TOX/2020/23

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

Potential risks from use of topically applied CBD-containing cosmetic products

Background and Introduction

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. There are currently two medicinal products that contain CBD approved for use in the UK: Epidiolex; and Sativex.

2. Non-medical CBD-containing products have also become increasingly popular with products now available in the food sector, including: beverages (beer, spirits, wine, coffee and soda style drinks); oils (tinctures, drops, syrup, olive oils); chewables (gum drops); and chocolate. These products are classified as novel foods which means there is no significant history of consumption in the EU.

3. The FSA has recently announced that anyone wanting to market CBD containing food products must submit a "valid novel food authorisation" by the 31st of March 2021[1]. Only products that have completed this application will be able to remain on the market after this date.

4. In addition, the FSA advised those who are pregnant, breastfeeding or taking any medication not to consume CBD products. Healthy adults are advised to think carefully before taking CBD, and the FSA recommends no more than 70mg a day (about 28 drops of 5% CBD) unless under medical direction. This new precautionary advice was based on the recent assessment by the Committee on Toxicity (COT) (see draft position paper TOX/2020/22 for discussion at the present meeting).

5. There are a range of CBD products readily available on the market in the cosmetic sector for topical use. These include, but are not limited to; serums; creams; washes/rinse-off products (cleansers, shampoos, conditioners, body washes, masks); bath products (capsules, oils, tablets and salts); deodorants; balms; and toothpastes. These products may contribute to CBD exposure via dermal absorption.

6. This paper presents the available information on toxicokinetics following dermal exposure and relevant evidence on toxicity following dermal exposure for the Committee to assess the potential risks from dermal exposure to CBD.

[1] https://www.food.gov.uk/business-guidance/cannabidiol-cbd

Legal Status of CBD cosmetic products

Cosmetics regulation 1223/2009

7. The safety of cosmetic products in the UK is regulated by the EU Cosmetics Regulation 1223/2009 ("the Regulation") as adopted into UK law[2]. Narcotic substances, as listed in Tables I and II of the Single Convention on Narcotic Drugs (UN Drug Control Conventions, 1972) are prohibited in cosmetic products via entry 306 of Annex II to the Regulation.

8. Once specific criteria are met (see Annex A), plant-derived and synthetic CBD are not controlled under the Single Convention on Narcotic Drugs and may therefore be used in finished cosmetic products.

9. In accordance with the ban on animal testing of cosmetic products in the EU, there is little *in vivo* testing data available for cosmetic products.

10. The Office for Product Safety and Standards (OPSS), a departmental office of BEIS has policy responsibility for cosmetics safety. Enforcement in cases where cosmetic products are found to non-compliant and/or unsafe is conducted primarily by Local Authority Trading Standards.

UK Drugs Act and Regulations

11. Cannabis and cannabis resin, cannabinol and cannabinol derivatives are Class B drugs under the Misuse of Drugs Act 1971. Any preparations or product containing the above substances are also controlled as Class B drugs.

12. CBD is not controlled under the Misuse of Drugs Act of 1971.

Previous COT discussions and recommendations

13. The toxicity of oral CBD has been assessed in previous COT discussions. This paper focuses on the potential risks arising from dermal exposure to CBD originating from topically applied cosmetic products.

14. In July 2019, a scoping paper (TOX/2019/32) on the potential adverse effects of CBD products was presented to the COT. This is attached in Annex B.

15. Following this in January 2020, further discussion paper (TOX/2020/02) on CBD in food products was presented to the COT. This is attached in Annex C. With the cooperation of GW Pharmaceuticals (the manufacturers of Epidiolex®), the FSA

[2] Cosmetic products must comply with EU Regulation 1223/2009 which sets down rules on the safety of the products. These rules apply to any cosmetic product placed on the UK market after 1st July 2013, regardless of the place of manufacture. Under the Regulation, all cosmetic products and their formulas must be presented for inclusion on a European database. There are also strict controls on the number of ingredients and restrictions or percentage limits on the use of some specific ingredients, including the use of preservatives. There is also provision for the reporting of serious undesirable effects.

Secretariat was able to examine and discuss newly available clinical and non-clinical data on the medicinal form of CBD.

16. A draft position paper based on the COT's discussion of these papers is presented at this meeting (TOX/2020/22).

Absorption Distribution Metabolism Excretion

Absorption

17. Transdermal administration avoids the first-pass metabolism effect that is associated with the oral route and thus could increase CBD bioavailability compared to the oral route. However, other factors are likely to decrease absorption such as the possibility of local irritation and the low skin penetration of chemicals that are strongly lipophilic such as CBD, which is estimated to have a log K_{ow}/log P value of approximately 6 (DrugBank, 2020).

18. One of the ways that transdermal absorption can be improved is the addition of permeation enhancers, to increase the penetration of permeants by disrupting the skins outer layer i.e. the stratum corneum and increasing penetrant solubility. There are numerous well-known permeation enhancers used in cosmetics to facilitate dermal absorption as well as being included for other functions. For example, propylene glycol, ethanol and several essential oils e.g. eucalyptus and camphor are all known permeation enhancers and used regularly in cosmetics, including in CBD containing cosmetics (Lizelle *et al.,* 2011).

19. No formal studies of the pharmacokinetics of dermally applied CBD in humans have been identified in the published literature, including where CBD has been proposed for treatment of diseases.

20. The limited available animal studies investigating dermally applied CBD seem to demonstrate that, depending on concentration, formulation and application site, CBD can enter the systemic circulation via the transdermal route (Millar *et al*., 2018).

21. In many of the available animal studies investigating dermally applied CBD, either no pharmacokinetic parameters have been measured or they have not been reported on. However, the treatment of disease in these studies appears to indicate that dermal application of CBD is a viable and effective route of administration (Hammel *et al*., 2016; Lodzki *et al*., 2003; Giacoppo *et al*., 2015; Liput *et al*., 2013

22. The pharmacokinetics of CBD administered by 3 delivery methods (CBD infused transdermal cream, oral CBD infused oil and oral microencapsulated CBD oil beads) at 2 different doses were assessed in healthy dogs (Bartner *et al*., 2018). Dogs treated with CBD-infused transdermal cream (110 mg/mL) were given a total daily dose of either 150 mg or 300 mg applied to the pinnae. The 2 doses corresponded with approximately 10 mg/kg body weight per day or 20 mg/kg body weight per day. It is noted that no indication is made regarding the body surface area

(BSA) that the transdermal CBD cream was applied to. In the first part of this 2-part study, CBD pharmacokinetics were measured during the initial 12 h of dose administration. Blood sampling for CBD plasma concentrations (1.3 mL) occurred before CBD was administered (0 min) and at times 30, 60, 120, 240, 360, 480, 600, and 720 min, for a total of 9 sample points. In the second part of the study, all dogs continued receiving a total daily dose of either 75 mg or 150 mg of their respective delivery method, for a total of 6 wk. At 2, 4, and 6 weeks after the first dose, blood was collected for CBD plasma concentrations.

