

Updated position paper on the potential risk of CBD in CBD food products

Background and Introduction

1. Cannabidiol (CBD) has been investigated and researched for potential medical applications for several years, including the treatment of epilepsy and seizures. However, CBD is now being used in non-medicinal CBD-containing products, which have become increasingly popular and have entered the food sector. These products include beverages (beer, spirits, wine, coffee and soda style drinks), edible oils (tinctures, drops, syrup, olive oils), chewables (gum drops) and chocolate. These products were confirmed as novel foods in January 2019, which means there was no significant history of consumption in the EU before May 1997 and that they now need to be evaluated and authorised before they can be placed on or continue on the market.
2. Risk assessment advice on CBD has been increasingly requested from the Food Standards Agency (FSA) so it was therefore considered timely for the available toxicological information on CBD to be reviewed.
3. The following position paper brings together the discussions that took place at the Committees on Toxicity (COT) and on Mutagenicity (COM) of Chemicals in Food, Consumer Products and the Environment (COM) meetings from July 2019-May 2020, and summarises the conclusions reached to date and explains how these were used by the FSA to formulate advice for consumers.

COT preliminary discussions: July 2019

4. In July 2019, a scoping paper on the potential adverse effects of CBD food products (TOX/2019/32¹) was presented to COT.
5. The Committee noted that some CBD products would contain not only CBD but also a range of other related cannabinoids including tetrahydrocannabinol (THC). The precise composition of individual CBD products depends on the production and extraction methods used. The presence of THC above certain levels would mean that the product would not be authorised as a novel food and would become the responsibility of the Home Office under legislation on the misuse of drugs.
6. The Committee agreed that there was potential for interactions between the cannabinoids present in different CBD products and this, in turn, could affect their adverse effects in a product specific way.

¹ <https://cot.food.gov.uk/sites/default/files/tox2019-32.pdf>

7. Based on the available *in vitro* and *in vivo* data, CBD appears to have the following adverse effects: hepatotoxicity, immunotoxicity, reproductive toxicity, and interactions with drug metabolizing enzymes (P450), suggesting a risk to consumers. In addition, the effects on drug metabolizing enzymes following CBD exposure indicate the potential for drug interactions between CBD and pharmaceutical drugs.

8. The Committee agreed that there was a gap in the available toxicological information, especially in the areas of reproduction and immunology.

9. The COT could not reach a conclusion on the safety in use of CBD products based on the information presented². The Committee agreed this topic should be reviewed once more data became available. It was further noted that the data from the medicinal/pharmaceutical sector would be very useful if it could be obtained as most of it was currently not publicly available. However, it was noted that the safety profile of the CBD preparations used in food might be different to that of medical grade products due to differences in production and composition.

10. As the available genotoxicity data were conflicting but indicated genotoxic potential in some, but not all, of the *in vivo* studies available, the Committee recommended the genotoxicity data be referred to the COM for consideration.

COM discussions: October 2019

11. A discussion paper (MUT/2019/10³) was reviewed by the COM which concluded that the *in vitro* and *in vivo* genotoxicity studies reviewed were inadequate and were not conducted to recognised test methods or Good Laboratory Practice (GLP) standards. Therefore, a conclusion on the genotoxic potential of CBD could not be reached.

COT discussions: January 2020

12. In January 2020, an updated CBD discussion paper was presented to the COT (TOX/2020/02⁴).

13. The paper provided an overview of the data submitted to the United States (U.S.) Food and Drug Administration (FDA) and the European Medical Agency for the approval of the candidate human medicine Epidiolex[®] by its manufacturers GW Pharmaceuticals⁵. It highlighted the key adverse reactions identified in clinical and non-clinical studies of this medicinal form of CBD. The available data are in summary form and in places, the published reports are redacted, though this rarely affected data interpretation. Data were available in effects on laboratory animal species, patients and healthy human volunteers.

14. Pharmaceutical grade CBD in its purest form is >98% CBD but other commercially available CBD products, as might be used in novel foods, may be less

² <https://cot.food.gov.uk/sites/default/files/cotdraftminutesjuly2019finalamended.pdf>

³ <https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in-food-consumer-products-and-the-environment/about#publications>

⁴ <https://cot.food.gov.uk/sites/default/files/tox202002cbd.pdf>

⁵ <https://www.gwpharm.co.uk/>

pure and might contain other cannabinoids, which would have their own toxicological effects, as well as potentially interacting with CBD itself and hence might affect the adverse effects of CBD. It is important to note that few data are available on these related substances.

15. Members noted that their interpretation of the data provided by GW Pharmaceuticals was from the perspective of CBD used as a food, and that this would differ from how the data would be assessed for the clinical use of CBD, where weight would be given to the balance between risks and benefits in patients.

16. The Committee noted that most of the data from clinical trials were from human patients, and that although clinical data from healthy volunteers existed, this was not currently in the public domain. Members requested the Secretariat to explore whether this data could be made available along with data on pharmacokinetics (especially at the lower doses tested) which would aid in identifying the lowest-observed-adverse-effect level (LOAEL) and/or no-observed-adverse-effect-level (NOAEL).

