseeable misuse may lead to lower or higher dosing than that specified (Bonn-Miller *et al*., 2017).

7. Risk assessment advice on CBD has been increasingly requested from the Food Standards Agency (FSA).

8. In order to provide appropriate advice, The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) is initially being asked to review a scoping paper on the toxicity risks of CBD.

9. This scoping paper will discuss the findings of a CBD literature survey and review of the available toxicological data as well as an overview of cannabis strains, methodologies of manufacturing CBD oil and summarise the current legal status.

[1] https://www.forbes.com/sites/debraborchardt/2016/12/12/the-cannabis-market-that-could-grow-700-by-2020/#55174c84be1e
[2] http://www.cowen.com/reports/cowen-collective-view-of-cbd/

Legal Status of CBD products

10. Products derived from cannabis have varying legal status (see Annex A for further details). This paper is largely concerned with CBD as a novel food.

Foods and Novel foods

11. The European Commission confirmed CBD's classification as a novel food in 2019 by updating the European Union (EU) Novel Food Catalogue. This means that this product was not significantly used as a food or food ingredient before 15th of May in 1997. Therefore, before it may be placed on the market in the EU as a food or food ingredient a safety assessment under the Novel Food Regulation is required.

12. Some indication of adverse health effects is needed to have unauthorised foods removed from the market.

13. Novel food authorisation would require the products to have low/negligible levels of tetrahydrocannabinol (THC) so that misuse of drugs legislation does not apply.

CBD in medicinal products

14. According to WHO[3], CBD has been demonstrated as an effective treatment of epilepsy in several clinical trials, with one pure CBD product (Epidiolex®) in the United States of America (USA). There is also preliminary evidence that CBD may be a useful treatment for a number of other medical conditions. CBD is generally well tolerated with a good safety profile. Reported adverse effects may be as a result of drug-drug interactions between CBD and patients' existing medications.

15. In the UK, there are only a limited number of licensed medicinal products derived from or related to cannabis. One of the most common ones is Nabiximols (Sativex®[4]) which is licensed in the UK to treat MS-related muscle spasticity. Use on the NHS is limited since it is not considered cost effective by The National Institute for Health and Care Excellence (NICE)[5].

CBD in vape products

16. Vape products may be subject to regulation by other bodies such as the Home Office, Medicines and Healthcare products Regulatory Agency (MHRA) or under specific regulations such as the tobacco regulations depending on their purpose and how they are being used.

17. This is due to the General Food Law (178/2002 EC) food which is defined as anything that people consume that isn't one of the specifically identified product types that are exempted. For example, medicines and tobacco products fall outside the definition of a food as they are subject to other legal frameworks.

[3] https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf
[4] https://www.mstrust.org.uk/a-z/sativex-nabiximols
[5] https://www.nice.org.uk/

CBD in pet food and pet products

18. Pet food and pet products containing CBD or CBD oil would be considered to be veterinary medicines and thus would require licensing. There are currently no CBD products licensed for veterinary use, but a veterinary surgeon could prescribe a legally obtained human product for use under the provisions of the prescribing cascade.

Introduction

19. A cannabinoid is one of a class of diverse chemical compounds that acts on cannabinoid receptors known as the endocannabinoid system in cells that alter neurotransmitter release in the brain.

20. Cannabinoids can be phytocannabinoids which occur naturally in the *Cannabis* plant (*Cannabis Sativa*) and some other plants; and synthetic cannabinoids, manufactured artificially.

21. At least 113 different cannabinoids have been isolated from the *Cannabis* plant. Some of the most studied cannabinoids include tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN).

22. CBD is a type of cannabinoid found in the *Cannabis* plant which was discovered in 1940 by Roger Adams (Adams *et al*., 1940).

Cannabis

23. Cannabis is an annual, dioecious, flowering herb. The leaves are palmately compound or digitate, with serrate leaflets (Hammond and Mahlberg 1973).

24. Cannabis is in the *Cannabaceae* family (Stearn, 1978). The number of species within the genus is disputed, however, three main species are recognized: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.

25. *Cannabis sativa* is an annual herbaceous flowering plant indigenous to eastern Asia but now of cosmopolitan distribution due to widespread cultivation (Potter, 2013). The word "sativa" means things that are cultivated. The species was first classified by Carl Linnaeus in 1753 and published in *Species Plantarum 2* (1753). *Cannabis sativa* is the most commonly grown variety of cannabis with both marijuana and hemp being derived from this strain.

26. *Cannabis indica*, is an annual plant in the *Cannabaceae* family originating from the Indian subcontinent. It is said that this subspecies of the cannabis plant can tolerate colder weather conditions across the Indo-Gangetic Plain. This is because of the often harsh and variable (extremely cold winters, and warm summers) climate of those parts, *C. indica* is well-suited for cultivation in temperate climates.

27. *Cannabis ruderalis* is a plant native to Central and Eastern Europe and Russia. Many scholars accept *Cannabis ruderalis* as its own species due to its

unique traits and phenotypes which distinguish it from *Cannabis indica* and *Cannabis sativa*; however, it is widely debated as to whether or not ruderalis is a sub-species of *Cannabis sativa*. It is considered to have a low-THC content.

28. Cannabis has been used as a source of industrial fibre, seed oil, food, recreation, religious and spiritual moods as well as medicinal purposes. Each part of the plant is harvested differently, depending on the purpose of its use (Andre *et al*., 2016).

29. The main psychoactive component of cannabis is THC, one of 483 known compounds in the plant including at least 65 cannabinoids.

30. It is believed that when THC enters the blood stream and reaches the brain, it binds to cannabinoid receptors. The endogenous ligand of these receptors is anandamide[6], the effects of which THC emulates. This agonism of the cannabinoid receptors results in changes in the levels of various neurotransmitters, especially dopamine and norepinephrine; neurotransmitters which are closely associated with the acute effects of cannabis ingestion, such as euphoria and anxiety.

31. There are two major strains of cannabis: marijuana and hemp (Figure 1). The major difference between them is that hemp plants contain no more than 0.3% (by dry weight) of THC whereas marijuana typically contains 5 to 30 % THC. The difference in THC content is why marijuana is considered psychoactive and hemp is considered non-psychoactive.

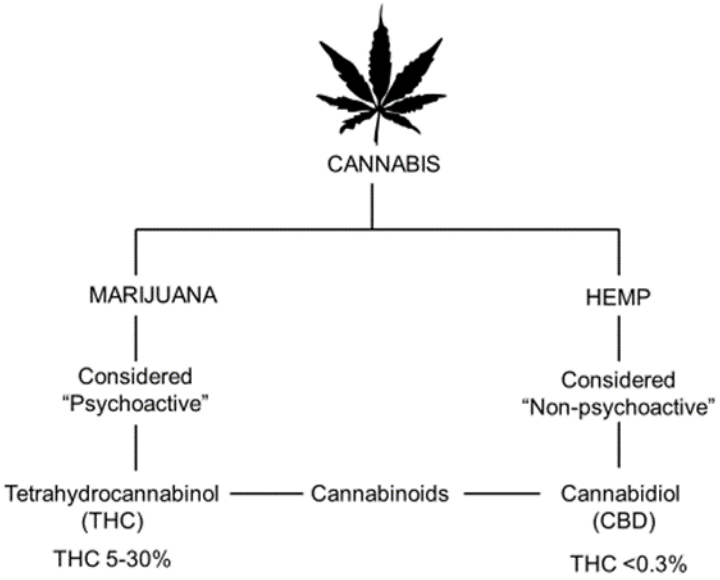

Figure 1. Flow diagram showing the differences of marijuana and hemp. The difference is that hemp plants contain no more than 0.3% (by dry weight) of THC. In contrast, marijuana typically contains 5 to 30 % THC.

[6] Anandamide: a fatty acid neurotransmitter derived from the non-oxidative metabolism of eicosatetraenoic acid, an essential ω-6 polyunsaturated fatty acid. The name is taken from the Sanskrit word ananda, which means "joy, bliss, delight", and amide.

Marijuana

32. Marijuana is a psychoactive variety of the *Cannabis* plant used for medical or recreational purposes. It is bred for its trans-delta-9-tetrahydrocannabinol (Δ9-THC) content in the female flowers (Nissen *et al*., 2018).

33. It is considered to be highly psychoactive with psychoactivity increasing in recent years due to breeding hybrid programs increasing the THC percentage ranging from 5-30% (De Meijer *et al*., 2014).

Hemp

34. Hemp is a strain of *Cannabis sativa* typically found in the northern hemisphere (Central North-East Asia) that contains less than 0.3% or less THC content by dry weight (Nissen *et al*., 2010).

35. Hemp stems consist of two main parts − the bast fibres[7] (35%) having a high cellulose content (57–77%) and low lignin[8] content (5–9%) and the woody core also known as shiv (65%), which has lower amounts of cellulose (40–48%) and a higher lignin content (21–24%) (Rehman *et al*., 2013).

36. Industrial hemp has been bred for high fibre content in the stem or for seeds (Nissen *et al*., 2010) and for minimal amounts of Δ9-THC (0.2% w/v), approximately 50 times less than that found in marijuana (Nissen *et al*., 2010).

37. In recent years there has been renewed interest in hemp cultivation in several European countries (Italy, Spain, Germany, Netherlands, United Kingdom and France) as well as other parts of the world including the USA (Ranalli and Venturi, 2004).

Uses of industrial hemp

38. Accordingly the Federation of American Scientists, hemp has more than 25,000 different uses[9]. It is grown for various industries and used in many commercial applications including textiles (clothing, shoes, rope, netting); building materials (oil paints, printing inks, fuel, solvents, coatings, insulation, hempcrete); body care (soaps, shampoos, lotions, balms, cosmetics); food/beverages and veterinary products (pet treats).

Cannabinoids

39. At least 113 different cannabinoids have been isolated from the *Cannabis* plant. Some of the most studied cannabinoids include tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN).

[7] Bast fibres: fibrous material from a plant, in particular the inner bark of a tree such as the lime, used as fibre in matting, cord, etc.
[8] Lignin: a class of complex organic polymers that form key structural materials in the support tissues of vascular plants and some algae.
[9] https://fas.org/sgp/crs/misc/RL32725.pdf

Tetrahydrocannabinol

40. THC is well known for its psychotropic properties.

41. THC is made up of 21 carbon, 30 hydrogen atoms and 2 oxygen atoms (Figure 2) and has a chemical formula of $C_{21}H_{30}O_2$. It has molecular weight of 314.469 g/mol.

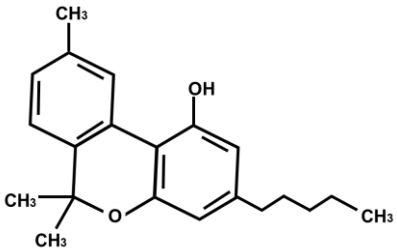

Figure 2. Chemical structure of THC

42. THC is thought to be part of the plants self-defence system against environmental stress and predation (Pate, 1994, Pate, 1983, Lydon *et al*., 1987).

Cannabidiol

43. Cannabidiol (CBD) is a cannabinoid discovered in 1940.

44. Cannabidiol is made up of 21 carbon, 30 hydrogen atoms and 2 oxygen atoms (Figure 3). CBD has a chemical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.469 g/mol.