23. Although CBD content was not equal to 100% of its labelled dose, the variability was 6.4% for the CBD-infused transdermal cream. The formulation of the transdermal cream was not provided, so it is difficult to establish whether there was an effect of other chemicals present.

24. The median C_{max} and standard deviation at 75mg q12h and 150 mg q12h for the CBD-infused transdermal cream group was 74.3 ± 127.2 ng/mL and 277.6 ± 476.10 ng/mL, respectively. The AUC_{0-T} was shown to be 11.7 ± 18.9 min*mg/mL and 29.7 ± 29.6 min*mg/mL for the 75mg q12h and 150 mg q12h groups, respectively.

25. The pharmacokinetic analysis results for part 1 and part 2 of this study are presented in Annex D in Table D1 and Figure D1a, respectively. It is noted in the first part of the study, Figure D1b shows that at the 720 min time point with the 150 mg dose, where the plasma CBD levels for CBD infused oil and oral microencapsulated CBD oil beads appear to be in the elimination phase, the plasma levels for the transdermal CBD cream appear to still be rising. This finding was not seen with the 75 mg transdermal dose as seen in Figure D1c. This is a finding that is not reported by the authors and likely a finding that if the measurements had continued for a longer period of time would have impacted the AUC and led to the relative bioavailability of the transdermal cream being higher with the higher dose cream.

26. In a study by Hammel *et al*., the efficacy of transdermal CBD for the reduction in inflammation and pain in a rat arthritic knee joint model was investigated (Hammel *et al*., 2016). Different volumes of 1% and 10% CBD gels were applied to different skin surface areas to give doses of 0.6, 3.1, 6.2 and 62.3 mg/day, applications were made for 4 consecutive days. All gels, including vehicle controls, were prepared by weighing the desired amount of CBD and dissolving it in ethanol (72.5% w/w). Once dissolved, nanopure water was added followed by isopropyl myristate. Carbopol® 980 polymer was added (0.9% w/w) and the solution sonicated for 10 min to ensure complete incorporation of the Carbopol® 980

27. Measurement of plasma CBD concentration following transdermal absorption revealed linearity with 0.6-6.2 mg/day doses. After four consecutive days of treatment, plasma CBD concentrations in all rats were 3.8 ± 1.4 ng/mL (n = 9), 17.5 ± 4.4 ng/mL (n = 8), 33.3 ± 9.7 ng/mL (n = 8) and 1629.9 ± 379.0 ng/mL (n = 4) for the doses 0.6, 3.1,6.2 and 62.3 mg/day, respectively. See Table D2 in Annex D for further details. It was demonstrated that CBD plasma concentrations after the application of the 62.3 mg/day dose did not follow the linear pharmacokinetic profile.

28. The 10% gel was close to solubility saturation and may have an increased absorption rate compared to 1% formulations. The lack of increased outcome for this highest CBD concentration was potentially due to maximally activated CBD effects or capacity-limit absorption and metabolism. This would account for the flattened linear pharmacokinetic profile effect of the 62.3 mg/day dose.

29. A transdermal delivery system for CBD using ethosomal carriers was investigated in a mouse model for its anti-inflammatory effects (Lodzki *et al*., 2003). Ethosomal carriers are mainly composed of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatidic acid), with a high concentration of ethanol and water. They are shown to be very efficient at enhancing dermal and transdermal delivery of various chemicals. The CBD ethosome delivery system used in this study contained 3% w/w CBD and 40% w/w ethosome in a carbomer gel.

30. Upon dermal application of 6 mg of the ethosomal system to the abdomen, steady-state levels were reached at about 24 hours and lasted at least until the end of the experiment at 73 hours. The plasma concentration of CBD stabilized at a value of 0.67 µg/ml. The actual transdermal dose of CBD penetrating the skin *in vivo* after 12 and 72 hours of application was calculated to be 1.37 ± 0.72 mg (22.83 ± 12% of the initial dose) and 2.60 ± 0.79 mg (43.33 ± 13.16% of the initial dose), respectively. Details of this can be seen in Figure D2 in Annex D. Based on a mouse weight of 30 g, the internal CBD dose was considered to be 45.7 ± 24.3 mg/kg body weight after 12 hours and 86.7 ± 26.3 mg/kg after 72 hours of application. Furthermore, transdermal application of ethosomal CBD prevented the inflammation and oedema induced by sub-plantar injection of carrageenan in the same animal model.

31. The therapeutic effects of dermally applied CBD cream were investigated in a mouse model of experimental autoimmune encephalomyelitis (Giacoppo *et al*., 2015). Pure CBD was solubilised in propylene glycol and basic dense cream to form of concentration of 1% CBD. The cream was applied to both hind limbs of the mouse to cover an area roughly 1 cm^2 (average body surface area of a mouse is 70 cm^2).

32. The results of the *in vivo* experiment showed that the steady-state plasma concentration of CBD was 6.1 ± 1.9 ng/mL, which were attained at 14.9 ± 12.0 h (T_{lag}). The C_{max} was 8.3 ± 2.1 ng/mL and the T_{max} was 38.2 ± 18.9. Further details of this can be found in the full table of results in Table D3 in Annex D.

33. The transdermal delivery of CBD was investigated for its effect on alcohol-induced neurodegeneration in a rat model of alcohol use disorder (Liput *et al*., 2013). In this study, 1.0%, 2.5% and 5.0% CBD gels were evaluated for neuroprotection. The active and vehicle gels. were composed of ethanol, propylene glycol, sterile water, Transcutol®, preservatives and a crosslinked polyacrylate polymer adjusted to the appropriate pH with triethanolamine to provide suitable rheological properties and pH dependent CBD stability.

34. Treatment with the 5.0% CBD transdermal gel resulted in day 3 CBD plasma concentrations of approximately 100.0 ng/mL. Figures D3a and D3b in Annex D provide further detail on the plasma levels.

35. The bioavailability of CBD after nasal and transdermal application and the effect of permeation enhancers was investigated in Guinea pigs (Kalpana *et al*., 2010). The gel formulation for transdermal delivery was prepared by making a solution of 80:20 propylene glycol:nanopure water. CBD was weighed out and the appropriate volume of solution was calculated to give an 18 mg/mL solution. From this solution, 6% was removed and replaced with Transcutol HP for the enhancer study. Transcutol HP at 6% (v/v) was used because this concentration has been shown to enhance the steady-state flux of CBD by 2.41- fold *in vitro* as compared to that of CBD alone (Stinchcomb and Nalluri., 2005).

36. 500 µL of the CBD gel formulation with or without the enhancer, Transcutol HP, was applied on the dorsal region of the hairless guinea pigs on both sides, and a patch was placed over the solution for containment. Patches remained on the guinea pig for 48 hours and were then removed.

