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

Interim position on the potential risk of CBD in CBD products

Background and Introduction

1. The potential medical applications of Cannabidiol (CBD) have been investigated and researched for several years, including its use in clinical trials for the treatment of epilepsy and seizures. However, non-medicinal CBD-containing food products have become increasingly popular. These products include beverages (beer, spirits, wine, coffee and soda style drinks), edible oils (tinctures, drops, syrup, olive oils), chewables (gum drops) and chocolate. CBD containing food 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 needed to be evaluated and authorised before they can be placed 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.

COT preliminary discussions July 2019

3. In July 2019, a scoping paper on the potential adverse effects of CBD products (TOX/2019/32[1]) was presented to the Committee on Toxicity of Chemicals in Food, Consumer Products and The Environment (COT).

4. The Committee noted that some CBD products would not only contain CBD but also a range of other related cannabinoids including tetrahydrocannabinol (THC). The precise composition of individual CBD products will depend on the production and extraction methods used. However, 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 mis-use of drugs.

5. The Committee agreed that there was potential for interactions between the cannabinoids present in different CBD products and this, in turn, could affect their potential adverse effects in a product specific way.

6. Based on the currently available in vitro and in vivo data, CBD appears to have the following adverse effects: hepatoxicity, immunotoxicity, reproductive toxicity, changes to organ weights and alterations to drug metabolizing enzymes (P450), suggesting adverse effects could occur in consumers. In addition, the changes to drug metabolizing enzymes following CBD exposure indicate the potential for drug interactions between CBD and pharmaceutical drugs.

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

7. The Committee agreed that there was a lack of toxicological information especially in the areas of reproduction and immunology.

8. The COT could not reach a conclusion on the safety in use of CBD products based on the information presented[2]. 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 not currently available publicly. However, COT noted that the safety profile of the CBD used in food might be different to that of medical grade products due to differences in production and composition.

9. 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 Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) for consideration.

COM discussions October 2019

10. A discussion paper (MUT/2019/10[3]) was reviewed by the COM which concluded that the *in vitro* and *in vivo* genotoxicity studies at present were inadequate and not being conducted to recognised test methods or Good Laboratory Practice (GLP) standards. Therefore, a conclusion on the genotoxic potential could not be reached.

COT discussions in January 2020

11. In January 2020, an updated CBD discussion paper was presented to the COT (TOX/2020/02[4]).

12. 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 Epidiolex® by the manufacturers GW Pharmaceuticals[5]. It highlighted some of the key adverse reactions identified in recent clinical and non-clinical studies of this medicinal form of CBD which have been made publicly available. The data are in summary form and in places, the published reports are redacted, though this rarely affected data interpretation. Data were available on laboratory animal species, patients and healthy human volunteers.

13. Pharmaceutical grade CBD in its purest form is >98% CBD but other commercially available CBD, as might be used in novel foods, may be less 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 possible adverse effects of CBD. It is important to note that few data are available on these related substances.

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[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/

14. Members noted that their interpretation of the data provided by GW Pharmaceuticals was from the perspective of CBD used as a novel food ingredient, 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.

15. The Committee noted that most of the data from the clinical trials were from human patients; although data from healthy volunteers data 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 with identifying the lowest-observed-adverse-effect level (LOAEL) and/or no-observed-adverse-effect-level (NOAEL).

16. The Committee agreed that there were no indications that pharmaceutical grade CBD was genotoxic based on the summary genotoxicity data from the range of tests available, and these would be adequate to assess the genotoxicity of CBD. However, it was suggested that these data also be reviewed by the COM.

17. The Committee discussed the pharmacokinetic 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. Members noted that 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.

18. 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. However, some general conclusions as discussed could be drawn that applied to CBD.

19. Members concluded that there were observable adverse effects from CBD exposure of humans, most notably the following[6]:

a) hepatic impairment (liver injury) at a CBD dose of ≤ 5 mg/kg body weight (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.
c) somnolence effects were noted at ≤ 10 mg/kg bw/day. 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 developmental effects in the offspring, however, the mechanism was unclear. CBD was not teratogenic.
e) Due to CBD's physiochemical properties it was likely to transfer into breastmilk and could therefore pose a risk to nursing infants as well as pregnant women.

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

20. The Committee agreed that when considering the data on medicinal products, it should be noted that there will be a balance between risks and benefits that does not apply to food.

COM Discussion February 2020

21. A discussion paper (MUT/2020/01[7]) was reviewed by the COM which concluded that the *in vitro* and *in vivo* genotoxicity studies provided from the non-clinical studies suggested that the pure form of CBD >98% did not have genotoxic potential. However, the COM requested the raw data from the studies to be provided to finalise their conclusion.

Food Standards Agency (FSA) Consumer Advice February 2020

22. In February 2020, the FSA published consumer advice[8] on the safety of CBD in CBD products which drew on the views of the COT.

23. For the safety of CBD in CBD 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 could occur at doses of less than 5 mg/kg bw/day in patients and in human volunteers but there are fewer data, so it is 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). The effect at lower doses is not known. Therefore, 1 mg/kg bw/day CBD represents a pragmatic upper level of intake until further data are available.

24. The FSA advised consumers to think carefully before taking any CBD products and recommends that healthy adults do not take more than 70 mg a day, unless a doctor agrees more. This doesn't mean that these levels are definitely safe, but that the evidence suggests adverse health effects could potentially be seen at doses above this level.

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

COT Statement

April 2020

[7] https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in-food-consumer-products-and-the-environment/about#publications
[8] https://www.food.gov.uk/safety-hygiene/cannabidiol-cbd