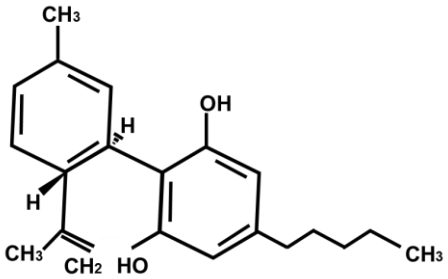

Figure 3. Chemical structure of CBD

45. Cannabidiol constitutes up to 40% of the extracts of the Cannabis sativa plant (Grlie, L., 1976). This varies with growing conditions. It was first isolated by Adams *et al* in 1940 and the structure was identified 23 years later.

Cannabinol

46. Cannabinol (CBN) is a mildly psychoactive cannabinoid found only in trace amounts in *Cannabis* (Karniol *et al*., 1975) and is mostly found in aged *Cannabis* plant.

47. Pharmacologically relevant quantities are formed as a metabolite of THC (McCallum *et al*., 1975).

48. CBN is made up of 21 carbon, 26 hydrogen atoms and 2 oxygen atoms and has a chemical formula of $C_{21}H_{26}O_2$. It has molecular weight of 310.4319 g/mol.

Cannabigerol

49. Cannabigerol (CBG) is the non-acidic form of cannabigerolic acid, the parent molecule from which other cannabinoids are derived. CBG is a minor constituent of cannabis.

Other cannabinoids

50. Other cannabinoids include: tetrahydrocannabivarin (THCV), cannabichromene (CBC), and their respective acids tetrahydrocannabinol acid (THCA), cannabidiol acid (CBDA), cannabigerol acid (CBGA), tetrahydrocannabivarin acid (THCVA), and delta-8 tetrahydrocannabinol (delta-8-THC), cannabidivarin (CBGV) and cannabinovarin (CBNV) (Andre *et al*., 2016).

51. The ratio between delta-9-THC and other cannabinoids, such as CBN and CBD can be used for the classification of hemp plants into “drug material” and “non-drug material” (de Meijer *et al*., 1992; Lachenmeier *et al*., 2004).

Other constituents in hemp

Terpenes

52. Terpenes are a large and diverse class of organic compounds, produced by a variety of plants. Some of the terpenes found in oils in cannabis plants are myrcene, limonene, caryophyllene, pinene, humulene and linalool. In nature, these act as fungicides, antibacterial, discourage animals from eating the plant as well as for protection and communication (Andre *et al*., 2016).

53. It has been suggested that the terpenes fingerprint may serve as an indicator of the quality of hemp varieties, while the lipid oxidation products profile could contribute in evaluation of the stability of the oil used as milieu for CBD rich extracts (Pavlovic *et al*., 2018).

Flavours

54. Notable flavour notes in the terpenes of cannabis (Beal, 2019):

Myrcene – mango, lemongrass, thyme, hops
Limonene – fruit rinds, rosemary, juniper, peppermint
Linalool – lavender, bay, basil
Caryophyllene – black pepper, cloves, cinnamon, caraway
Pinene – pine needles, rosemary, basil, parsley, dill
Humulene – hops, coriander, cloves, basil
Terpinolene – nutmeg, tea tree, conifers, apples, cumin, lilac
Ocimene – mint, parsley, basil, mangoes, orchids, kumquats

Methods of manufacturing

55. There are various ways of manufacturing CBD which are listed below, these include: Liquid solvents and supercritical carbon dioxide (CO_2) extraction. As the methodology will vary, so may the composition of the products and extracts. This in turn should be taken into consideration in the risk assessment of the CBD products. Methods of manufacture have been briefly summarised below.

Liquid Solvents

56. This is the most common method of extraction as it is low cost. In this method, plant material including flowers is trimmed into a container. A liquid solvent (usually alcohols (isopropyl alcohol, ethanol) and non-polar hydrocarbons (butane, hexane) is pumped through the plant matter to strip it of cannabinoids/terpenes.

57. The remaining solvent is removed either by evaporation in open systems or under vacuum in closed systems to leave a concentrate of oil (Beal, 2019). The inability to completely remove the solvents from the product due to azeotrope formation, where the boiling point of the desired product is too close to that of the solvent, makes complete solvent removal impossible in some cases.

58. The oil that remains after the solvent has been removed contains plant lipids, waxes, fats, terpenes and cannabinoids including CBD. Additional processing to remove the plant lipids and waxes is necessary to produce a more desirable extract product. A process called winterization is applied to remove these plant lipids, fats and waxes. Winterization involves dissolving the extract into ethanol and cooling to -20°C at which point these undesirable components precipitate and can be filtered out.

Supercritical fluid extraction (SFE)

59. SFE is a technology used in for large scale extraction of essential oils and a range of bioactive components from vegetable matrices (Reverchon *et al*., 2006, Attard *et al*., 2018).

CO_2 Extraction (super critical CO_2 ($scCO_2$)

60. The advantages of using scCO2 as a solvent are simple operating conditions and low environmental impact. The extraction can be partially controlled by small variations in the working temperature and/or pressure.

61. During the decompression process the extract becomes solvent-free (Grijo *et al*., 2019). It is usually done with a piece of equipment called a ‘closed-loop extractor’. This consists of a series of three chambers: the first chamber holds solid dry pressurised CO_2 (commonly known as ‘dry ice’) (Fig.4A), the second chamber contains dry plant material (Fig.4B) and the third chamber separates the finished product (Fig.4C).

62. When performing the extraction, the solid CO_2 from the first chamber is pumped into the second with the plant material. This second chamber is kept at a

specific pressure and temperature which causes the CO_2 to behave more like a liquid also referred to as “supercritical CO_2”. This in turn runs through the plant material and extracts chemicals and flavours, much like in the liquid solvent process.

63. The CO_2-cannabinoid mixture is then pumped into a third chamber where it is kept at an even lower pressure and higher temperature so that the CO_2 gas rises to the top of the chamber while the oils containing chemicals and flavours from the plant material fall to the bottom to be collected for consumption.

64. The additional benefits of this method are that it doesn’t require a long evaporation process like a liquid solvent extraction and there is minimal risk of contaminants in the finished product.

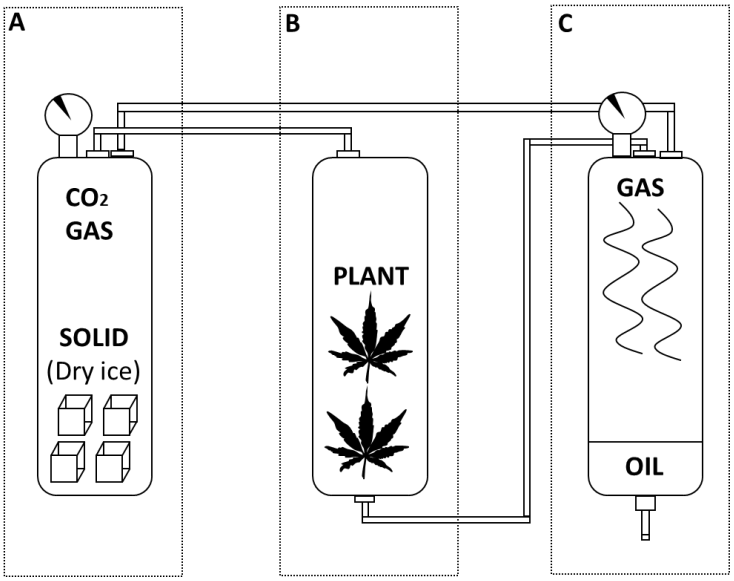

Figure 4. Supercritical fluid CO_2 extraction method A. solid dry pressurised CO_2 (commonly known as ‘dry ice’ B. dry plant material C. CO_2-cannabinoid mixture is then pumped into a third chamber where it is kept at an even lower pressure and higher temperature so that the CO_2 gas rises to the top of the chamber while the oils containing chemicals and flavours from the plant material fall to the bottom to be collected for consumption.

Oil Extraction

65. This extraction method is the oldest, inexpensive and usually uses olive oil.

66. The raw plant material must be decarboxylated first (or heated). Plant material is then added to olive oil and heated to 100°C for 1-2 hours to extract the cannabinoids.

67. With this method, the olive oil cannot be evaporated away after the process, so users must consume much higher quantities of this type of extracted oil than the highly-concentrated oil produced by other methods.

68. Infused olive oil is also highly perishable, and so must be stored in cold, dark place.

CBD NanoDelivery Technology

69. Some new CBD oils are now nano encapsulated for maximum uptake efficacy. This nano encapsulated CBD oil uses liposomes at the nano scale (<100nm) which are artificially constructed vesicles consisting of a phospholipid bilayer (Nakano *et al*., 2019).

70. This, in turn, will change the uptake and should be considered when evaluating dose and effect.

Usual testing for safety in CBD products

71. On the websites for some of the CBD products reviewed, it was stated that their product had gone through rigorous analytical testing claiming the following:

- Physical identity and foreign matter inspection
- Moisture determination
- Cannabinoid profiling and potency determination by high pressure liquid chromatography (HPLC)
- Aflatoxin B1, B2, G1 and G2 by HPLC
- Heavy metal elemental analysis
- Microbiological screening for moulds, certain bacteria, mycotoxins, and fungus
- Pesticide screening
- Residual solvents
- Terpene profiles
- Ingestion *vs* Inhalation
- Efficacy/Side effects/Safety
- Current uses for medicinal purposes
- Drug interactions as potential adverse effects
- Short term/ Long term effects

72. It is important to note, that in some CBD products cannabinoid profiling *i.e*. analytical data demonstrated other cannabinoids present.

Decarboxylation

73. Decarboxylation is an important step for efficient production of the major active components in cannabis: THC, CBD and CBG. These cannabinoids do not occur naturally in significant concentrations in cannabis but can be formed by decarboxylation of their corresponding acids, the predominant cannabinoids in the plant (Wang *et al*., 2016).

74. THC and CBD are derived from their acidic precursors THCA and CBDA. THCA and CBDA are both derived from cannabigerolic acid (CBGA). The final step differs, with THCA synthase and CBDA synthase producing THCA or CBDA,

respectively, from CBGA. Subsequent decarboxylation of THCA and CBDA via light exposure, heating, or aging, results in THC or CBD (Marks *et al*., 2009, Taura *et al*., 2007).

75. For the edible market (*i.e.* for CBD products intended to be consumed), decarboxylation conditions need to be closely controlled because if THC is exposed to intense heat it will oxidize producing CBN in the presence of oxygen and light.

Absorption Distribution Metabolism Excretion

Absorption

76. Due to its poor aqueous solubility, the absorption of CBD from the gastrointestinal tract is erratic, and the resulting pharmacokinetic profile is variable.

77. In human studies, when CBD was given at doses of 5, 10 and 20 mg/kg/d to children ages 4-10 with Dravet syndrome[10], dose proportional increases in area under the curve (AUC) plasma concentrations were produced for CBD and its metabolites (Devinsky *et al*., 2018).

78. In healthy male volunteers given 600 mg oral CBD, mean ± SD whole blood levels of CBD were 0.36 (0.64) ng/mL, 1.62 (2.98) ng/mL and 3.4 (6.42) ng/mL, respectively 1, 2 and 3 hours after administration (Santos *et al*., 2012).