37. The $AUC_{0\text{-}48}$ was found to be 276 ± 93 ng/mL/h and 888 ± 419 ng/mL/h for the CBD only and CBD + Transcutol HP transdermal gels, respectively. The C_{max} was found to be 8.6 ± 2.5 ng/mL and 35.6 ± 11.6 ng/mL CBD only and CBD + Transcutol HP transdermal gels, respectively. Finally, the T_{max} was found to be 38.4 ± 19.2 hours for CBD alone and 31.2 ± 29.4 hours for CBD + Transcutol HP. These results can be seen in full in Table D4 and Figure D4 in Annex D

38. The *in vitro* skin permeation of the cannabinoids: CBD, 8-tetrahydrocannabinol (8-THC) and cannabinol (CBN) was investigated, (Stinchcomb *et al*., 2004). Flux, permeability, tissue concentration and lag times were measured in the diffusion experiments. A summary of these diffusion properties can be found in Table D5 in Annex D.

39. Tissue concentrations of 8-THC were significantly higher than for CBN. Lag times for CBD were significantly smaller than for CBN. The permeabilities of CBD and CBN were 10-fold higher than for 8-THC.

40. The absorption findings cited from the studies above are summarised in Table 1 below.

Table 1. Summary of absorption findings following dermal CBD application

CBD content/dose	**Cream/gel co-formulants**	**Species (application site)**	**AUC**	**C_{max}**	**Other**	**Bioavailability**	**Study**
10 mg/kg/bw **20 mg/kg/bw**	N/A	Dog (pinnae)	11.7 ± 18.9 min*µg/mL 29.7 ± 29.6 min* µg/mL	74.3 ± 127 ng/mL 277.6 ± 476 ng/mL	N/A	8.6% 9.9% (Relative bioavailability compared with -oral administration)	Bartner *et al.*, 2016 2018
0.6 mg/day **3.1 mg/day** **6.2 mg/day** **62.3 mg/day**	Ethanol, nanopure water,isopropyl myristate, sodium hydroxide.	Rat (back)	N/A	N/A	Plasma concentrations: 4.3 ± 2.6 ng/mL 18.8 ± 2.6 ng/mL 34.6 ± 11.0 ng/mL 1470.1 ± 260.7 ng/mL	N/A	Hammel *et al.*, 2016
6 mg/day	CBD ethosome delivery system used in this study contained 3% w/w CBD and 40% w/w ethosome in a carbomer gel	Mouse (abdomen)	N/A	N/A	Plasma concentrations After 12 hours: 1.37± 0.72 mg (22.83 ± 12% of the initial dose) After 72 hours: 2.60 ± 0.79 mg (43.33 ± 13.16% of the initial dose)	N/A	Lodzki *et al.*, 2003.

CBD content/dose	Cream/gel co-formulants	Species (application site)	AUC	C_{max}	Other	Bioavailability	Study
1% CBD Cream	Pure CBD solubilized in propylene glycol and basic dense cream O/A to a concentration of 1 % of CBD.	Mouse (both hind legs)	N/A	8.3 ± 2.1 ng/mL	Steady State plasma concentration: 6.1 ± 1.9 ng/mL attained at 14.9 ± 12.0 h (Tlag)(	N/A	Giacoppo, *et al* 2015
1% CBD gel **2.5% CBD gel** **5.0% CBD gel**	CBD formulated with ethanol, propylene glycol, sterile water, Transcutol®, preservatives and a crosslinked polyacrylate polymer.	Rats (Dorsal)	N/A	N/A	Plasma concentration: ~10 ng/mL ~45 ng/mL ~100 ng/mL	N/A	Liput *et al*., 2013
18 mg/mL CBD solution	CBD formulated in a solution of 80:20 propylene glycol:nanopure water, with Transcutol HP then added to 6% v/v.	Guinea Pigs (Dorsal)	AUC_{0-48} CBD only =276 ± 93 ng/mL/h CBD + Transcutol = 888 ± 419 ng/mL/h	CBD only = 8.6 ± 2.5 ng/mL CBD + Transcutol = 35.6 ± 11.6 ng/mL	T_{max}: CBD only = 38.4 ± 19.2 hours CBD + Transcutol = 31.2 ± 29.4 hours	N/A	Paudel *et al*., 2010.

Distribution

41. Little data has been identified on distribution following dermal application of CBD. Based on this lack of information, and the fact that CBD's behaviour once into the systemic circulation will be the similar regardless of administration route, generic findings on the distribution of CBD will be presented below. Unless specifically referenced these are taken from the previous COT discussion papers TOX/2019/32 and TOX/2020/02.

42. Cannabinoids, as a chemical class, rapidly distribute into well-vascularized organs (e.g. lung, heart, brain, liver) with subsequent equilibration into less vascularized tissue (Gaston and Friedman, 2017; Dinis-Oliveira, 2016; Hunt and Jones, 1980). Distribution may be affected by body size and composition, and disease states influencing the permeability of blood–tissue barriers.

43. CBD is rapidly distributed into the tissues with a high volume of distribution of approximately 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).

44. Following the transdermal application of CBD in mice, a significant accumulation of the drug was found in the skin and in the underlying muscle (Lozki *et al*., 2003).

Metabolism

45. As with distribution, studies investigating the metabolism of CBD following application to skin are limited. The findings presented are for the most part derived from alternative routes of exposure to CBD. Unless specifically referenced these are taken from the previous COT discussion papers TOX/2019/32 and TOX/2020/02.

46. 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).

47. The findings from the Epidiolex data package (see TOX/2020/02) showed the same mechanism of metabolism, where CBD is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms.

48. After repeat dosing, the active metabolite of CBD, 7-OH-CBD, has a 38% lower AUC than the parent drug. The 7-OH-CBD metabolite is converted to 7-COOH-CBD, which has an approximately 40-fold higher AUC than the parent drug. Based on preclinical models of seizure, the 7-OH-CBD metabolite is active; however, the 7-COOH-CBD metabolite is not active.

49. It has been demonstrated that CBD interferes with hepatic drug metabolism of some compounds 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 (Samara *et al*., 1990). CBD has been demonstrated to inhibit the metabolism of THC and its primary metabolite 11-hydroxy-THC (Hollister, 1973).

Excretion

50. Minimal literature is available on the mechanics of excretion following dermal CBD exposure. The information presented below outlines excretion behaviour following alternative routes of administration. Unless specifically referenced these are taken from the previous COT discussion papers TOX/2019/32 and TOX/2020/02.

51. In human studies 16% of total dose was excreted in urine within 72 hours, indicating that renal excretion is a minor route of excretion for CBD.

52. A large proportion of CBD was excreted unchanged in faeces. In humans, hepatic clearance is a major route of CBD metabolism. The mean oral clearance (CL/F) of CBD in healthy subjects ranged between 375 and 1909 L/h (fasted after a single dose of between 200-6000 mg)

53. Following a single oral dose of 14C-CBD at 5 mg/kg, radioactivity was excreted predominantly via the faecal route (84%) and smaller proportions of administered radioactivity recovered in the urine (8%). The total recovery after 168 hours was 94%.

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

55. 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 2 mg/kg and 2,658 (1,753-3,048) ng-hr/mL at 8 mg/kg (Wakshlag *et al*., 2018).

56. There are no human studies on excretion of CBD in breast milk. EMA Assessment Product report states that: Given that CBD is highly protein bound and will likely pass freely from plasma into milk.

