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

Position paper on the potential risk of CBD in CBD food products: additional text summarising committee discussions relating to dermal and inhalation exposure

Background

1. The COT 'Position paper on the potential risk of CBD in CBD food products' summarised discussions and conclusions of the COT and COM from July 2019 to May 2020 on available toxicological information of relevance to cannabidiol (CBD) in non-medicinal food products (COT, July 2020).

2. At the May 2020 COT meeting, the Committee discussed data of relevance to dermal exposure to CBD from CBD-containing cosmetics products (TOX/2020/23 and corresponding minutes) and at the December 2020 COT meeting some information on inhalation exposure to CBD was considered (TOX/2020/62 and corresponding minutes).

3. Further to previous discussions, the following paragraphs summarise information from some additional publications relating to dermal and inhalation exposure to CBD, with a relevant figure presented in Annex A.

4. Draft sections on dermal and inhalation exposure for inclusion in an updated position paper are presented in Annex B.

Further literature on dermal exposure to CBD

5. An *in vitro* human skin permeation model was used to test different formulations of CBD used for topical administration (Casiraghi et al. 2020). *In vitro* permeation and retention studies were performed under occlusive conditions at 37°C using donor human skin. Test formulations were prepared to contain a concentration of 1% CBD[1] (w/w). In initial experiments, four different solvent systems were tested: liquid paraffin (LP), virgin olive oil (VOO), 80% propylene glycol (PG), and 80% polyethylene glycol (PEG) 400. Of these, the two in which CBD was less soluble (liquid paraffin and 80% PG) showed the highest rates of CBD permeation and retention. These two vehicles were taken forward to prepare semi-solid formulations, a lipophilic ointment (containing 49% LP) and a hydrophilic gel (containing 79% PG), both containing 1% CBD. The PG-based hydrophilic gel showed significantly higher skin retention and permeation rate than the LP-based ointment. However, the semi-solid formulations showed lower overall effectiveness than the corresponding

[1] Details of CBD source and purity were not provided other than the note that "CBD was kindly gifted by Indena Spa (Milan, Italy)".

solutions. Finally, a transdermal patch system with 1% CBD was tested, resulting in lower effectiveness in terms of permeation and retention than the semi-solid preparations.

Further literature on inhalation exposure to CBD

6. Spindle and colleagues published two reports relating to comparative studies of the pharmacokinetics and/or pharmacodynamics of CBD exposure via oral and inhalation exposure (Spindle et al. 2020a, Spindle et al. 2020b).

7. The paper by Spindle et al. (2020b) describes urinary pharmacokinetic parameters measured over a five-day period in a group of six study participants (3 women, 3 men) who reported prior experience of inhaling cannabis. All cannabis use had been ceased for at least one month prior to the study. Four test periods were completed in a randomised order, with a washout of at least one week between each test period. The duration of each test period was five days, with Days 1-3 conducted in clinical confinement. Test conditions were as follows:

i. oral ingestion of placebo CBD[2] followed by inhalation of 100 mg vaporised CBD[3]

ii. oral ingestion of 100 mg CBD followed by inhalation of vaporised placebo cannabis[4]

iii. oral ingestion of placebo CBD followed by inhalation of CBD-dominant cannabis[5]

iv. oral ingestion of placebo CBD following by inhalation of placebo cannabis.

8. The dose selection of 100 mg CBD was chosen as representing a typical amount of cannabis that a user would consume from a 1 g cannabis cigarette containing 10% CBD. The ratio of CBD: Δ9-THC in the CBD-dominant cannabis was considered to be representative of the ratio present in hemp products marketed in the US.

[2] Oral dosing was given as a 'gelcap' filled with cellulose, either containing CBD or not (placebo).
[3] The CBD used for ingestion and for inhalation was 100% pure crystalline CBD powder, containing no Δ9-tetrahydrocannabinol (Δ9-THC).
[4] Placebo cannabis was obtained from the US National Institute on Drug Abuse Drug Supply Program, and contained (w/w) 0.001% Δ9-THC, 0.003% CBD, and 0.005% cannabinol (CBN), but no detectable Δ8-THC.
[5] CBD-dominant cannabis was obtained from the US National Institute on Drug Abuse Drug Supply Program and contained (w/w) 10.5% CBD, 0.39% Δ9-THC, 0.02% Δ8-THC, 0.05% CBN.