79. In studies, it has been demonstrated that once orally consumed, after a significant first-pass effect, CBD bioavailability is 6% (Hawksworth *et al*., 2004) or between 13% and 19% (Grotenhermen, 2003). In contrast, intravenously administered CBD, which is lipophilic, quickly diffuses and easily crosses the blood–brain barrier (BBB), while in turn its elimination is prolonged (Grotenhermen, 2003).

Distribution

80. CBD is rapidly distributed into the tissues with a high volume of distribution of ~32 L/kg. Like THC, CBD may preferentially accumulate in adipose tissues due to its high lipophilicity (Fasinu *et al*., 2016, Ohlsson *et al*., 1986).

Metabolism

81. CBD is extensively metabolized by experimental animals and humans (Huestis, 2005). Metabolism of CBD is regulated by biotransformation routes usually observed for phytocannabinoids (Harvey & Mechoulam, 1990; Samara, Bialer, & Harvey, 1991), although several metabolic pathways have been described in different animal species and in humans.

82. Furthermore, CBD is subjected to multiple reactions including hydroxylation, oxidation to carboxylic acids, conjugation, epoxidation and beta-oxidation (Harvey & Mechoulam, 1990; Samara, Bialer, & Harvey, 1990a).

[10] Dravet syndrome: previously known as severe myoclonic epilepsy of infancy (SMEI), is a type of epilepsy with seizures that are often triggered by hot temperatures or fever.

83. CBD is extensively metabolised in the liver. The primary route is hydroxylation to 7-OH-CBD which is then metabolised further. A study in human liver microsomes (HLMs) demonstrated that CBD was metabolized by pooled HLMs to eight monohydroxylated metabolites. Seven recombinant human CYP enzymes were identified as capable of metabolising CBD: CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5. The two main isoforms involved are CYP3A4 and CYP2C19 (Jiang *et al*., 2011).

84. It has been demonstrated that CBD interferes with hepatic drug metabolism of some compounds (Samara, Brown, & Harvey, 1990) by inactivating cytochrome P450s of 3A and 2C subfamilies. Such interactions have to be considered in case of CBD co-administration with other drugs metabolized through these routes.

85. CBD has been demonstrated to inhibit the metabolism of THC and its primary metabolite 11- hydroxy- THC (Hollister *et al*., 1973)

Excretion

86. CBD in its free state and as its glucuronide are primarily excreted in urine and has a half-life of 9 h (Samara, Bialer, & Harvey, 1990b). The metabolites derived from 7-OH-CBD are excreted in faeces and urine (Hawksworth *et al*., 2004).

87. A single-dose pharmacokinetic study in beagle dogs using oral doses of 2 mg/kg/ and 8 mg/kg CBD, demonstrated that the CBD half-life of elimination median was 4.2 h (3.8–6.8 h). Median maximal concentration of CBD oil in serum were 102.3 ng/mL (60.7–132.0 ng/mL; 180 nM) and 590.8 ng/mL (389.5–904.5 ng/mL; 1.2 µM) respectively and was reached after 1.5 and 2 h. The AUC time 0-24 hours were 367 (183-437) ng-hr/mL at the 2mg/kg and 2,658 (1,753-3,048) ng-hr/mL at 8mg/kg (Wakshlag *et al*., 2018).

Pharmacodynamics

88. Across a range of measures in humans and animals, CBD had been shown to have very different effects from those of THC. In mice, CBD failed to produce the behavioural characteristics (*e.g.* suppression of locomotor activity, hypothermia, antinociception[11]) associated with CB1 activation, whereas THC generated all of the effects which occur when CB1 is activated (Pertwee *et al*., 2008, Long *et al*., 2010).

89. Neuroimaging studies in humans and animals have shown that CBD has effects which are generally opposite to those of THC (Batalla *et al*., 2014). In contrast to THC, CBD has no effect on heart rate or blood pressure under normal conditions, but in animal models of stress it reduces heart rate and blood pressure (Sultan *et al*., 2017).

90. CBD does not appear to act directly at CB1 receptors, with a number of studies reporting that there is no measurable response in binding assays. In studies examining potential agonist effects at CB1 receptors, most find no effect, with one

[11] Antinociception: Reduced sensitivity to pain.

report of a weak agonist and one of a weak antagonist effect, each at high concentrations (>10µM). CBD also shows low affinity at CB2 receptors (McPartland *et al*., 2015).

Therapeutic effects

91. CBD is a nonpsychotic constituent considered to have pharmacological actions such as anxiolytic[12], antipsychotic, antiemetic[13] and anti-inflammatory properties.

92. The effect of CBD has been investigated on a wide range of therapeutic and medical conditions of which some are briefly described below. Information from therapeutic studies has been included as it may be of relevance to the likely activity of CBD.

93. The available studies include but are not limited to: epilepsy (Maa 2014, Cilio *et al*., 2014), Parkinson's disease (Zuardi *et al*., 2009), schizophrenia (McGuire *et al*., 2017), anxiety disorder (Crippa *et al*., 2011, Blessing *et al*., 2015), Huntington's disease (Iuvone *et al*., 2009, Sagredo *et al*., 2011), hypoxia ischemia injury (Pazos *et al*., 2012, Hayakawa *et al*., 2007), pain (Crippa *et al*., 2015, Gomes *et al*., 2015), anxiety (Lemos *et al*., 2010, Almeida *et al*., 2013), depression (El-alfy *et al*., 2010, Hsiao *et al*., 2012, Shoval *et al*., 2016), cancer (Rocha *et al*., 2014, Ramer *et al*., 2014), nausea (Parker *et al*., 2002), inflammatory diseases (Ribeiro *et al*., 2012, Mecha *et al*., 2012), rheumatoid arthritis (Malfait *et al*., 2000), inflammatory bowel and Chron's diseases (Sacerdote *et al*., 2005, De Flilippis *et al*,. 2011), cardiovascular diseases (Durst *et al*., 2007, Booz 2011) and diabetic complications (Weiss *et al*., 2006, Rajesh *et al*., 2010).

94. Studies have shown that CBD and its precursor CBG can moderate or influence the psychoactive effects of Δ9-THC (Aizpurua-Olaizola *et al*., 2014, Solowij *et al*., 2014, Wang *et al*., 2016).

95. Biphasic effects of cannabinoids have been shown in processes such as feeding behaviour, motor activity, motivational processes and anxiety responses.

Anti seizure activity : Epilepsy

96. The clinical use of CBD is most advanced in the treatment of epilepsy. In clinical trials, CBD has been demonstrated as an effective treatment for at least some forms of epilepsy, with one pure CBD product (Epidiolex®[14]).

97. In June 2018, U.S. Food and Drug Administration (FDA) approved the first oral solution drug (Epidiolex®-a purified form of CBD oil) comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy[15].

[12] Anxiolytic: a medication or other intervention that inhibits anxiety.
[13] Antiemetic: a medication that is effective against vomiting and nausea.
[14] https://www.epidiolex.com/
[15] https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms

Specifically, for treating two types of epilepsy: Lennox-Gastaut syndrome[16] and Dravet syndrome[17].

98. Studies, such as Cunha *et al* (1980) have reported improvement in seizures in individuals treated with CBD oil.

99. There are over 549 registered CBD clinical trials on the USA National Institute of Health (NIH) National Library[18] which include healthy volunteers as well as humans with conditions. Of those, 274 are shown to be completed.

Anxiety and depression

100. CBD has attracted increasing interest as a potential anxiolytic treatment.

101. One preliminary study by Bermagamaschi *et al* (2011) aimed to compare the effects of a simulation public speaking test (SPST) on healthy control (HC) patients and treatment-naïve Social Anxiety Disorder (SAD) patients who received a single dose of CBD or placebo (corn oil). A total of 24 never-treated patients with SAD were allocated to receive either one dose of CBD (600 mg; n=12) or placebo (placebo; n=12) in a double-blind randomized design 90 mins before the test. The same number of HC (n=12) performed the SPST without receiving any medication. Each volunteer participated in only one experimental session in a double-blind procedure. Subjective ratings on the Visual Analogue Mood Scale (VAMS) and Negative Self-Statement scale (SSPS-N) and physiological measures (blood pressure, heart rate, and skin conductance) were measured at six different time points during the SPST. The results were submitted to a repeated-measures analysis of variance. Pre-treatment with CBD significantly reduced anxiety, cognitive impairment and discomfort in their speech performance, and significantly decreased alert in their anticipatory speech. The placebo group presented higher anxiety, cognitive impairment, discomfort, and alert levels when compared with the control group as assessed with the VAMS. The SSPS-N scores evidenced significant increases during the testing of placebo group that was almost abolished in the CBD group. No significant differences were observed between CBD and HC in SSPS-N scores or in the cognitive impairment, discomfort, and alert factors of VAMS. The increase in anxiety induced by the SPST on subjects with SAD was reduced with the use of CBD, resulting in a similar response as the HC. This study did not report any adverse reactions or toxicological effects results.

102. Another study investigated the effects of CBD patients with generalized social anxiety disorder (SAD) using functional neuroimaging. Regional cerebral blood flow (rCBF) at rest was measured twice using (99m) Tc-ECD SPECT in 10 treatment-naïve patients with SAD. In the first session, subjects were given an oral dose of CBD (400 mg) or placebo, in a double-blind procedure. In the second session, the same procedure was performed using the drug that had not been administered in the previous session. Within-subject between-condition rCBF comparisons were performed using statistical parametric mapping. Relative to placebo, CBD was

[16] Lennox–Gastaut syndrome (LGS): a complex, rare, and severe childhood-onset epilepsy.
[17] Dravet syndrome: previously known as severe myoclonic epilepsy of infancy (SMEI), is a type of epilepsy with seizures that are often triggered by hot temperatures or fever.
[18] https://clinicaltrials.gov/ct2/results?cond=&term=CBD&cntry=&state=&city=&dist

associated with significantly decreased subjective anxiety ($p < 0.001$), reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus ($p < 0.001$, uncorrected), and increased ECD uptake in the right posterior cingulate gyrus ($p < 0.001$, uncorrected). The authors suggested that CBD reduces anxiety in SAD and that this is related to its effects on activity in limbic and paralimbic brain areas (Crippa *et al*., 2010). This study did not report any adverse reactions or toxicological effects.

Alzheimer's disease

103. Inflammation and oxidative stress are crucial events in Alzheimer's pathophysiology (Candore *et al*., 2010).

104. CBD has been found *in vitro* to be neuroprotective (Esposito *et al*., 2006). CBD protected differentiated pheochromocytoma[19] PC12 cells from the damaging action of Aβ peptide, via a combination of its antioxidant, anti-apoptotic and anti-inflammatory properties (Esposito *et al*., 2006; De Filippis *et al*., 2008; De Filippis *et al*., 2011, Hayakawa *et al*., 2007). Survival of cultured neurons and attenuation of Aβ-induced molecular changes can be ascribed to CBD antioxidant effects (Iuvone *et al*., 2004) via mechanisms not displayed by classic antioxidant drugs (Esposito *et al*., 2006). CBD weakened Aβ-induced GSK-3β activation that has a crucial role in the WNT/β-catenin pathway, so being able to prevent tau protein[20] hyperphosphorylation and the following neurofibrillary tangle formation (Esposito *et al*., 2006).

105. CBD has been shown to reduce p38 mitogen activated protein kinase (MAPK) phosphorylation, so preventing NF-κB translocation into the nucleus and the consequent transcription of pro-inflammatory genes like inducible nitric oxide synthase (Esposito *et al*., 2006).