Drug - Interactions

57. It has repeatedly been demonstrated that CBD is not only a substrate but also an inhibitor of CYP450 enzymes, and this, it could interfere with the metabolism of other xenobiotics including THC and medicine products (Istvan Ujvary and Lumır Hanus , 2016).

58. During a Phase I study with healthy male subjects, potential drug–drug interactions of THC/CBD oromucosal spray (Sativex, nabiximols) in combination of CYP450 inducers and inhibitors were assessed using various dose regimens (Stott *et al*., 2013).

59. The antibiotic rifampicin, an inducer of CYP3A4 involved in the metabolism of CBD, significantly reduced the peak plasma concentration of CBD, while the antifungal ketoconazole, a CYP3A4 inhibitor, nearly doubled the peak plasma concentration of CBD; however, the moderate CYP2C19 inhibitor omeprazole, a proton-pump inhibitor used to treat gastroesophageal reflux disease, did not significantly alter the pharmacokinetics of CBD. The presence and role of CBD metabolites in the observed drug interactions were not reported.

60. An 8-week trial studied the interaction of the anticonvulsant drug clobazam and CBD in 13 children with refractory epilepsy (Geffrey *et al*., 2015). It was observed that co-administration of the CBD increased clobazam plasma level by 60 – 80%, while the level of its active metabolite norclobazam increased by 500 ± 300%. This allowed the reduction of the initial average 1 mg/kg daily clobazam dose in most subjects thereby alleviating consequential side effects.

61. In the GW Pharmaceuticals submission of scientific data (see TOX/2020/02), a significant drug-drug interaction with warfarin was identified.

62. It was shown in healthy volunteers that CBD can cause potentially clinically significant CYP2C19 inhibition at doses as low as 1 mg/kg/day.

63. Prolonged CBD administration may induce specific CYP450 isoenzymes, as it has been shown in mouse liver CYP3A and CYP2B1096 (Bornheim *et al*., 1994) as well as for human CYP1A1 *in vitro* (Yamaori *et al*., 2015).

64. Also, 6a-OH-CBD, but not 6-oxo-CBD, was found to be an effective inducer of CYP2B10.96 The resorcinol moiety apparently plays a pivotal role in CYP450 induction (Bornheim *et al*., 1994).

65. The CYP450-mediated metabolism of anandamide *in vitro* by liver microsomes isolated from mice treated *ip* with 120 mg/kg CBD was shown to be inhibited, but the physiological significance of this finding has not been explored Bornheim *et al*., 1993.

66. Furthermore, CBD has been shown to interact *in vitro* with P-glycoprotein efflux transporters involved in multidrug resistance, and thus, it may affect the pharmacokinetics of anticancer drugs (Zhu *et al*., 2006; Holland *et al*., 2008; Arnold *et al* 2012).

67. CBD has also been showed to potentially impact the placental permeability in pregnant women who consume CBD-containing preparations following research *in vitro* (Feinshtein *et al*., 2013).

Pharmacodynamics

68. Generally, 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, reduced sensitivity to pain) associated with CB1 activation, whereas THC generated all of the effects which occur when CB1 is activated (Pertwee., 2008; Long *et al*., 2010).

69. 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).

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

71. In a transdermal CBD study, it was shown that transdermal and IP delivery of CBD produced similar magnitudes of neuroprotection in an ethanol induced neurodegeneration rat model (Liput *et al.,* 2013). It is postulated in this study that the neuroprotection observed following transdermal and IP CBD are possibly mediated through different mechanisms. It is possible that CBD plasma concentrations achieved following transdermal delivery are conducive to receptor mediated (possibly 5-HT_{1A}) neuroprotection, while higher IP doses, although out of range for receptor mediated, have effects primarily through antioxidant effects. Alternatively, the neuroprotection observed following transdermal CBD and IP CBD could be related to the different pharmacokinetic profiles expected following each route of administration. This paper also noted a study which found that C_{max} and AUC in the brain was higher following oral administration compared to IP, suggesting that different routes of administration and their resulting pharmacokinetic profiles may affect CBD accumulation in the brain (Deiana *et al*., 2012). Therefore, an alternative interpretation to explain the similar magnitudes of neuroprotection following transdermal and IP administration of CBD could be that transdermal administration at these doses optimizes brain distribution of CBD.

72. *In vitro* studies in human sebocytes, sebum-producing epithelial cells, have shown CBD (10 μM), was found to exert complex anti-acne effects by normalizing several pro-acne agents-induced excessive sebaceous lipogenesis (SLG), and by exerting anti-proliferative and anti-inflammatory actions, without influencing homeostatic SLG or viability of human sebocytes (Olad *et al*., 2014). The lipostatic and anti-proliferative effects were found to be mediated by the TRPV4 →[Ca2+]IC↑ → ERK1/2 MAPK↓ and nuclear receptor interacting protein 1 (NRIP1, a.k.a. RIP140)↓ signaling pathway, whereas the anti-inflammatory actions were coupled to

the (most likely indirect) activation of the adenosine A2A receptor → cAMP↑ → tribbles homolog 3 (TRIB3)↑ → p65-NF-κB↓ pathway.

Therapeutic effects

73. The theorised potential therapeutic effects of dermally applied CBD are broad ranging.

74. Zynerba® Pharmaceuticals is developing a CBD gel (ZYN002) that is designed for transdermal use. The target indications for ZYN002 are Fragile X syndrome (FXS), adult refractory focal epilepsy and encephalopathies that are developmental and epileptic in nature. This formulation is currently in open-label Phase 2 testing for FXS. Dosing recommendations are to begin at 50 mg/day with increases up to 250 mg/day (Zynerba., 2020; Heussler *et al*., 2019).

75. CBD was investigated for its potential for the treatment of Acne Vulgaris in a clinical trial (Spleman *et al*., et al 2018). A pure synthetic form of CBD was manufactured for topical delivery and formulated in a novel, simple, proprietary formulation known as PermetrexTM. A completed Phase 1 study in 20 healthy volunteers demonstrated that a 5% formulation of CBD (BTX 1503) applied twice daily was well tolerated. Preliminary results show that 5% BTX 1503 is safe and well tolerated and activity in acne has been observed.

76. Table D6 in Annex D shows the in-development forms of cannabinoids for potential inflammation and pain treatment and their delivery systems (Bruni *et al*., 2018).

77. Dermally applied CBD is also being investigated in animal models for numerous other potential therapeutic uses including treatment of multiple Sclerosis (Giacoppo *et al*., 2015), symptom relief in arthritis (Hammel *et al*., 2016) and reduction of alcohol-based neurodegeneration (Liput *et al.,* 2013).

Mechanism of action

Endocannabinoids system

78. The endocannabinoid system (ECS) is a biological system composed of endocannabinoids, which are endogenous lipid-based retrograde neurotransmitters 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.

79. 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 post-natal 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).