9. On study Day 1, participants ate a low-fat meal, ingested an oral gelcap containing the designated test product, and one hour later inhaled the vaporised product over a 10-minute period, using a Volcano Medic vaporiser at an operating temperature of 204°C. Urine voids were collected during the 58 hours following oral dosing, and single-dose urine samples were collected on Days 4 and 5. Urine was analysed by immunoassay and by liquid chromatography with tandem mass spectrometry (LC-MS/MS analysis) for several cannabinoids[6]. Results were detailed for CBD and for Δ9-THCCOOH (a metabolite of Δ9-tetrahydrocannabinol, Δ9-THC).

10. Mean measured values were as follows.

i. 100 mg CBD by oral administration: Cmax for CBD, 776.3 ng/mL; Tmax for CBD, 5.3 h; total percentage of CBD excreted in urine, 0.3%. CBD was detected in urine on Day 5 in 3/6 participants.

ii. 100 mg CBD by vaporisation: Cmax for CBD, 261 ng/mL; Tmax for CBD, 0.8 h; total percentage of CBD excreted in urine, 0.10%. CBD was detected in urine on Day 5 in 2/6 participants.

iii. CBD-dominant cannabis (100 mg CBD/3.7 mg Δ9-THC): Cmax for CBD, 307 ng/mL; Tmax for CBD, 1.2 h; total percentage of CBD excreted in urine, 0.12%. CBD was detected in urine on Day 5 in all study participants. Cmax for Δ9-THCCOOH, 1.2-29.9 ng/mL (range); Tmax for Δ9-THCCOOH, 3-23 h (range). Δ9-THCCOOH was detected in urine on Day 5 in 3/6 participants. Several other cannabinoids were detected in the urine of some of the participants after inhalation of CBD-dominant cannabis.

11. The authors' comments and conclusions relate primarily to use of Δ9-THCCOOH as a marker in urinary drug-testing protocols. In this context, the authors noted that administration of 100 mg (pure) oral or vaporised CBD did not produce positive urine toxicology results based on current US drug testing guidelines, whereas inhalation of cannabis containing 100 mg CBD and 3.7 mg Δ9-THC resulted in positive test results for 2/6 participants. The authors also commented that urinary CBD concentrations were higher, and peaked later, following ingestion compared with inhalation.

12. A subsequent report by Spindle and colleagues described pharmacodynamic (subjective, cognitive, physiological) and pharmacokinetic measurements over an eight-hour period in a group of 18 participants (9 females and 9 males) (Spindle et al. 2020a). The test regimes were essentially equivalent to those described by Spindle et al. (2020b) [paragraph 6, above], except that for oral CBD, three different types of formulation were tested: 100 mg CBD in a gelcap filled with cellulose (n=6

[6] Other cannabinoids were either undetectable or present at only trace levels (<1 ng/mL).

participants); 1 mL Epidiolex[7] mixed with 9 mL pharmacy-grade cherry-flavoured syrup (n=6); 100 mg CBD suspended in 10 mL pharmacy-grade cherry-flavoured syrup. Data relating to these three oral exposure regimes were combined in the subsequent analysis as no differences were observed between these different oral-dose formulations.

13. The following measurements were recorded at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h following oral dosing, with the 1-h time point measurements made immediately after the inhalation exposure: subjective drug measures ('Drug Effect Questionnaire'); cognitive/psychomotor tasks; physiological measures (blood pressure and heart rate); whole-blood CBD and THC concentration determined by LC-MS/MS.

14. Vaporised CBD and CBD-dominant cannabis were associated with higher level subjective effects compared with the placebo, including 'drug effect', 'pleasant drug effect', 'like drug effect', heart racing, dry mouth, irritated throat, and difficulty with routine tasks. Ratings were generally higher for vaporised CBD compared with oral CBD and for vaporised CBD-dominant cannabis compared with vaporised CBD exposure. Cognitive/psychomotor performance was not significantly altered under different dosing conditions. Heart rate was higher after inhalation of CBD-dominant cannabis compared with the placebo or vaporised CBD.