106. CBD also has exhibited beneficial effects also in a murine model of neuroinflammation induced by Aβ (1–42) fragment. In this model, CBD blocked reactive gliosis by reducing glia activation and the production of pro-inflammatory mediators (Esposito *et al*., 2007).

107. In a study using rat primary microglia and in N13 microglial cells, CBD reduced ATP-induced enhancement of intracellular calcium, through the involvement of cannabinoid and likely A(2A) adenosine receptors. In the same study, CBD administered for 3 weeks in Aβ-injected mice, increased cytokine gene expression and counteracted cognitive deficit (Martin Moreno *et al*., 2011).

108. In another study in APPxPS1 transgenic mice, the effects of CBD were examined on the cognitive impairments associated with Alzheimer's. Chronic CBD treatment reversed alterations in social recognition without affecting anxiety-related behaviours (Cheng *et al*., 2014). In the same model, the preventive properties of long-term CBD treatment were evaluated. The prevented social recognition impairment was not accompanied by modifications in oxidative damage or amyloid

[19] Pheochromocytoma: a rare tumour of adrenal gland tissue. It results in the release of too much epinephrine and norepinephrine, hormones that control heart rate, metabolism, and blood pressure.
[20] Tau protein: proteins that stabilize microtubules.

load. Moreover, an effect of CBD on dietary phytosterol retention, cholesterol, and neuroinflammation was described (Cheng *et al*., 2014).

Parkinson's disease

109. A neuroprotective effect exerted by CBD in an animal model of Parkinson was found. In these animals, 6-hydroxydopamine injections reduced, 2 weeks post-injection, dopamine contents and tyrosine hydroxylase (TH) activity in the caudate-putamen, and TH-mRNA levels in the substantia nigra[21]. Daily administration of CBD (3 mg/kg), during these two weeks post-lesion, attenuated the dopaminergic impairment, also causing a complete recovery of the control values in some cases, without inducing tolerance (Lastres-Becker, Molina-Holgado, Ramos, Mechoulam, & Fernández-Ruiz, 2005).

110. In a successive study, the same research group demonstrated that CBD was able to recover 6-hydroxydopamine-induced dopamine depletion only when it was administered immediately after the lesion and that its neuroprotective effect was related to a reduction of oxidative stress (García-Arencibia *et al*., 2007).

111. Only a few trials have been conducted on Parkinson's disease patients. In one of these, a double-blind trial was conducted on 21 patients, divided into 3 groups with seven participants each (Chagas *et al*., 2014). Patients received a placebo of corn oil or doses of CBD (75 mg/day or 300 mg/day) for 6 weeks. Significant improvements in measures of well-being of Parkinson's disease patients treated with CBD 300 mg/day, compared to the group that received placebo, were found; no statistically significant differences concerning the motor symptoms were highlighted.

Mechanism of Action

Endocannabinoids system

112. The endocannabinoid system (ECS) is a biological system composed of endocannabinoids, which are endogenous lipid-based retrograde neurotransmitters[22] that bind to cannabinoid receptors, and cannabinoid receptor proteins that are expressed throughout the vertebrate central nervous system (including the brain) and peripheral nervous system.

113. The ECS is involved in regulating a variety of physiological and cognitive processes including fertility (Klein *et al*., 2012) pregnancy (Wang *et al*., 2006) during pre and postnatal development (Fride, 2004) appetite, pain sensation, mood, memory, and is believed to be involved in mediating the pharmacological effects of cannabis (Donvito *et al*., 2018).

114. The ECS is also involved in mediating some of the physiological and cognitive effects of voluntary physical exercise in humans and other animals, such as contributing to exercise-induced euphoria as well as modulating locomotor activity

[21] The substantia nigra: a basal ganglia structure located in the midbrain that plays an important role in reward and movement.
[22] Retrograde signalling in biology is a process whereby the function of one part of a cell is controlled by feedback from another part of the cell, or where one cell sends reciprocal messages back to another cell that regulates it.

and motivational salience for rewards (Tantimonaco *et al*., 2014, Raichlen *et al*., 2012)

115. Endocannabinoids (eCBs) and their receptors are found throughout the human body: nervous system, internal organs, connective tissues, glands, and immune cells.

116. eCBs are endogenous lipid messengers that act on the same receptors that are activated by the active component of cannabis. The most well understood are anandamide and 2-arachidonoylglycerol (2-AG), the synthetic pathways of which have been elucidated. Other putative ligands include noladin[23] ether and virodhamine[24] (Piomelli *et al*., 2003).

117. Endocannabinoid signalling is attenuated by transport and hydrolysis. Transport of endocannabinoids into neurons is rapid and selective, although the transporter has not been identified and transport might be mediated by facilitated diffusion. Once inside cells, anandamide is broken down by fatty acid amide hydrolase, whereas 2-AG is hydrolysed by two less well-characterized enzymatic activities.

118. eCBs can also suppress the release of glutamate at excitatory synapses in the hippocampus, cerebellum and other brain areas, although the function of this suppression is unclear. Cannabinoid agonists also seem to influence the release of other neurotransmitters such as acetylcholine and amines (Piomelli *et al*., 2003).

CB1 and CB2 receptors

119. Two primary endocannabinoid receptors have been identified: cannabinoid type I (CB1) and cannabinoid type II (CB2). These are G protein coupled receptors, CB1 and CB2, which are highly expressed in the hippocampus and other parts of the central nervous system (Jones *et al*., 2010).

120. CB1 receptors are normally found in the central nervous system but can also be found in the pituitary gland, gastrointestinal system, reproductive system and immune system as well as peripheral tissues (Cacciola *et al*., 2010, Turu *et al*., 2010).

121. When activated, CB1 receptors inhibit synaptic transmission through action on voltage-gated calcium and potassium channels, which are known to modulate epilepsy and seizure activity (Falenski *et al*., 2009).

122. The cannabinoid receptor CB1 is the most abundant G-protein-coupled receptor in the brain and mediates most of the behavioural actions of cannabinoid drugs. The signalling events initiated by this receptor include closure of Ca^{2+} channels, opening of K^{+} channels, inhibition of adenylyl cyclase activity and stimulation of protein kinases. These signalling pathways can modulate synaptic communication and neuronal gene expression.

[23] Noladin: 2-Arachidonyl glyceryl ether is a putative endocannabinoid
[24] Virodhamine is an endocannabinoid and a non classic eicosanoid, derived from arachidonic acid.

123. CB1 receptors are expressed on many glutamatergic synapses that have been implicated in seizure threshold modulation (Reddy and Golub 2016). CBD may act at CB1 receptors to inhibit glutamate release by receptor interference. Studies have shown changes in the expression of CB1 receptors during epileptogenesis[25] and after recurrent seizures. CB1 receptor expression is upregulated at GABAergic synapses and shown to be downregulated at glutamatergic synapses in epilepsy, contributing to lowering seizure thresholds.

124. Other targets for CBD include transient receptor potential (TRP) channels that are involved with the modulation of intracellular calcium. Cannabinoids are highly lipophilic, allowing access to intracellular sites of action, resulting in increases in calcium in a variety of cell types including hippocampal neurons. CBD actions on calcium homeostasis may provide a basis for CBD neuroprotective properties.

CBD and THC competition

125. There is structural overlap between CBD and THC but the conformational structures differ significantly (Regio *et al*., 1995).

126. Whereas THC exists in an essentially planar conformation, CBD adopts a conformation in which the two rings are more or less at right angles to each other. This in turn means that CBD does not bind to or activate the CB1 receptor an action that THC is capable of doing. As a result, leads to a complete lack of psychoactivity by CBD unlike THC, which is the psychoactive principle of *Cannabis*. The basis of this is a so-called 'region of steric interference' on the CB1 receptor that allows THC to bind but interferes with CBD binding (Regio *et al*., 1993).

Entourage Effect

127. It has been demonstrated that endocannabinoid system established an "entourage effect" in which a variety of "inactive" metabolites and closely related molecules markedly increased the activity of the primary endogenous cannabinoids, anandamide and 2-arachidonoylglycerol (Ben-Shabat *et al*., 1998).

128. In animal studies of analgesia, pure CBD produces a biphasic dose-response curve such that smaller doses reduce pain responses until a peak is reached, after which further increases in dose are ineffective.

129. Therefore, it is postulated that CBD acts as an entourage molecule, reducing the collateral effects of delta-9-THC.

Toxicology

130. A comprehensive review by Bergamaschi *et al*. (2011) describes the safety profile of CBD. Some of the key *in vitro*/*in vivo* studies have been considered below. A more recent Huestis *et al* (2019) review also reported the effects described below in the *in vivo/in vitro* studies.

[25] Epileptogenesis: the gradual process by which a normal brain develops epilepsy.

Animal Studies

131. There are a number of mouse and rat studies using the intravenous (i.v) and intraperitoneal (i.p) route of CBD exposure which showed no significant effects on the following: weight gain, locomotor activity, blood glucose levels, catalepsy, antinociception, hypothermia, motor changes, gastrointestinal motility, blood pH, rectal temperature, blood pressure, cardiovascular parameters, respiratory parameters (Reidel *et al*., 2009, El-Remessy *et al*., 2006, Wiley *et al*., 2005, Zuardi *et al*., 1991, Varvel *et al*., 2006, Pertwee *et al*., 1972, Zanelati *et al*., 2010, Guimães *et al*., 1990, de Fillipis *et al*., 2008, Hayakawa *et al*., 2007, Hiltunen *et al*., 1998, Hampson *et al*., 2000, Resstel 2006, Shook *et al*., 1989, Graham *et al*., 1973). The doses used ranged from 1-100 mg/kg/bw.

In vivo animal studies

Animal Studies: Systematic Effects

Acute effects

132. In an early acute study, pure CBD (through aqueous emulsion) was injected into rhesus monkeys at doses of 150, 200, 225, 250, or 300 mg/kg bw i.v. One pair received the emulsion vehicle (sesame oil). Tremors were evident at all doses and the central nervous system inhibition progressed from sedation to prostration within 30 min. Convulsions and emesis[26] occurred at intermediate doses. Hyperpnoea[27] was observed at the lowest dose and hypopnoea at higher doses. Changes in rectal temperatures were of borderline significance but declined rapidly at higher doses. A dose and time related bradycardia occurred, which terminated in cardiac failure at the higher doses. Respiratory arrest and cardiac failure accounted for the death of the monkeys at doses above 200 mg/kg bw. After smaller doses, survivors recovered in one to three days and liver weights increased from 19 to 142%; no changes in liver weight were observed at 300 mg/kg bw, a dose that caused rapid death. There was a marked 57% decrease in relative testicular weight at 200 mg/kg bw and a 33% increase in ovarian weight at this same dose. The LD_{5O} for monkeys after exposure to CBD was estimated to be 212 mg/kg with 95% confidence limits of 199-225 mg/kg (Rosenkratz *et al*., 1981).

133. In a more recent CBD (powder and sunflower oil) acute 14-day repeated dose oral toxicity study (1000, 2000, and 4000 mg/kg bw/day) in healthy 49–52-day-old Hsd.Han Wistar rats showed mean body weight gain was statistically significantly decreased in all test groups compared to controls. The vehicle (sunflower oil) was used in the controls. Food consumption was statistically significantly reduced in animals of all test article groups throughout the study. Feed efficiency was also affected by treatment, with most animals experiencing a significant decrease; however, feed efficiency was not evaluated in some cases due to the body weight loss of the animals (Marx *et al*., 2018).