80. Experimental efforts over the last two decades have confirmed that cutaneous cannabinoid signalling is deeply involved in the maintenance of skin homeostasis,

barrier formation and regeneration, and its dysregulation has been implicated to contribute to several highly prevalent diseases and disorders, e.g., atopic dermatitis, psoriasis, scleroderma, acne, hair growth and pigmentation disorders, keratin diseases, various tumours, and itch (Toth *et al.,* 2019).

81. It has been shown that abuse of synthetic, hyperpotent cannabinoids (e.g., “Bonsai”, “fake weed”, “K2”, and “Jamaica”) can result in dermatological disorders, such as premature skin aging, hair loss and greying, or acne, indicating that cannabinoid signalling can profoundly influence skin biology.

82. Evidence demonstrates that both endogenous and phytocannabinoids can exert various biological effects in the skin, implicating cannabinoid signalling as a key contributor to cutaneous homeostasis. The presence of different endocannabinoids, cannabinoid receptors, as well as other members of the ECS has already been shown on many different cell types of the skin, including, but not limited to epidermal keratinocytes, melanocytes, mast cells, fibroblasts, sebocytes, sweat gland cells, as well as certain cell populations of hair follicles.

83. Associations have been made between the dysregulation of the ECS in the skin and dermatological disorders such as atopic dermatitis, psoriasis, scleroderma and skin cancer (Del Río *et al*., 2018). Numerous studies have reported that phytocannabinoids and their biological analogues modulate a complex network pharmacology involved in the modulation of ECS, focusing on classical cannabinoid receptors, transient receptor potential channels (TRPs), and peroxisome proliferator-activated receptors (PPARs).

Toxicology

Dermal route of administration

84. The literature in the public domain on dermal application of CBD is predominantly clinical trial reports secondary findings from animal proof of concept and mechanistic studies.

85. In a phase 1 and 2, open-label assessment of the safety, tolerability, and efficacy of transdermal CBD gel for the treatment of Fragile X Syndrome, gel was administered twice daily for 12 weeks, titrated from 50 mg to a maximum daily dose of 250 mg (Heussler *et al*., 2019). The surface area of the skin that the treatment was applied to was not provided. No serious adverse events (SAEs) were reported. Seventeen of the 20 treated patients (85%) reported at least one treatment-emergent adverse event (AE)[3] during the 12-week treatment phase. Six (30%) patients experienced at least one AE considered possibly or probably related to treatment. Treatment related application site disorder AEs were seen in two patients: one with mild dryness and the other moderate rash. Additionally, further treatment related AEs were seen in three patients who presented with psychomotor hyperactivity, stereotypy, and nightmare. These are also symptoms of FXS. One patient

[3] A treatment emergent adverse event is an are undesirable event not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

discontinued treatment due to worsening of pre-existing eczema. The majority of treatment emergent AEs were mild in severity (70%) and resolved by the end of the 12-week treatment period with no dose adjustment.

86. Other AEs reported in 10% or more of the treated patients included gastroenteritis (25%), vomiting (10%), and upper respiratory tract infection (10%); these were not considered treatment-related. No significant changes were observed in ECGs, physical or neurological examinations, or vital signs (e.g., blood pressure, heart rate, respiratory rate). There were no clinically meaningful trends in laboratory values (including testosterone levels), except for an increase in eosinophil count at day 83 in the patient noted above who had a moderate rash, who completed the study. This same patient had a repeat blood collection carried out one-month post dose and showed a slightly above normal eosinophil count. There were no clinically significant changes in liver function tests. For a summary of the AE findings see Table D7 in Annex D.

87. 20 patients with the two common skin disorders: psoriasis (n=5) and atopic dermatitis (n=5) and resulting outcome scars (n=10), patients were administered topically enriched ointment to lesioned skin areas twice daily for three months (Palmieri *et al*., 2019). The product, hemptouch organic skin care ointment (Hemptouch Ltd, Novo mesto, Slovenia) contained CBD seed oil and natural ingredients, including Mangifera Indica, Calendula officinalis, Lavendula officinalis, Chamomile, Amyris Balsamifera, and butyrospermum (shea butter). No details regarding ingredient concentrations, including CBD, were available. No irritant or allergic reactions were documented during the period treatment.

88. The therapeutic effects of dermally applied CBD cream were investigated in a mouse model of experimental autoimmune encephalomyelitis (Giacopp *et al.,* 2015). Pure CBD was solubilised in propylene glycol and basic dense cream to form of concentration of 1% CBD. The cream was applied daily to both hind limbs of the mouse to cover an area roughly 1 cm^2 for a period of 14 days. The CBD transdermal cream was well tolerated at both a local cutaneous level and systemic level. Potential for allergic response was assessed every 48 hours by alteration in the percentage of leukocytes; no change was detected over the course of the 14 days.

Other routes of administration

89. The COT has previously reviewed two separate CBD submissions: TOX/2019/32 and TOX/2020/02., in which publicly available literature and the Epidiolex data shared by GW pharmaceuticals were reviewed, respectively. These are available in their entirety in the Annex B and Annex C, respectively.

Official reports of Adverse reactions

RAPEX

90. The Rapid Exchange of Information System (RAPEX) is the EU rapid alert system for unsafe consumer products and consumer protection. RAPEX, also known as Safety Gate, does not encompass food and pharmaceutical products and drugs.

91. There have been no alerts on the RAPEX system for dermally applied CBD containing cosmetics.

Product Safety Database (PSD)

92. OPSS has also recently developed a UK Product Safety Database (PSD) for use by UK regulators including Local Authority Trading Standards to report unsafe consumer products, share and collate information on unsafe and non-compliant products and improve consumer protection.

93. There have been no reported unsafe or adverse reports of CBD containing cosmetic products on the PSD.

MHRA – Yellow card reports

94. The following two yellow card reports were the reported incidents of adverse reactions following topical CBD application between the years 2005-2020 (Yellow Card, 2020).

95. Case 1. Year of receipt 2019 - Female patient taking cannabidiol, both topically and orally, for osteoarthritis experienced indigestion, extreme daytime sleepiness, difficulty sleeping, itchy skin. The onset time from first dose was one day. The outcome given at the time of the report was “not recovered/not resolved”.

96. Case 2. Year of receipt 2020 – Male patient taking topical cannabidiol for eczema and dihydrocodeine (route unknown) for analgesia. Reported reactions were dizziness aggravated, hyperkinetic reaction, nausea aggravated, pharmacokinetic interaction, pyrexia, serum serotonin increased and vomiting. The onset time from first dose was one day. Outcome at time of report was “recovering”.

CBD content of cosmetic products

97. Publicly available literature has shown that CBD concentrations within products often measure below the claimed amount (Labelling Accuracy of Cannabidiol Extracts Sold Online., 2017; CBD IN THE UK., 2019). These studies also demonstrated that products can contain illicit psychoactive substances above the levels permitted under the Misuse of Drugs Act.