15. Mean (SD) peak whole blood concentrations were as follows. For CBD: 11.1 (14.7) ng/mL (oral CBD active-dosing condition); 104.6 (76.5) ng/mL (vaporised CBD active-dosing condition); 181.4 (160.8) ng/mL (CBD-dominant cannabis condition). For THC: 6.2 (7.8) ng/mL (CBD-dominant cannabis condition[8]). Concentration-versus-time curves are presented in Figure 3 of the paper by Spindle et al. (2020a), which is reproduced as Figure 1 at Annex A of this discussion paper.

Additional narrative on dermal and inhalation exposure for the COT position paper on CBD

16. At present, the COT 'Position paper on the potential risk of CBD in CBD food products' (COT, July 2020) primarily addresses toxicological aspects of oral exposure to CBD.

17. To update the position paper to include the Committee's opinions and conclusions relating to dermal and inhalation exposure, some further narrative is provided at Annex B. The intention is that these paragraphs would be inserted within the body text of the existing position paper on CBD in food products.

[7] An oral CBD product produced by GW Pharmaceuticals, Greenwich, England); one single unit dose of Epidiolex contains 100 mg CBD.
[8] Blood THC measurements were not reported for other exposure conditions.

Questions for the Committee

18. Members are invited to review the further literature provided in this discussion paper and the narrative presented at Annex B and to consider the following questions:

i. Does the publication of Casiraghi et al (2020) provide any additional information that would impact on the Committee's conclusions relating to dermal exposure to CBD?

ii. Do the two publications by Spindle et al (2020a, 2020b) provide any additional information that would impact on the Committee's conclusions relating to inhalation exposure to CBD?

iii. Do Members have any comments on the suitability of the narrative sections on dermal and inhalation exposure to CBD that are presented at Annex B? Does this narrative accurately and fully represent the Committee's opinions and conclusions?

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Abbreviations

CBD	Cannabidiol
CBN	Cannabinol
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LP	Liquid paraffin
PEG	Polyethylene glycol
PG	Propylene glycol
THC	Tetrahydrocannabinol
VOO	Virgin olive oil

References

Casiraghi, A., U. M. Musazzi, G. Centin, S. Franzè & P. Minghetti (2020) Topical Administration of Cannabidiol: Influence of Vehicle-Related Aspects on Skin Permeation Process. *Pharmaceuticals (Basel),* 13.

Spindle, T. R., E. J. Cone, E. Goffi, E. M. Weerts, J. M. Mitchell, R. E. Winecker, G. E. Bigelow, R. R. Flegel & R. Vandrey (2020a) Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. *Drug Alcohol Depend,* 211**,** 107937.

Spindle, T. R., E. J. Cone, D. Kuntz, J. M. Mitchell, G. E. Bigelow, R. Flegel & R. Vandrey (2020b) Urinary Pharmacokinetic Profile of Cannabinoids Following Administration of Vaporized and Oral Cannabidiol and Vaporized CBD-Dominant Cannabis. *J Anal Toxicol,* 44**,** 109-125.

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Figure 3 of Spindle et al. (2020a). Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users

Reference:
Spindle, T. R., E. J. Cone, E. Goffi, E. M. Weerts, J. M. Mitchell, R. E. Winecker, G. E. Bigelow, R. R. Flegel & R. Vandrey (2020a) Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. *Drug Alcohol Depend,* 211**,** 107937.

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Figure 1: Mean (SEM) whole blood concentrations (ng/mL) for CBD (top panels) and THC (bottom panels) over time for three active dosing conditions: 100 mg CBD (oral); 100 mg CBD (vaped); 100 mg CBD/3.7 mg THC (vaped) (n = 9 women and 9 men). Oral doses were administered at time zero (baseline, BL), inhaled doses were administered at 1 hour.

Reproduced from Figure 3 of Spindle et al. (2020a). Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users.

TOX/2021/16 Annex B

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Draft text on dermal and inhalation exposure to CBD to be included in updated position paper

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Proposed additional narrative to insert into the COT position paper on CBD.