[26] Emesis: the action or process of vomiting.
[27] Hyperpnoea: increased depth and rate of breathing.

134. The main results showed statistically significant dose-related changes in the absolute and relative weights of liver, thymus, spleen, and adrenal glands at 1000, 2000, and 4000 mg/kg bw/day were noted. Histological examination of these organs revealed alveolar cytoplasmic vacuolation in the cortical zones of adrenal glands, cytoplasmic vacuolation of hepatocytes in the liver and of proximal convoluted tubules in the kidneys, accelerated involution of thymus, and lymphocyte depletion in the spleen (Marx *et al*., 2018).

Sub chronic effects

135. Four rhesus monkeys/sex/dose received oral treatment with pure CBD in sesame oil at doses of 30, 100, or 300 mg/kg bw daily for 90 days. One pair received the emulsion vehicle (sesame oil). Clinical measures, growth rates, rectal temperatures and electrocardiogram recordings were within normal limits. Significant changes were observed in organ relative weights (ratio to brain weight). Liver weights of both sexes increased 13 to 56% and kidney weights increased 16 to 22%. These increases were not strictly related to the dose administered. Heart weights increased 16 to 22% at the highest dose. A dose related decrease in testicular size was observed after 90 days. After a 30-day recovery interval, testicular size remained diminished. Inhibition of spermatogenesis occurred in all monkeys that received the highest dose of CBD (Rosenkratz *et al*., 1981).

136. A more recent 90-day repeated dose oral toxicity study was performed in rats using doses of CBD (powder and sunflower oil) at 100, 360, and 720 mg/kg bw/day, followed by a 28-day recovery period for two satellite groups. The vehicle (sunflower oil) was used in the controls. Significant decreases in body weight, body weight gain, and differences in various organ weights compared to controls were detected in males in the 360 and 720 mg/kg bw/day groups and in females in the 720 mg/kg bw/day group.

137. At the end of the recovery period, many of the findings were trending toward normal; thus, the changes appeared to be reversible. The no-observed-adverse-effect-level (NOAEL) for the hemp extract in Hsd.Han Wistar rats was considered by the authors to be 100 mg/kg bw/day for males and 360 mg/kg bw/day for females (Marx *et al*., 2018).

Animal Studies: Hepatoxicity

138. A recent study investigated the effects of CBD extract and hepatotoxicity in 8-week-old male B6C3F1 mice. Animals were gavaged with either 0, 246, 738, or 2460 mg/kg of CBD (acute toxicity, 24 h) or with daily doses of 0, 61.5, 184.5, or 615 mg/kg for 10 days (sub-acute toxicity). Sesame oil was used for controls. These doses were then allometrically scaled mouse equivalent doses (MED) of the maximum recommended human maintenance dose of CBD in Epidiolex® (20 mg/kg). In the acute study, significant increases in liver-to-body weight (LBW) ratios, plasma alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin were observed for the 2460 mg/kg dose. In the sub-acute study, 75% of mice gavaged with 615 mg/kg developed a moribund condition between days three and four. As in the acute phase, 615 mg/kg CBD increased LBW ratios, ALT, AST, and total bilirubin. Hepatotoxicity gene expression arrays revealed that CBD differentially

regulated more than 50 genes, many of which were linked to oxidative stress responses, lipid metabolism pathways and drug metabolizing enzymes (Ewing *et al*., 2019).

Animal Studies: Reproductive toxicity

139. The effects of repeated oral CBD (powder in sunflower oil) exposure on the male reproductive system was investigated in 21-day-old male Swiss mice at doses of 15 and 30 mg kg/day (CBD 15 and 30 groups, respectively), with a control group receiving sunflower oil, for 34 consecutive days. After a 35 day recovery period, the following parameters were evaluated: weight of reproductive organs, testosterone concentration, spermatogenesis, histomorphometry[28], daily sperm production and its morphology. The CBD 30 group had a 76% decrease in total circulating testosterone, but it remained within the physiological normal range (240–1100 ng dl^{-1}). CBD treatment induced a significant increase in the frequency of stages I–IV and V–VI of spermatogenesis, and a decrease in the frequency of stages VII–VIII and XII. A significant decrease in the number of Sertoli cells was observed only in the CBD 30 group. In both CBD groups the number of spermatozoa in the epididymis tail was reduced by 38%, sperm had head abnormalities, and cytoplasmic droplets were observed in the medial region of flagellum (Carvalho *et al*., 2018).

140. In another study by the same authors, 21-day old male Swiss mice were exposed to CBD (powder in sunflower oil) for 34 consecutive days at doses of either 15 or 30 mg/kg, and a control group received sunflower oil. Body weight gain and circulating progesterone concentration did not significantly change in CBD-treated animals. In the sexual behaviour analysis, the CBD 15 group presented a delay in performing the first mount and intromission, and a reduced number of mounts and ejaculations. The CBD 30 group showed a 30% reduction in fertility rate and a 23% reduction in the number of litters. The study said that the results indicated that chronic CBD exposure promotes functional impairment of the reproductive system of male Swiss mice (biphasic effects on male copulation) (Carvalho *et al*., 2018).

141. A 14-day repeated oral dose CBD extract study conducted in Wistar rats at 1000, 2000, and 4000 mg/kg bw/day (control group received sunflower oil) resulted in statistically significant, apparently dose-related changes in the absolute and relative weights of liver, thymus, spleen, and adrenal glands at 1000, 2000, or 3000/4000 mg/kg bw/day. Statistically significant absolute and relative changes in various other organ weights were noted in all dose groups. With regard to the male reproductive system, decreased amounts of (Grade 1) or lack of (Grade 2) secretion in the seminal vesicles or prostate and decreased average diameter of the tubules were observed; additionally, a lack of mature spermatozoa and spermatids was observed in a proportion of seminiferous tubules, indicating decreased intensity of spermatogenesis (Grade 1, 10–20%; Grade 2, 20–50%; Grade 3, 50–60%) in the testes observed at 3000/4000 mg/kg bw/day doses (Marx *et al*., 2018).

142. On the Epidiolex® safety data sheet it stated the following studies under pregnancy. As far as we are aware these have not been published and therefore no further details are currently available.

[28] Histomorphometry: measurement of the shape or form of a tissue. Quantitative analysis of bone architecture is achieved using bone histomorphometry which provides valuable information on the amount of bone and its cellular activity.

143. Oral administration of CBD (0, 75, 150, or 250 mg/kg/day) to pregnant rats throughout the period of organogenesis resulted in embryofetal mortality at the highest dose tested. There were no other drug-related maternal or developmental effects. The highest no-effect dose for embryofetal toxicity in rats was associated with maternal plasma cannabidiol exposures (AUC) approximately 16 times that in humans at the recommended human dose (RHD) of 20 mg/kg/day.

144. Oral administration of CBD (0, 50, 80, or 125 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in decreased fetal body weights and increased fetal structural variations at the highest dose tested, which was also associated with maternal toxicity. Maternal plasma cannabidiol exposures at the no-effect level for embryofetal developmental toxicity in rabbits were less than that in humans at the RHD.

145. When CBD (75, 150, or 250 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, decreased growth, delayed sexual maturation, neurobehavioral changes (decreased activity), and adverse effects on male reproductive organ development (small testes in adult offspring) and fertility were observed in the offspring at the mid and high dose. These effects occurred in the absence of maternal toxicity. The no-effect dose for pre-and postnatal developmental toxicity in rats was associated with maternal plasma cannabidiol exposures approximately 9 times that in humans at the RHD.

Genotoxicity and mutagenicity

In vitro

146. Marx *et al* (2018) found no evidence of genotoxicity in a bacterial reverse mutation test (Ames). In the experiment, no substantial increases in revertant colony numbers were observed in any of the five tester strains following treatment with the test article in the presence or absence of metabolic activation (S9) at any concentration level (5, 16, 50, 160, 500,1600, and 5000 µg/plate). Sporadic increases in revertant colony numbers compared to vehicle control were observed in both experiments, reflecting the biological variability of the applied test system; however, there was no tendency of dose related increases and mutation rates remained within the historical control data range.

147. CBD was found to induce DNA damage in single cell gel electrophoresis (SCGE) experiments in a human liver cell line (HepG2) and in buccal-derived cells (TR146) at low levels (≥ 0.2 µM). Results of micronucleus (MN) cytome assays showed that the damage leads to formation of micronuclei (MNi) which reflect chromosomal aberrations and leads to nuclear buds and bridges which are a consequence of gene amplifications and dicentric chromosomes. Additional experiments indicate that these effects are caused by oxidative base damage and that liver enzymes (S9) increase the genotoxic activity (Russo *et al*., 2019).

In vivo

148. Zimmerman and Raj (1980) tested CBD in mice (10 mg/kg (i.p) / dimethyl sulfoxide for controls) and found evidence for induction of MNi in bone marrow cells of mice, which are formed as a consequence of structural and numerical chromosomal aberrations in bone marrow cells. Furthermore, the same authors reported increased rates of chromosomal aberrations (CA) in the same target tissue by CBD (Zimmerman and Raj 1980). It has been stated that induction of MN and CA *in vivo* in bone marrow of mice, indicate that CBD is a potent mutagen (Russo *et al*., 2019).

149. No data from long-term carcinogenicity experiments with rodents are available at present.

In vitro studies: Effects on cells

150. The Bergamaschi review reported no significant effects on the following on cells: non transformed cells, embryonic development, porcine monoamine oxidase activity, no effects on luteinizing hormone excretion (Ligresti *et al*., 2006, Massi *et al*., 2006, Massi *et al*., 2008, Schurr *et al*., 1976, Steger *et al*., 1990).

151. In contrast there are a number of studies looking into the effects of CBD on cell viability, effects on CYP enzymes, cytokines and endocrine disrupting chemical effects as well as inhibiting both the activity and expression of the multidrug transporter, P-glycoprotein.

Cell viability

152. The induction of apoptosis by the cannabinoids has been demonstrated primarily in leukaemia, breast carcinoma, and glioma cells CBD induces ROS and concomitant activation of caspase-8 caspase-9 initiation (Wu *et al*., 2008).

153. Exposure of splenocytes to pure CBD (4–8 μM) elicited an early production of ROS with peak response at 1h post-CBD treatment and a parallel gradual decrease in cellular glutathione. In addition, CBD treatment (8 μM) significantly stimulated caspase-8 activation. Although it did not demonstrate a positive impact on reactive oxygen species (ROS) production, pre-treatment of splenocytes with a cell-permeable inhibitor for caspase-8 significantly attenuated CBD-mediated apoptosis in a concentration-dependent manner (Wu *et al*., 2008). In another study, it was further confirmed that pure CBD increases splenocyte apoptosis via ROS-dependent activation of caspase-8 (Lee *et al*., 2008).

154. This pro-apoptotic property induced by CBD in normal lymphocytes could contribute to the immunosuppressive effects (elucidated below) induced by this cannabinoid.

Effects in the Human Immune System Cells/Biphasic response

155. Scientific studies have demonstrated that CBD alters cytokines and has inhibitory capacities on cells of the human immune system.

156. CBD has a strong ability to inhibit the production of inflammatory cytokines, including IL-1β, IL-6, and interferon-β (IFN-β), in LPS-stimulated murine microglial cells (Kozela *et al*., 2010).