98. OPSS commissioned screen testing of 62 CBD-containing cosmetic products (oils, serums, creams, face masks, hair treatments, body and hair washes, balms, gels and a bath bomb) to determine CBD content in these product types. CBD levels in 44 % of products measured lower than the instrument limit of quantification; for this report, only CBD content measuring >0.002 % w/v in product is reported however, it is worth noting that lower CBD concentrations were detected but varied greatly based on sample matrix. Where CBD was quantified, levels ranged from >0.002 – 1.96 % w/v (equivalent to approx. >5 – 559 mg per volume) ±20 % with average CBD content in leave-on body products notably higher than other product categories. Results across six cosmetic product categories are shown in Table 2. The highest CBD levels were found in a body oil, facial oil and body cream at 1.96,

1.47 and 1.12 % w/v (equivalent to 196 mg in 10 mL, 441 mg in 30 mL and 559 mg in 50 mL), respectively. A more detailed summary of individual CBD weights measured per product volume is presented in Tables 3(a)-(d). Similar to other report findings, CBD products with a stated content (n=24) were found to contain lower CBD levels than those claimed.

Table 2. Average CBD content and ranges across six cosmetic product categories.

Product type (no. tested)				
	CBD content	CBD content	CBD content	CBD content
	Range (% w/v)	Average (% w/v)	Range (mg per product)	Average (mg per product)
Body Balms and Gels (n=6)	<0.002 – 0.688	0.391 (n=5)	<5 – 353	251 (n=5)
Body Creams, Oils and Water (n=19)	<0.002 – 1.96	0.318 (n=11)	<5 – 559	172 (n=11)
Face Creams, Oils, Serums and Masks (n=30)	<0.002 – 1.47	0.385 (n=12)	<5 – 441	80 (n=12)
Bath bomb (n=1)	n/a	0.019 (n=1)	n/a	26 (n=1)
Hair treatments (n=3)	n/a	<0.002	n/a	<5
Washes (n=3)	n/a	<0.002	n/a	<5

Table 3(a). CBD (mg per product) measured in body creams, oils and tanning water.

Product type	Product volume (mL)	CBD content (mg per product)
Cream	50	559
Oil	100	450
Cream	150	270
Oil	200	200
Oil	30	120
Oil	100	80
Oil	10	75
Oil	50	45
Sun cream	100	40
Oil	100	30
Oil	8	21
Oil	150	<5
Oil	100	<5
Oil	50	<5
Oil	30	<5
Oil	30	<5
Cream	170	<5
Cream (hands)	100	<5
Tanning Water	100	<5

Table 3(b). CBD (mg per product) measured in body gels and balms.

Product type	Product volume (mL)	CBD content (mg per product)
Gel	100	353
Balm	50	344
Balm	100	278
Balm	50	226
Balm	30	56
Gel	300	<5
Gel	100	353

Table 3(c). CBD (mg per product) measured in facial oils, creams, serums and masks.

Product type	Product volume (mL)	CBD content (mg per product)
Oil (facial)	30	441
Oil (facial)	10	196
Oil (facial)	20	94
Serum (facial)	20	54
Cream (facial)	48	50
Serum (facial)	50	37
Cream (facial)	60	21
Serum (facial)	30	18
Serum (facial)	30	18
Serum (facial)	30	18
Oil (facial)	30	12
Cream (facial)	50	6
Oil (facial)	30	<5
Oil (facial)	30	<5
Oil (facial)	30	<5
Oil (facial)	15	<5
Serum (facial)	30	<5
Serum (facial)	30	<5
Serum (facial)	30	<5
Serum (facial)	30	<5
Cream (facial)	100	<5
Cream (facial)	50	<5
Cream (facial)	50	<5
Cream (facial)	50	<5
Cream (facial)	50	<5
Cream (facial)	30	<5
Cream (facial)	30	<5
Face Mask	22	<5
Face Mask	22	<5
Face Mask	21	<5

Table 3(d). CBD (mg per product) measured in other cosmetic products such as bath bombs, hair treatment and washes.

Product type	Product volume (mL)	CBD content (mg per product)
Bath bomb	135	26
Hair Treatment	250	<5
Hair Treatment	150	<5
Hair Treatment	100	<5
Wash	250	<5
Wash	250	<5
Wash	200	<5
Bath bomb	135	26

Summary

99. CBD-containing cosmetics are readily available on the market for use by all consumer types. CBD content is often not stated on the product and testing has shown CBD levels in cosmetic products can vary greatly and for products with a stated content, levels have been found to be lower than those claimed.

100. In the clinical and animal studies presented in this report, dermally applied CBD has been shown to be effective and likely pharmacologically active in treating the intended disease states. This demonstrates that despite the lipophilic nature of CBD, and perceived difficulty in penetrating the skin barrier, dermal application is potentially a viable CBD delivery method.

101. It has also been shown that the formulation and composition of dermally applied CBD products can greatly impact the ability of the CBD to enter systemic circulation.

102. Given the varied compositions of cosmetics, including the use of well-known permeation enhancers, this presents a situation where the exposure to CBD maybe non-linear and dependent on each individual cosmetics formulation.

103. From the safety and tolerability information presented in this report on dermally applied CBD, there appears to be few acute toxicity findings.

104. However, longer duration studies using dermal administration, investigating the majority of toxicological endpoints, including skin irritation, skin sensitisation, repeat-dose toxicity, chronic toxicity, reproductive and developmental toxicity, immuno-toxicity and carcinogenicity, do not exist at present, or are not available in the public domain.

105. Product testing has shown that CBD has been found in products on the UK market, so there is potential exposure of UK consumers to CBD when using CBD-

containing cosmetic products. With the information showing potential for systemic exposure, there is also potential for aggregate exposure to arise from the use of multiple CBD-containing products.

Questions for the Committee:

106. The Committee is asked to consider the information presented in this paper, and in particular:

- Does the pharmacokinetic profile of topically applied CBD pose a safety concern or raise any further questions regarding the use of topically applied CBD cosmetics?
- Is there adequate information on the pharmacokinetics and toxicity of topical CBD to generate an adequate risk assessment regarding the safety of dermally applied CBD cosmetics?
- Do the Committee have any comments on the potential for drug interactions arising from topical CBD exposure and how this relates to topical CBD cosmetic use?
- Considering the toxicity and PK profile of topically applied CBD and the levels of CBD determined in various cosmetic products, does their use pose a potential safety concern?
- Do the Committee, given the information presented, consider there to be a risk arising from the cumulative exposure arising from the use of multiple CBD products including but not limited to cosmetics?
- Do the Committee have any comments on where research would ideally be targeted to address any data gaps?
- Do the Committee agree we should revisit this topic when more data becomes available?

Office for Product Safety and Standards, Department for Business, Energy and Industrial Strategy
April 2020

References

Arnold JC, Hone P, Holland ML, Allen JD. CB2 and TRPV1 receptors mediate cannabinoid actions on MDR1 expression in multidrug resistant cells. Pharmacol Rep. 2012;64:751–757.

Bartner, L. R., Mcgrath, S., Rao, S., Hyatt, L. K. & Wittenburg, L. A. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. Can J Vet Res. 2018 Jul;82(3):178-183.