17. The Committee agreed that there were no indications that pharmaceutical grade CBD was genotoxic based on the summary genotoxicity data from an adequate range of tests performed, which were sufficient to assess the genotoxic potential of CBD. However, it was suggested that these data also be reviewed by the COM.

18. The Committee discussed the pharmacokinetics parameters of CBD and noted that although CBD has low fasting bioavailability (<10%), consumption with food could increase CBD uptake by, for example, up to 5-fold if taken with a high fat meal. In addition, Members noted that some CBD products were currently being formulated to increase CBD uptake. Therefore, the information on CBD potency may be an underestimate of that of CBD when consumed as a novel food.

19. Members agreed that there were insufficient data to undertake a provisional risk assessment as it was not possible to determine a reliable point of departure such as a NOAEL. However, some general conclusions could be drawn that applied to CBD as a novel food.

20. Members concluded that there were observable adverse effects from CBD (Epidiolex[®] formulation) exposure of humans, most notably the following⁶:

- a) adverse effects on the liver (hepatic injury) at a CBD dose of ≤ 5 mg/kg bodyweight (bw)/day.
- b) inhibitory interactions with some medications at a CBD dose of ≤ 1 mg/kg bw/day, but there was insufficient information to determine the overall range of drugs that might be affected.

⁶ https://cot.food.gov.uk/sites/default/files/cotdraftminutesjan2020final_0.pdf

- c) somnolence effects were noted at ≤ 10 mg/kg bw/day⁷. Members agreed that the British National Formulary warning regarding driving and operating machinery should be noted.
- d) reproductive toxicity was observed in laboratory animals treated with CBD as well as developmental effects in the offspring. However, the mechanism was unclear. CBD was not teratogenic.
- e) due to CBD's physiochemical properties it is likely to transfer into breastmilk and could therefore pose a risk to nursing infants.

21. The Committee recognised that the balance between risks and benefits needs to be considered when assessing medicinal products. However, different considerations apply when assessing additives to food and novel foods.

COM Discussion: February 2020

22. A discussion paper (MUT/2020/01⁸) was reviewed by the COM which concluded that the *in vitro* and *in vivo* genotoxicity studies provided from the non-clinical trials of CBD suggested that, in its pure form (>98%), CBD did not have genotoxic potential. However, the COM requested the raw data from the studies be provided to finalise their conclusion.

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 unlikely to be greater than from oral exposure (see paragraph 18) and may be lower. The Committee noted that absorption of CBD from cosmetic products may also occur via inhalation of sprays and mists generated during product use.

⁷ Somnolence effects have been noted at 5 mg/kg bw/day in other studies (Devinsky, O., Patel, A.D., Thiele, E.A., Wong, M.H., Appleton, R., Harden, C.L., Greenwood, S., Morrison, G., Sommerville, K. and GWPCARE1 Part A Study Group, 2018. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology*, 90(14), pp.1204-1211).

⁸ <https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in-food-consumer-products-and-the-environment/about#publications>

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.

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.

Food Standards Agency (FSA) Consumer Advice February 2020

23. In February 2020, the FSA published consumer advice⁹ on the safety of CBD in CBD food products which drew on the views of the COT.

24. For the safety of CBD in CBD food products, the FSA noted that signs of adverse effects on the liver were observed at a CBD dose of 5 mg/kg bw in patients and in healthy human volunteers. This is equivalent to 350 mg in a 70 kg adult. However, adverse effects on the liver might occur at doses of less than 5 mg/kg bw/day but there were fewer data, so it was not possible to draw definite conclusions. CBD has also been shown to cause inhibitory interactions with some medications at doses of 1 mg/kg bw/day (equivalent to 70 mg in a 70 kg adult – *i.e.* 1 mg per kg bw)¹⁰. The effect at lower doses is not known. Therefore, 1 mg/kg bw/day of CBD represents a pragmatic upper level of intake above which there would be clear concerns about safety, until further data are available.

25. The FSA advised consumers to think carefully before taking any CBD food products and recommends that healthy adults do not take more than 70 mg a day in total, unless a doctor advised otherwise. This applies to a person having an average body weight of 70 kg and those having lower body weights should reduce their dose accordingly. Further, this advice does not mean that these levels are definitely safe, but that there is evidence adverse health effects could occur at intakes above this level.

26. As a precaution, FSA recommends that CBD should not be consumed by pregnant or breastfeeding women or by people taking medication.

27. It is important to note that the CBD intake deemed acceptable will ultimately be determined by an individual's weight and health status.

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⁹ <https://www.food.gov.uk/safety-hygiene/cannabidiol-cbd>

¹⁰ According to the Office of National Statistics in the United Kingdom (UK) the average male weighs 84 kg and the average female weighs 70 kg ; therefore this would equate to 84 mg and 70 mg of CBD, respectively (<https://www.ons.gov.uk/> (2018)).