157. It is known that microglia act as primary responding cells or pathogen infection and injury, but a prolonged or excessive activation may result in pathological forms of inflammations that contribute to the progression of neurodegenerative (Parkinson's and Alzheimer's diseases, multiple sclerosis and HIV-associated dementia) and neoplastic diseases (Saijo & Glass, 2011).

158. CBD also decreased the transmigration of blood leukocytes by downregulating the expression of vascular cell adhesion molecule 1 (VCAM-1, vascular cell adhesion molecule-1) and chemokines (chemokine C-C motif ligand 2 (CCL2) and 5 (CCL5)), partially through Adenosine A2A receptors (Mecha *et al*., 2013). These actions resulted in an amelioration of motor deficits (Mecha *et al*., 2013), as well as of the severity of the clinical signs of autoimmune encephalomyelitis (EAE) in myelin oligodendrocyte glycoprotein injected mice, where CBD primary suppressed microglial activity and the proliferation of encephalitogenic T cells (Kozela *et al*., 2011).

159. CBD has been shown to exert an anti-inflammatory effect in the retina, as evidenced by decreased TNF-α secretion after LPS treatment (Liou *et al*., 2008); strongly inhibit IL-10 production by HUT-78 T-cells (Srivastava *et al*., 1998), increase IL8- macrophage inflammatory protein 1α (MIP-1α) and macrophage inflammatory protein 1β (MIP-1β) production in SRIS-EOSL cells (Srivastava *et al*., 1998). In the same study, CBD decreased production of IL-8 and CC chemokines (MIP-1α and MIP-1α) by B-cells (SRIH B (ATL) cells). Therefore, it is suggested a person of infection with human immunodeficiency virus – 1 (HIV-1) or other infectious organisms may increase, along with a risk of disease progression, tumour genesis, metastases, and even exacerbate allergic inflammation in the lung (Srivastava *et al*., 1998).

160. CBD has been shown to have biphasic responses. A study using CBD in human peripheral blood mononuclear cells showed an enhancement of mitogen induced indoleamine 2,3-dioxygenase activity and secretion of interferon (IFN)-γ by CBD (10-100 ng/ml) and suppression of these activities at higher doses (1-10 µg/ml) (Jenny *et al*., 2009).

161. CBD exhibited a generalized suppressive effect on T cell functional activities, via inducing CD11b(+) Gr-11(+) myeloid-derived suppressor cells (MDSC) (Hegde, Nagarkatti, & Nagarkatti, 2011; Hegde, Singh, Nagarkatti, & Nagarkatti, 2015); inducing a caspase 8-dependent apoptosis (Lee *et al*., 2008; Wu *et al*., 2008); inhibiting their proliferative potential (Kozela *et al*., 2011); reducing cytokine secretion including IL-17, a key autoimmune factor (Kozela *et al*., 2013, 2016); inducing anergy[29] (Kozela *et al*., 2015), and hampering antigen presentation and promoting T cell exhaustion/tolerance (Kozela *et al*., 2016).

[29] Anergy: absence of the normal immune response to a particular antigen or allergen.

162. In study using a murine model of lipopolysaccharide (LPS)-induced acute lung injury (ALI), CBD by enhancing the endogenous adenosine signalling, mainly through the inhibition of its uptake, potently reduced the inflammatory lung response in an adenosine A2A receptor-dependent manner (Ribeiro *et al*., 2012).

163. Later evidence by the same group showed that CBD was also able to decrease total lung resistance and elastance, neutrophils, macrophages and lymphocytes migration into the lungs, myeloperoxidase activity in tissue and the production of both pro-inflammatory cytokines tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and chemokines monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-2 (MIP-2) in the bronchoalveolar lavage supernatant (Ribeiro *et al*., 2015).

In vitro effects in reproductive cells

164. The progesterone 17alpha-hydroxylase activity, which is one of the steroidogenic enzymes in rat testis microsomes, was significantly inhibited at 1 mM of CBD (Watanabe *et al*., 2005). In this same study, testosterone metabolism decreased in rat liver microsomes.

165. Decreased steroid accumulation was also demonstrated in rat Graafian follicle[30] at 100-200 µM of CBD (Reich *et al*., 1982) as well as a decrease in ABCG2 activity in mouse embryonic fibroblasts (Holland *et al*., 2007). ABCG2 is a constitutively expressed ATP-binding cassette (ABC) transporter that protects many tissues against xenobiotic molecules. Its activity affects the pharmacokinetics of commonly used drugs and limits the delivery of therapeutics into tumour cells, thus contributing to multidrug resistance.

166. Suppression of follicular steroidogenesis (production of testosterone, progesterone and estradiol-17β) has been demonstrated *in vitro* at a wide range of CBD concentrations (100-200 µM). Luteinizing hormone-stimulated accumulation of progesterone and testosterone decreased, while oestradiol accumulation was only slightly affected. A probable mechanism is that cannabinoids modulate the release of cholesterol from its ester storage in lipid droplets and, thus, limit the availability of the substrate for steroidogenesis (Reich *et al*., 1982). Contradicting these results, no significant effect of CBD (0.1, 1 and 10 mg/kg bw) treatment was observed on luteinizing hormone levels, plasma follicle-stimulating hormone levels or testosterone levels in rats. None of the treatments altered rat luteinizing releasing hormone content. Moreover, CBD administration did not change luteinizing hormone secretion after *in vitro* luteinizing releasing hormone stimulation (Sterger *et al*., 1990).

167. The enzyme progesterone 17β-hydroxylase generates precursors for the synthesis of glucocorticoids and sex steroids. It was inhibited by a high concentration of CBD (1mM) but was not significantly affected at lower concentrations (100 µM), which can lead to time and concentration dependent inactivation. CBD treatment (10 and 120 mg/kg bw) in rats showed inhibition of hepatic testosterone hydroxylase (Narimatsu *et al*., 1990*,* Bornheim *et al*., 1990, Watanabe *et al*., 2005).

[30] Graafian follicle: a fluid-filled structure in the mammalian ovary within which an ovum develops prior to ovulation.

Human Studies

168. There are a number of human studies in the Bergamaschi review that reported no significant effect/side effects (including heart rate, blood pressure, psychological measurements, urine examinations) CBD dosing range from 5-1500 mg per person (Hollister *et al*., 1973, Crippa *et al*., 2011, Crippa *et al*., 2010, Fusar-Poli *et al*., 2009, Crippa *et al*., 2004, Zuardi *et al*., 1993, Consroe *et al*., 1979, Hallack *et al*., 2010, Mincis *et al*., 1973, Zuardi *et al*., 2006, Zuardi *et al*., 2010).

169. From the limited data available it appears that single doses of CBD between 20-1500 mg per person do not cause side effects and are considered to be well tolerated (Bergamaschi *et al*., 2011). However, there are limited/no long term data available.

Acute Studies

170. In the 1970s, human studies showed that single dose oral CBD (crystalline/powder) intake from 15 to 160 mg per person (Hollister, L.E., 1973; Carlini 1981), intravenous injection from 5 to 30 mg per person (Perez Reyes *et al*., 1972, Hollister 1973) were not followed by physiological ill effects.

171. In the Cunha *et al* study (1980) 8 healthy participants were given CBD (crystalline) (3 mg/kg bw daily for 30 days) with a control of another 8 volunteers receiving the same number of identical capsules containing glucose as placebo in a double-blind setting. Results reported that CBD was tolerated well, and no signs of toxicity or serious side effects were detected on examination.

172. Studies have shown that CBD does not interfere with several psychomotor and psychological functions in humans. A number of CBD studies reported no side effects at single doses of up to 600 mg per person including heart rate, blood pressure, or performance in the verbal paired-associate learning test as measured by recall score (Zuardi *et al*., 1982, Karniol *et al*., 1974, Bermaschi *et al*. 2011, Consoroe *et al*., 1979 Hallak *et al*., 2011, Hallack *et al*., 2010, Bhattacharyya *et al*., 2010).

Repeat dose studies

173. A pilot study reported that oral administration in healthy volunteers of 10 mg CBD extract daily for 21 days did not induce any changes in neurological (including electroencephalogram (EEG)), clinical (including electrocardiogram (ECG)), psychiatric, blood or urine examinations (Mincis *et al*., 1973).

174. In a double-blind procedure, 15 patients with “secondarily generalized epilepsy with temporal focus,” were randomly divided into two groups. Each patient received 200-300 mg daily of CBD (crystalline) or placebo (glucose) for up 135 days in combination with their existing prescribed antiepileptic medications (which were no longer effective in the control of their symptoms). Results demonstrated that CBD was well tolerated, and no signs of toxicity or serious side effects were detected on neurological and physical examinations, blood and urine analysis, or EKG and EEG, which were performed at weekly intervals (Cunha *et al*., 1980).

175. Furthermore, one study reported CBD (powder in sunflower oil) at an average daily dose of about 700 mg/day for 6 weeks was neither symptomatically effective nor toxic, relative to placebo (sunflower oil) (Consoroe *et al*., 1991).

CBD Drug Interactions

Effects on cytochrome p450

176. CBD is a potent inhibitor of hepatic drug metabolism and it has been shown that CBD interacts with drug metabolizing enzymes *i.e.* the cytochrome p450[31] family (Bih *et al*., 2015, Jones *et al*., 1972, Stout, 2014).

177. CBD is metabolized, among others, via the CYP3A4 enzyme. Various drugs such as ketoconazole, itraconazole, ritonavir and clarithromycin inhibit this enzyme (Apothekerverbände, 1986). This leads to slower CBD degradation and can consequently lead to higher CBD doses with longer pharmaceutical activity.

178. CBD can inactivate cytochrome P450s after acute administration and can also induce P450s after repeated use in mice. Bornheim and Correia (1989) showed that acute CBD treatment decreased the mouse hepatic cytochrome P450 content, while multiple CBD treatment regimens induced cytochrome P450s, which was indistinguishable from induction by phenobarbital, suggesting the involvement of the 2B subfamily (Comelli *et al*., 2008). Mice treated with CBD showed initial inactivation of P450s 3A and 2C, with a subsequent increase in mRNA encoding P450s 3A, 2C, and 2BlO after repeated administration (Bornheim *et al*., 1994).

179. Hexobarbital[32] is a CYP2C19 substrate, which is an enzyme that can be inhibited by CBD and can consequently increase hexobarbital availability in the organism (Karlgren and Bergström, 2015, Pelkonen *et al*., 1998). Studies also propose that this effect might be caused *in vivo* by one of the CBD metabolites (Ujváry and Hanuš 2016, Bornheim *et al*., 1994).

180. In another study, the enzymes CYP3A and CYP2B10 were induced after prolonged CBD administration in mice livers, as well as for human CYP1A1 (Ujváry and Hanuš 2016, Bornheim *et al*., 1994).

181. CBD can inactivate human P450 3A4 (Jaeger *et al*., 1996) which is responsible for metabolizing more than 60% of clinically prescribed drugs (Guengerich *et al*., 1995).

Effects on p glycoprotein activity and other drug transporters

182. P-glycoprotein (P-gp) is a protein that plays an important role in the disposition of many endogenous and exogenous compounds. P-gp is an ATP-dependent efflux transporter coded by the multidrug resistance 1 (MDR1) gene.