Batalla, A., Crippa, J.A., Busatto, G.F., Guimaraes, F.S., Zuardi, A.W., Valverde, O., Atakan, Z., McGuire, P.K., Bhattacharyya, S. and Martin-Santos, R. Neuroimaging studies of acute effects of THC and CBD in humans and animals: a systematic review. Current pharmaceutical design, 2013 pp.2168-2185.

Bornheim LM, Everhart ET, Li J, Correia MA. Induction and genetic regulation of mouse hepatic cytochrome P450 by cannabidiol. Biochem Pharmacol. 1994;48:161–171.

Bornheim LM, Kim KY, Chen B, Correia M. The effect of cannabidiol on mouse hepatic microsomal cytochrome P450-dependent anandamide metabolism. Biochem Biophys Res Commun. 1993;197:740–746.

Bruni N, Pepa CD, Oliaro-Bosso S, Pessione E, Gastaldi D and Dosio F. Cannabinoid Delivery Systems for Pain and Inflammation Treatment. Molecules 2018, 23(10), 2478; https://doi.org/10.3390/molecules23102478

CBD IN THE UK: https://irp-cdn.multiscreensite.com/51b75a3b/files/uploaded/Exec%20Summary%20-%20CBD%20.pdf

Chelliah, M.P.; Zinn, Z.; Khuu, P.; Teng, J.M.C. Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. Pediatr. Dermatol. 2018, 35, 224–227

Deiana S, Watanabe A, Yamasaki Y, Amada N, Arthur M, Fleming S, Woodcock H, Dorward P, Pigliacampo B, Close S, Platt B, Riedel G. Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Delta(9)-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBDaction on obsessive-compulsive behaviour. Psychopharmacology (Berl). 2012; 219:859–73. [PubMed: 21796370]

Del Río CD, Millán E, García V, Appendino G, DeMesa J, Muñoz E. The endocannabinoid system of the skin. A potential approach for the treatment of skin disorders. Biochem Pharmacol. 2018 Nov;157:122-133. doi: 10.1016/j.bcp.2018.08.022. Epub 2018 Aug 20.

Dinis-Oliveira RJ. Metabolomics of delta9-tetrahydrocannabinol: implications in toxicity. Drug Metab Rev 2016; 48: 80–7.

Donvito, G., Nass, S.R., Wilkerson, J.L., Curry, Z.A., Schurman, L.D., Kinsey, S.G. and Lichtman, A.H. The endogenous cannabinoid system: a budding source of targets for treating inflammatory and neuropathic pain. Neuropsychopharmacology. 2018 Jan;43(1):52-79. doi: 10.1038/npp.2017.204. Epub 2017 Aug 31.

DrugBank: https://www.drugbank.ca/drugs/DB09061

Fasinu, P.S., Phillips, S., ElSohly, M.A. and Walker, L.A. Current status and prospects for cannabidiol preparations as new therapeutic agents. Pharmacotherapy: Pharmacotherapy. 2016 Jul;36(7):781-96. doi: 10.1002/phar.1780.

Feinshtein V, Erez O, Ben-Zvi Z, Erez N, Eshkoli T, Sheizaf B, Sheiner E, Huleihel M, Holcberg G. Cannabidiol changes P-gp and BCRP expression in trophoblast cell lines. PeerJ. 2013;1:e153.

Fride, E. The endocannabinoid-CB1 receptor system in pre-and postnatal life. European Journal of Pharmacology Volume 500, Issues 1–3, 1 October 2004, Pages 289-297.

Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. Epilepsy Behav 2017; 70 (Pt B): 313–8.

Geffrey AL, Pollack SF, Bruno PL, et al. Drug–drug interaction between clobazepam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015;56:1246–1251

Giacoppo, S., Galuppo, M., Pollastro, F., Grassi, G., Bramanti, P. and Mazzon, E. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. Daru. 2015 Oct 21;23:48. doi: 10.1186/s40199-015-0131-8.

Hammell, D. C., Zhang, L. P., Ma, F., Abshire, S. M., Mcilwrath, S. L., Stinchcomb, A. L. & Westlund, K. N. Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. Eur J Pain. 2016 Jul; 20(6): 936–948. Published online 2015 Oct 30. doi: 10.1002/ejp.818

Hawksworth, G. and McArdle, K. Metabolism and pharmacokinetics of cannabinoids. The Medicinal Uses of Cannabis and Cannabinoids (Guy GW, Whittle BA, Robson PJ, eds.). Pharmaceutical Press: London. 2004 pp.205-228Hegde, V.L

Heussler, H., Cohen, J., Silove, N., Tich, N., Bonn-Miller, M. O., Du, W., O'neill, C. & Sebree, T. A phase 1/2, open-label assessment of the safety, tolerability, and efficacy of transdermal cannabidiol (ZYN002) for the treatment of pediatric fragile X syndrome. J Neurodev Disord. 2019 Aug 2;11(1):16. doi: 10.1186/s11689-019-9277-x.

Holland ML, Allen JD, Arnold JC. Interaction of plant cannabinoids with the multidrug transporter ABCC1(MRP1). Eur J Pharmacol. 2008;591:128–131.

Hollister, L.E. Cannabidiol and cannabinol in man. Experientia. 1973;29(7):825-6.

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

Hunter, D. Oldfield, G. Tich, N. Messenheimer, J. Sebree, T. Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis. Royal North Shore Hosp. and Inst. of Bone and Joint Res., Sydney, Australia;z Pendlebury Res., Adamstown, Australia; x Zynerba Pharmaceuticals, Devon, PA, USA. Osteoarthritis and Cartilage 2018 April; Volume 26, S26

Istvan Ujvary and Lumır Hanus. Human Metabolites of Cannabidiol: A Review on Their Formation, Biological Activity, and Relevance in Therapy. Cannabis and Cannabinoid Research Volume 1.1, 2016 DOI: 10.1089/can.2015.0012

Jiang, R., Yamaori, S., Takeda, S., Yamamoto, I. and Watanabe, K. Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. Life Sci. 2011 Aug 1;89(5-6):165-70. doi: 10.1016/j.lfs.2011.05.018. Epub 2011 Jun 16.

Kalpana S. Paudel, Dana C. Hammell, Remigius U. Agu, Satyanarayana Valiveti, and Audra L. Stinchcomb. Cannabidiol bioavailability after nasal and transdermal application: effect of permeation enhancers. Drug Dev Ind Pharm. 2010 Sep;36(9):1088-97. doi: 10.3109/03639041003657295.

Klein, C., Hill, M.N., Chang, S.C., Hillard, C.J. and Gorzalka, B.B. Circulating endocannabinoid concentrations and sexual arousal in women. J Sex Med. 2012 Jun;9(6):1588-601. doi: 10.1111/j.1743-6109.2012.02708.x. Epub 2012 Mar 29.

Labelling Accuracy of Cannabidiol Extracts Sold Online: https://jamanetwork.com/journals/jama/fullarticle/2661569

Liput, D. J., Hammell, D. C., Stinchcomb, A. L. & Nixon, K. Transdermal delivery of cannabidiol attenuates binge alcohol-induced neurodegeneration in a rodent model of an alcohol use disorder. Pharmacol Biochem Behav. 2013 Oct;111:120-7. doi: 10.1016/j.pbb.2013.08.013. Epub 2013 Sep 5.