1] Summary text on dermal exposure: to replace paragraphs 23 and 24 of the July 2020 position paper, based on COT discussions May 2020: potential for additional exposure through topical-applied CBD

23. COT discussed the potential risks arising from dermal exposure to CBD in cosmetic products (TOX/2020/23). Such products include serums, creams, washes/rinse-off products, bath products, deodorants, balms, and toothpastes. The Committee agreed that it would be helpful if more attention could be paid to clear and accurate labelling of the CBD content in products. A general distinction was noted between dermal pharmaceutical CBD products and cosmetic CBD products, as these may have different specifications and formulations, with the latter formulated to maximise dermal absorption.

24. Dermal exposure to CBD might contribute to systemic exposure and/or local effects. Although absorption levels would probably be low because the compound is lipophilic, repeat application could lead to accumulation in the stratum corneum and subsequent slow diffusion into the systemic circulation. Overall, the Committee considered that dermal absorption of CBD was likely to be less than 10% compared with oral absorption. The Committee noted that absorption of CBD from cosmetic products may also occur via inhalation of sprays and mists generated during product use.

25. There was insufficient information on the pharmacokinetics and toxicity of dermal CBD to conduct a risk assessment of the safety of CBD in cosmetic products. No conclusions could be drawn on whether dermally applied CBD poses a safety concern, nor on the potential for drug interactions. The risk from aggregate exposure to multiple CBD products, including cosmetics, could not be determined due to lack of information. No good quality *in vivo* or *in vitro* data were available to allow estimation of systemic doses. Overall, the Committee noted that additional exposure through topically applied CBD could potentially occur and this would increase overall systemic exposure of CBD. However, there are data gaps that need to be addressed to be able to evaluate the potential for adverse effects related to dermal exposure to CBD.

2] Summary text on inhalation exposure: insert after paragraph 24 of the July 2020 position paper, based on COT discussions December 2020: potential adverse effects associated with exposure to CBD by inhalation

26. COT discussed data of relevance to potential adverse effects associated with exposure to CBD by inhalation (TOX/2020/62). Inhalation exposure to CBD may occur via various sources, for example smoking CBD-containing plant material, use of electronic nicotine (and non-nicotine) delivery systems (E(N)NDS) containing e-

liquids to which CBD has been added, or from aerosolised therapeutic applications. The type of source material would impact on a risk assessment, for example in terms of the presence or absence of thermal degradation products, and because different delivery methods may affect bioavailability of CBD. It was noted that CBD concentrations stated on products are not always accurate.

27. The available evidence base relating to potential adverse effects of inhaled CBD was small. A well-conducted pharmacokinetic study in five human smokers indicated that CBD has a long half-life with a large volume of distribution. The Committee considered that these characteristics, in addition to the lipophilic nature of CBD, indicated that there could be accumulation of CBD with repeat dosing. A study in rats suggested that inhaled CBD induced hypothermia, which was partially blocked by a 5-HT_{1A} receptor agonist, however the study did not provide sufficient good-quality information for the Committee to draw any firm conclusions regarding these findings.

28. The Committee considered that although the evidence base regarding inhaled CBD was limited, some conclusions on the likelihood of toxicity from inhalation of CBD could be inferred based on oral data. The Committee agreed that inhalation exposures pose a potential safety concern and that adverse effects could be greater than those from an equivalent oral dose as the bioavailability of inhaled CBD is often higher compared with oral exposure. Following absorption across the lung, the type of adverse effects occurring would be independent of route of exposure. Inhibitory drug interactions would be expected at levels comparable to those following oral exposure, given the apparent higher bioavailability across the lung compared with the gut. Effects on the central nervous system would be expected following inhalation, thus a health warning might be necessary relating to driving or using heavy machinery. The Committee agreed that some experimental data suggesting a possible interaction of CBD with steroids could be a cause for concern, however this is an area of research that is currently not well understood.

29. Overall, there was insufficient information to generate a risk assessment regarding the safety of use of CBD in products intended for inhalation, but the available data indicated caution. The Committee agreed that the recommended upper limit of 1 mg/kg body weight per day established for dietary exposure to CBD should be applied to total combined exposure, including that from inhalation.