[31] Cytochromes P450: family of enzymes containing heme as a cofactor that function as monooxygenases. In mammals, these proteins oxidize steroids, fatty acids, and xenobiotics, and are important for the clearance of various compounds, as well as for hormone synthesis and breakdown
[32] Hexobarbital: barbiturate derivative having hypnotic and sedative effects.

Usually, P-gp activity is measured in the distal region of the small intestine where basal expression levels of this protein are higher than in other regions of the body. Human polymorphisms in the MDR1 gene can alter P-gp expression and function, yielding altered drug pharmacokinetics and pharmacodynamics. MDR1 polymorphisms are one of the primary mechanisms responsible for the low oral bioavailability and limited brain penetration of many therapeutic drugs (Zhu *et al*., 2006).

183. An *in vitro* P-gp activity assay was performed using different CBD concentrations (0.1, 1, 25, 50 and 100 µM). Depending on the P-gp substrates, CBD (3-100µM) exhibited potent inhibitory effects on P-gp efflux and on Pgp ATPase activity, leading to an increased intracellular accumulation of these substrates (Comelli *et al*., 2008, Zhu *et al*., 2006). One hour of CBD exposure did not inhibit P-gp activity in drug-selected human MDR leukaemia cells that over-expressed P-gp, but 3 days of repeat exposure to CBD decreased P-gp expression in these cell lines (Holland *et al*., 2006).

Interaction of cannabidiol and alcohol

184. There are already CBD consumer products on the market which are in alcoholic beverages such as beer and spirits. It is known from past research that alcohol *i.e.* ethanol and drugs can affect each other's absorption, distribution, metabolism and excretion. When ingested together, ethanol can increase drug absorption by enhancing the gastric solubility of drugs and by increasing gastrointestinal blood flow. However, high concentrations of ethanol induce gastric irritation causing a pyloric spasm which in turn may delay drug absorption and/or reduce bioavailability (Linnoila *et al*., 1979).

185. There are a very limited number of science studies on the interaction of cannabidiol and alcohol specifically the toxicokinetic interactions.

186. One of the more comprehensive studies involving humans used six male and four female healthy volunteers were given oral placebo (glucose capsule and orange juice), (CBD (powder) 200 mg capsule and orange juice), alcohol (1 g/kg in orange juice and glucose capsule), and CBD (200 mg capsule) plus alcohol (1 g/kg in orange juice) in a double-blind, crossover, randomized design. Treatments were spaced one week apart. Parameters measured were a finger tap test (motor performance), cancellation and differential aptitude tests (psychomotor performance), a 1 minute time production task, subjective effects (66 item adjective-pair semantic differential), and breathalyser estimations of blood alcohol levels. Compared to placebo, alcohol and alcohol plus CBD, but not CBD alone, produced significant impairments of motor and psychomotor performances, overestimations of time production and subjective responses indicating an accurate self-perception of their intoxication and deficits. The combination of alcohol plus CBD resulted in significantly lower blood alcohol levels compared to alcohol given alone, however, there were few differences observed between the pharmacological effects of the two alcohol conditions (Consroe *et al*., 1979).

Adverse Reactions

MHRA

187. The Medicines and Healthcare products Regulatory Agency has received some adverse reaction reports from CBD products through the yellow card scheme[33] which are described in Table 1.

Table 1: UK spontaneous suspected Adverse Drug Reaction reports associated with Cannabidiol received by the Yellow Card Scheme. Data Extract Date: 25.04.19

Case	Drug Name (Indication)	Drug Dose (mg)	Patient route of administration	Treatment duration (days)	Reaction(s) + Outcome(s)	Onset first dose (days)	Medical History	Year Received
1	Cannabis extract (CBD) (Skin disorder)		Oral	1	Irritability (Not recovered/not resolved), Rash (Not recovered/not resolved), Urticaria[34] (Not recovered/not resolved			2016
2	Cannabidiol	1	Oral	26	Deep vein thrombosis (Recovering/resolving), Off label use (Unknown)	25	Pregnancy, deep vein thrombosis	2017
3	Cannabidiol				Headache (Unknown), loss consciousness (Unknown)	0.3		2018
4	Cannabidiol Nicotinamide (Radiotherapy)	6000	Oral	18	Balance disorder (Recovered/resolved), Cold sweat (Recovered/resolved), Disorientation (Recovered/resolved), Drug interaction (Unknown), Malaise[35] (Recovered/resolved), Pallor[36] (Recovered/resolved), Somnolence[37] (Recovered/resolved)	1		2018
5	Cannabidiol		Oral		Alanine aminotransferase increased (Unknown)			2018
6	Cannabidiol (Arthralgia[38])		Oral		Alanine aminotransferase increased (Unknown)			2018
7	Cannabidiol (Fibromyalgia[39])		Inhalation		Asthma (Recovering/resolving), Chest pain (Recovering/resolving), Cough (Recovering/resolving), Dyspnoea[40] (Recovering/resolving)			
8	Cannabidiol (Abdominal pain)	2	Oral	1	Dyspnoea (Recovering/resolving), Palpitations (Recovering/resolving), Sinus tachycardia (Recovering/resolving)	1		2018
9	Cannabidiol				Diplopia[41]			2018
10	Cannabis extract (CBD)		Oral	14	Hypernatraemia[42] (Recovered/resolved)			2018

[33] https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/
[34] Urticaria: a rash of round, red welts on the skin that itch intensely, sometimes with dangerous swelling, caused by an allergic reaction, typically to specific foods
[35] Malaise: a general feeling of discomfort, illness, or unease whose exact cause is difficult to identify.
[36] Pallor: an unhealthy pale appearance.
[37] Somnolence (alternatively "sleepiness" or "drowsiness") is a state of strong desire for sleep, or sleeping for unusually long periods (compare hypersomnia)
[38] Arthralgia: pain in a joint.
[39] Fibromyalgia: a rheumatic condition characterized by muscular or musculoskeletal pain with stiffness and localized tenderness at specific points on the body.
[40] Dyspnoea: difficult or laboured breathing.
[41] Diplopia: technical term for double vision.
[42] Hypernatraemia: is a high concentration of sodium in the blood (exceeding 145 mmol/L).

11	Midazolam[43] Improvement CBD	2.5	Intravenous/Oral	1	Potentiating drug interaction (Recovered/resolved), Sedation complication (Recovered/resolved)	1		2018
12	Cannabidiol (Groin pain)		Oral		Hallucination, visual (Recovered/resolved)	1	Non-Hodgkin's lymphoma	2018
13	Cannabidiol (Complex regional pain syndrome)	3	Oral	5	Attention deficit/hyperactivity disorder (Recovering/resolving), Condition aggravated (Recovering/resolving)	1	Attention deficit/hyperactivity disorder	2018
14	Cannabidiol (Neuralgia)	1	Oral	19	Anxiety (Recovering/resolving), Dyspnoea (Recovering/resolving), Ear congestion (Recovering/resolving), Oropharyngeal pain (Unknown), Panic attack (Recovering/resolving), Respiratory tract congestion (Unknown)			2019
15	Cannabidiol				Liver function test abnormal (Not recovered/ not resolved)	1		2019
16	Cannabidiol (Epilepsy with myoclonic-atonic seizures) Clobazam	300	Oral	137	Abdominal pain (Recovering/resolving), Drug interaction (Unknown), Dystonia (Recovering/resolving), Hypotonia (Recovering/resolving), Somnolence (Not recovered/not resolved)	152	Seizure	2019
17	Cannabidiol (Fibromyalgia)		Oral		Muscle spasms (Not recovered/not resolved), Night sweats (Not recovered/not resolved)	1		2019
18	Provacan Cannabidiol (Massage, Osteoarthritis)		Topical/oral		Dyspepsia (Not recovered/not resolved), Insomnia (Not recovered/not resolved), Pruritus[44] (Not recovered/not resolved), Somnolence (Not recovered/not resolved)			2019
19	Celtic Wind Crops	500	Oral	1	Abdominal pain upper (Not recovered/not resolved), Asthenia[45] (Not recovered/not resolved), Decreased appetite (Recovering/resolving), Fatigue (Not recovered/not resolved), Feeling abnormal (Not recovered/not resolved), Feeling jittery (Not recovered/not resolved), Hypotension (Recovering/resolving), Mood altered (Not recovered/not resolved), Myalgia (Not recovered/not resolved), Nausea (Recovering/resolving), Night sweats (Unknown), Obsessive thoughts (Recovering/resolving), Panic attack (Not recovered/not resolved), Poor quality sleep (Not recovered/not resolved)	1		2019
20	Cannabis Extract (CBD)	3	Oral	31	Antipsychotic drug level increased (Recovered/resolved)	29		2019

Epidiolex

[43] Midazolam: marketed under the trade name Versed, among others, is a medication used for anaesthesia, procedural sedation, trouble sleeping, and severe agitation. It works by inducing sleepiness, decreasing anxiety, and causing a loss of ability to create new memories. It is also useful for the treatment of seizures
[44] Pruritus: severe itching of the skin, as a symptom of various ailments
[45] Asthenia: abnormal physical weakness or lack of energy.

188. On the Epidiolex® safety data sheet[46] for the USA the most common adverse reactions stated (10% or more for Epidiolex® and greater than placebo) are: somnolence; decreased appetite; diarrhoea; transaminase elevations (hepatocellular injury) fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor quality sleep; and infections. Some of the adverse reactions and experiment data will be briefly described below.

Hepatocellular Injury

189. Epidiolex® causes dose-related elevations of liver transaminases ALT and/or AST. In controlled studies for Lennox-Gastaut syndrome and Dravet syndrome, the incidence of ALT elevations above 3 times the upper limit of normal was 13% in Epidiolex®-treated patients compared with 1% in patients on placebo. Less than 1% of Epidiolex®-treated patients had ALT or AST levels greater than 20 times the ULN. There were cases of transaminase elevations associated with hospitalization in patients taking Epidiolex®. In clinical trials, serum transaminase elevations typically occurred in the first two months of treatment initiation; however, there were some cases observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate. Resolution of transaminase elevations occurred with discontinuation of Epidiolex® or reduction of Epidiolex® and/or concomitant valproate in about two-thirds of the cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with Epidiolex®, without dose reduction.

Somnolence and sedation

190. Epidiolex® can cause somnolence[47] and sedation. In controlled studies for Lennox-Gastaut syndrome and Dravet syndrome, the incidence of somnolence and sedation (including lethargy) was 32% in Epidiolex®-treated patients, compared with 11% in patients on placebo and was dose-related (34% of patients taking Epidiolex® 20 mg/kg/day, compared with 27% in patients taking Epidolex®10 mg/kg/day). The rate was higher in patients on concomitant clobazam (46% in Epidiolex®-treated patients taking clobazam compared with 16% in Epidiolex®-treated patients not on clobazam). In general, these effects were more common early in treatment and may diminish with continued treatment. Other central nervous system depressants, including alcohol, could potentiate the somnolence and sedation effect of Epidiolex®.

Suicidal behaviour and ideation

191. Antiepileptic drugs (AEDs) such as Epidiolex® has been shown to increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication.

192. It has been demonstrated that there are significant correlations between the decrease of tryptophan levels induced by CBD (Jenny *et al*., 2009) and the

[46] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[47] Somnolence: is a state of strong desire for sleep, or sleeping for unusually long periods (compare hypersomnia).

increased susceptibility of patients to mood disturbances and depression (Widner *et al*., 2002, Huang *et al*., 2002, Capuron *et al*., 2003).