Lizelle T. Fox, Minja Gerber, Jeanetta Du Plessis and Josias H. Hamman. Transdermal Drug Delivery Enhancement by Compounds of Natural Origin. Molecules 2011, 16, 10507-10540; doi:10.3390/molecules161210507

Lodzki, M.; Godin, B.; Rakou, L.; Mechoulam, R.; Gallily, R.; Touitou, E. Cannabidiol—Transdermal delivery and anti-inflammatory effect in a murine model. J. Control. Release 2003, 93, 377–387.

Long, L.E., Chesworth, R., Huang, X.F., McGregor, I.S., Arnold, J.C. and Karl, T. A behavioural comparison of acute and chronic Δ9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. International Journal of Neuropsychopharmacology 2010, 13(7), pp.861-876.

McPartland, J.M., Duncan, M., Di Marzo, V. and Pertwee, R.G. Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. British Journal of Pharmacology 2015, 172(3), pp.737-753.

Millar, S. A., Stone, N. L., Yates, A. S. & O'Sullivan, S. E. 2018. A systematic review on the pharmacokinetics of cannabidiol in humans. Front Pharmacol. 2018 Nov 26;9:1365. doi: 10.3389/fphar.2018.01365. eCollection 2018.

Ohlsson, A., Lindgren, J.E., Andersson, S., Agurell, S., Gillespie, H. and Hollister, L.E. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. Biomed Environ Mass Spectrom. 1986 Feb;13(2):77-83.

Oláh A., Tóth B.I., Borbíró I., Sugawara K., Szöllõsi A.G., Czifra G., Pál B., Ambrus L., Kloepper J., Camera E., et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. J. Clin. Investig. 2014;124:3713–3724. doi: 10.1172/JCI64628.

Palmieri B, Laurino C, Vadalà M. A therapeutic effect of cbd-enriched ointment in inflammatory skin diseases and cutaneous scars. Clin Ter. 2019 Mar-Apr;170(2):e93-e99. doi: 10.7417/CT.2019.2116.

Pertwee, R.G. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. British journal of pharmacology 2008, 153(2), pp.199-215.

Samara, E., Bialer, M. and Harvey, D.J. Identification of glucose conjugates as major urinary metabolites of cannabidiol in the dog. Xenobiotica 1990, 20(2), pp.177-183.

Spleman L, Sinclair R, Freeman M, Davis M and Gebauer K. The safety of topical cannabidiol (CBD) for the treatment of acne. Investigative Dermatology May, 2018.DOI: 10.1016/j.jid.2018.03.1074

Stinchcomb AL, Nalluri BN. Transdermal delivery of cannabinoids. 2005. US patent no. 20050266061.

Stinchcomb AL, Valiveti S, Hammell DC, Ramsey DR. Human skin permeation of Delta8-tetrahydrocannabinol, cannabidiol and cannabinol. J Pharm Pharmacol. 2004 Mar;56(3):291-7.

Stott C, White L, Wright S, et al. A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. Springerplus. 2013;2:236.

Sultan, S.R., Millar, S.A., England, T.J. and O'Sullivan, S.E. A systematic review and meta-analysis of the haemodynamic effects of Cannabidiol. Frontiers in Pharmacology 2017, 8, p.81.

Tóth, Kinga Fanni. Dorottya, Ádám.Tamás, Bíró. Attila Oláh. Molecules. 2019 Mar; 24(5): 918. Published online 2019 Mar 6. doi: 10.3390/molecules24050918

TOX/2019/32 - Scoping paper on CBD:
https://cot.food.gov.uk/sites/default/files/tox2019-32.pdf

TOX/2020/02 - Update on CBD:
https://cot.food.gov.uk/sites/default/files/tox202002cbd.pdf

UN Drug Control Conventions:
https://www.unodc.org/unodc/en/commissions/CND/conventions.html

Wakshlag, J.J., Frye, C.F., Gamble, L.J., Boesch, J., Schwark, W.S., Brown, H., Wolfe, L., Mann, S. and Berthelsen, E.S. Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs. Frontiers in veterinary science 2018, 5, p.165.

Wang, H., Xie, H. and Dey, S.K. Endocannabinoid signaling directs periimplantation events. The AAPS journal, 8(2), pp.E425-E432.Alzheimer's disease. Frontiers in pharmacology 2006, 8, p.20.

Yamaori S, Kinugasa Y, Jiang R, Takeda S, Yamamoto I, Watanabe K. Cannabidiol induces expression of human cytochrome P450 1A1 that is possibly mediated through aryl hydrocarbon receptor signalling in HepG2 cells. Life Sci. 2015;136:87–93.

Yellow Card Scheme: https://yellowcard.mhra.gov.uk/

Zhu H-J, Wang J-S, Markowitz JS, Donovan JL, Gibson BB, Gefroh HA, Devane CL. Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. J Pharmacol Exp Ther. 2006;317:850–857.

Zynerba® Pharmaceuticals. Available from: http://zynerba.com/

TOX/2020/23 – Annex A

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

Potential risks from use of topically applied CBD-containing cosmetic products

Position paper from the Cosmetic, Toiletry and Perfumery Association: The Legal Status of Cannabis and Cannabis Extracts in Finished Cosmetics in the UK

This paper is attached. It is not being made publicly available for copyright reasons. It can be downloaded here: https://www.ctpa.org.uk/file.php?fileid=3422

Office for Product Safety and Standards, Department for Business, Energy and Industrial Strategy
April 2020

TOX/2020/23 – Annex B

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

Potential risks from use of topically applied CBD-containing cosmetic products

COT discussion paper TOX/2019/32

This paper is attached. It is available here:
https://cot.food.gov.uk/sites/default/files/tox2019-32.pdf

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April 2020

TOX/2020/23 – Annex C

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

Potential risks from use of topically applied CBD-containing cosmetic products

COT discussion paper TOX/2020/02

This paper is attached. It is available here:
https://cot.food.gov.uk/sites/default/files/tox202002cbd.pdf

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April 2020

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

Potential risks from use of topically applied CBD-containing cosmetic products

Tables D1-D7 and Figures D1a – D4 referenced in paper

Table D1 - Bartner et al 2018 – Table II

Table D2 - Hammel et al., 2016 – Table 1

Table D3 - Giacoppo et al 2015 – Table 1

Table D4 - Kalpana et al., 2010 – Table 2

Table D5 - Stinchcomb et al., 2004 – Table 2

Table D6 - Extract from Bruni et al., 2018 – Table 1

Table D7 - Heussler et al., 2019 – Table 2

Figure D1a - Bartner et al., 2018 – Figure 2

Figure D1b - Bartner et al., 2018 – Figure 1

Figure D1c - Bartner et al., 2018 – Figure 1

Figure D2 - Lodzki et al., 2003 – Figure 4

Figure D3a and D3b - Liput et al., 2013 – Figure 4

Figure D4 - Kalpana et al., 2010 – Figure 5

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