Other studies demonstrating adverse reactions

193. An open label study was conducted by Devinsky *et al* (2016) consisting of 214 patients, aged 1–30 years, (with severe, intractable, childhood-onset, treatment-resistant epilepsy) who were receiving stable doses of antiepileptic drugs before study entry. Patients were given oral CBD, initially at 2–5 mg/kg per day, and then titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day, dependent on study site. Adverse events reported in more than 10% of patients were somnolence, decreased appetite, diarrhoea, fatigue, and convulsion. Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, of which 20 (12%) experienced severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]).

194. A study was conducted by Devinsky *et al* (2018) recently reported the results of a controlled trial of CBD treatment for Dravet syndrome. Human subjects were assigned to receive either CBD oral solution (20 mg per kilogram per day) or placebo. Adverse events that occurred more frequently in the CBD group than in the placebo group included diarrhoea (31% vs 10%), loss of appetite (28% vs 5%) and somnolence (36% vs 10%). Other adverse effects noticed were vomiting, fatigue, pyrexia[48] and abnormal results on liver-function tests. Adverse effects led to the withdrawal of eight patients in the cannabidiol group compared with one in the placebo group (Devinsky *et al*., 2018).

195. It has been suggested that some of the adverse effects of CBD observed in the clinical studies may relate to interactions with other antiepileptic drugs. For example, a recent study by Geffrey *et al* (2015) evaluated thirteen subjects with refractory epilepsy concomitantly taking clobazam and CBD. Nine of 13 subjects had a >50% decrease in seizures, corresponding to a responder rate of 70%. Side effects were reported in 10 (77%) of the 13 subjects but were alleviated with clobazam dose reduction. It was reported that all subjects tolerated CBD well.

196. In contrast, there have also been some negative reports regarding the effectiveness of CBD. In a trial reported in 1986, a dose of CBD of 200–300 mg/day for a month resulted in no significant differences between the treatment and placebo groups (Ames *et al*., 1986). Similarly, a 6 month double blind study administering CBD 100 mg 3 times each day did not result in any changes in seizure frequency or improvement in cognition or behaviour (Tumbly *et al*., 1990).

Conclusions

197. CBD products have entered the food sector and are available for consumption in products including beverages (beer, spirits, wine, coffee and soda style drinks), topicals (tinctures, drops, syrup, olive oils, oils) chewables (gum drops) and chocolate. These products are classified as novel foods which means there is no

[48] Pyrexia: raised body temperature; fever.

significant history of consumption and that they need to be authorised before being placed on the market. At present, there are no authorised novel foods. Novel food authorisation would require the products to have low/negligible levels of THC so that misuse of drugs legislation does not apply.

198. It is important to note that CBD products may vary in composition and might contain other cannabinoids such as THC depending on the extraction / manufacturing process.

199. In animals, the adverse effects of CBD included developmental toxicity, embryo-fetal mortality, spermatogenesis reduction, central nervous system inhibition and neurotoxicity, organ weight alterations, hepatocellular injuries, male reproductive system alterations, and hypotension, although at doses higher than recommended for human pharmacotherapies. Preliminary data sets suggest adverse reproductive effects.

200. There are limited data on genotoxicity, but micronuclei formation and chromosome aberrations have been reported *in vivo*.

201. Human CBD studies for epilepsy and psychiatric disorders reported CBD-induced drug-drug interactions, hepatic abnormalities, diarrhoea, fatigue, vomiting, and somnolence.

202. In contrast, other human trials of CBD have reported that CBD has been generally tolerated well, however the details were limited.

203. CBD is a potent inhibitor of hepatic drug metabolism and it has been shown that CBD interacts with drug metabolizing enzymes *i.e.* the cytochrome p450 family.

204. *In vitro* studies demonstrate effects on the immune system via cytokines and interacting with the cytochrome p450 family, therefore people already taking prescription drugs, in theory, may be at risk of competing for p450 enzymes of xenobiotics compounds.

205. The toxicity data available for CBD are limited, particularly long term data and for endpoints such as reproduction and genotoxicity/carcinogenicity. However, this is a very active research area and it is likely that more data will become available in the near future.

<u>Questions to be asked of the Committee:</u>

i). Do the Committee have any comments on the potential adverse effects of CBD?

ii) Do the Committee have any comments on the potential for drug interactions arising from CBD exposure?

iii). Do the Committee consider that there are toxicological data gaps? If so, what are the most important

iv). Do the Committee consider it would be prudent to treat CBD as an *in vivo* genotoxin based on the CA and MN?

v). Do the Committee have any comments on whether assessments can only be made on a specific product or whether they could be extrapolated between products?

vi). Do the Committee agree we should revisit this topic when more data become available?

vii). Do the Committee have any other comments on this paper?

Secretariat June 2019

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Abbreviations

AEDs	antiepileptic drugs
2-AG	2-arachidonoylglycerol
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the curve
BBB	blood–brain barrier
CA	chromosomal aberrations
CBD	cannabidiol
CBDA	cannabidiolic acid
CBN	cannabinol
CBG	cannabigerol
CB1	cannabinoid type I
CB2	cannabinoid type II
CBGA	cannabigerolic acid
CBGV	cannabidivarin
CBC	cannabichromene
COT	The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
CO_2	Carbon dioxide
CYP450	cytochrome p450
eCBs	endocannabinoids
EAE	encephalomyelitis
ECS	endocannabinoid system
EU	European Union
FDA	U.S. Food and Drug Administration
FSA	Food Standards Agency
HC	healthy control
HPLC	high pressure liquid chromatography
HLM	human liver microsome
HepG2	human liver cell line
HIV-1	human immunodeficiency virus – 1
IFN-β	interferon-β
IL-6	interleukin-6
(i.v.)	intravenous
(i.p)	intraperitoneal injection
LBW	liver-to-body weight
MAPK	mitogen activated protein kinase
MDR	multidrug resistance
MDSC	myeloid-derived suppressor cells
MCP-1	monocyte chemoattractant protein-1
MED	mouse equivalent doses
MHRA	Medicines and Healthcare products Regulatory Agency
NOAEL	no-observed-adverse-effect-level
RASFF	Rapid Alert System for Food and Feed
RHD	recommended human dose
ROS	reactive oxygen species
SAD	Social Anxiety Disorder

SFE	supercritical fluid extraction
SCGE	single cell gel electrophoresis
SPST	simulation public speaking test
SSPS-N	Negative Self-Statement scale
TH	tyrosine hydroxylase
THC	tetrahydrocannabinol
THCA	tetrahydrocannabinolic acid
THCV	tetrahydrocannabivarin
TNF-α	tumour necrosis factor-α
TRP	transient receptor potential
VAMS	Visual Analogue Mood Scale
VCAM-1	vascular cell adhesion molecule 1
WHO	World Health Organisation

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Legal status of CBD products

As discussed in this paper, numerous types of CBD products exist. These may be regulated in a number of different ways, for example, as medicines, novel foods or tobacco products (vapes). CBD products may also be regulated via misuse of drugs legislation. Thus, when considering the status of CBD products, account must be taken as to whether the product may be subject to other legal frameworks depending on the composition and nature of the product. If a product is considered to be a controlled substance or a medicine, it would be outside the definition of food and regulated by those regulatory frameworks.

Medicinal products

In the UK, there are a limited number of licensed medicinal products derived from or related to cannabis.

A cannabis-based product for medicinal use (CBPM) can be prescribed by a specialist prescriber to fulfil an unmet clinical need and this would be supplied as an unlicensed medicine (a 'Special') in line with the scheme which already exists for the supply of unlicensed medicines. The indications which have been identified for the administration of CBPMs are rare or severe forms of epilepsy or for adults with nausea or vomiting following chemotherapy. In both cases, prescriptions are rare and would only be considered if other treatments were unavailable or had not worked (NHS, 2019).

The CBD medicine Epidiolex®, which contains "pure'' CBD isolated from Cannabis, for children and adults with Lennox-Gastaut and Dravet syndromes, both rare forms of epilepsy. Epidiolex is currently going through the EU licensing system and is available from the manufacturer via a compassionate use programme. As noted above CBPMs can also be prescribed for rare epileptic conditions.

The medicinal product Nabilone, contains a synthetic, non-natural cannabinoid which mimics THC, is licensed to treat nausea and vomiting from chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Nabiximols (Sativex®) is licensed in the UK to treat MS-related muscle spasticity, but availability on the NHS is limited since it is not considered cost effective by NICE.

To obtain a Marketing Authorisation (Product Licence) as a medicine an applicant would need to demonstrate safety quality and efficacy for the product. Products are not permitted to make medicinal claims unless they are licensed. A product may also be considered medicinal by function meaning that it has a pharmacological effect.

Medicinal status is considered on a case-by-case basis for individual products and responsibility for the classification of medicinal products falls to the MHRA.

Foods and Novel foods

While a significant history of consumption exists for industrial hemp strains of *Cannabis sativa* (plants, seeds and oils with no or low cannabinol and cannabinin content), there is no such established history of use for selective extracts of CBD.

The European Commission, in consultation with all Member states, including the UK, confirmed that CBD oil products are considered to be novel foods, meaning that they require authorisation before they could be sold, unless a history of consumption can be demonstrated. This applies to CBD extracts, synthesised CBD and other related products. The manufacturers would be required to demonstrate safe consumption, meaning that it will be some years before they would legally be on the market.

Novel food authorisation would require the products to have low/negligible levels of THC so that misuse of drugs legislation does not apply.

Misuse of drugs legislation

The Home Office is responsible for the Misuse of Drugs Act 1971 and its associated regulations.

The cannabis plant as a whole is strictly controlled under the Misuse of Drugs Act 1971 (‘the 1971 Act’), although certain parts, when separated from the rest of the plant are not; these are:

a) Mature stalk or any such plant,
b) Fibre produced from mature stalk of any such plant and
c) Seed of any such plant.

Pure CBD would not be controlled by the Misuse of Drugs act. ‘CBD oil’ type products may be caught by misuse of drugs legislation if they contain more than 1 mg THC (or any other controlled cannabinoid) as a contaminant whether intentionally or unintentionally. In addition, the THC should not be easily recoverable, and the products should not have been designed with the intention of administering a controlled drug. Products containing less than 1 mg THC (or other controlled cannabinoid) could still be considered controlled drugs if they were not regulated by an equally rigorous alternative standard. See Home Office (2019) for a published explanation of this.

The CBD products are usually made from extracts of the parts of the plant where THC is also present, therefore it is possible that this cannabinoid constituent will also be present in CBD products, however, analytical data are not available to verify whether or not that is the case.

Other products

Vape products

Vape products are likely to be subject to regulation by other bodies such as the Home Office, MHRA or under specific regulations such as the tobacco regulations depending on their purpose and how they are being used.

Under the General Food Law (178/2002 EC) food is defined as anything that people consume that isn't one of the specifically identified product types that are exempted. For example, medicines and tobacco products fall outside the definition of a food as they are subject to other legal frameworks.

Pet food and pet products

Pet food and pet products containing CBD or CBD oil in would be considered to be veterinary medicines and thus would require licensing. There are currently no CBD products licensed for veterinary use, but a veterinary surgeon could prescribe a legally obtained human product for under the provisions of the prescribing cascade.

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