Minutes

Joint Subgroup of the Advisory Committee on Novel Foods and Processes (ACNFP) and Committee on Toxicity (COT) on CBD and Hemp Derived Products. Minutes of the 2nd CBD Meeting held on the 28th of September 2022

These minutes are subject to confirmation by the Subcommittee.

Members are required to declare any personal interest in matters under discussion; where Members have a particularly close association with any item, the Chairman will limit their involvement in the discussion. In cases where an item is to be discussed in their absence, a Member may make a statement before leaving.

Minutes of the 2nd meeting of the Joint Subgroup of the Advisory Committee on Novel Foods and Processes (ACNFP) and Committee on Toxicity (COT) on CBD and Hemp Derived Products, held on 28th of September 2022, online using Microsoft Teams.

Attendance

Committee Chair

Dr Camilla Alexander-White - Chair of ACNFP

Committee Members

Professor Alan Boobis - Chair of COT

Mrs Alison Austin - ACNFP

Dr Cheryl Scudamore - COT

Dr Stella Cochrane - COT

Professor Gunter Kuhnle - COT

Dr Lesley Stanley - ACNFP

Dr Mac Provan - COT

Professor Shirley Price - COT

Dr Simon Wilkinson - COT

Apologies

Prof. Gary Hutchinson - COT

Dr James Coulson - COT

Observers (FSA)

Mr. Will Smith - ACNFP Secretariat

Dr Olivia Osborne - COT Secretariat

Dr Cath Mulholland - Technical Secretary COT

Mrs Rachael J. Oakenfull - ACNFP Secretariat

Secretariat

Mrs Ruth Willis - Technical Secretary ACNFP

Mr Ben Haynes - Lead Secretariat for Subgroup

Dr Tahmina Khan - ACNFP Secretariat

Mrs Afielia Choudhry - ACNFP Secretariat

Miss Victoria Balch - ACNFP and subgroup Administrative Secretariat

The Joint Subgroup of the Advisory Committee on Novel Foods and Processes (ACNFP) and Committee on Toxicity (COT) on CBD and Hemp Derived Products has

considered an update on data on a CBD isolate and Synthetic CBD during their meeting on 28th September 2022. They identified several issues that need to be addressed in order to with the safety assessment of CBD Novel Food applications.

1. Apologies and Announcements

Apologies were received from Prof. Gary Hutchinson and Dr. James Coulson.

2. Minutes from the 1st meeting and the future circulation of minutes

CBD/02/MINS

The chair welcomed the Members, representatives from the FSA, the observers and the Secretariat team. The chair noted that the minutes from the previous subgroup meeting were currently delayed until the next meeting.

The lead secretariat thanked the members for their previous comments regarding how to better present the relevant CBD datasets and extensive amount of information during the initial ACNFP/COT Subgroup meeting. The Secretariat explained that whilst the previous minutes have been written up they were undergoing internal review before being circulated to subcommittee members for comment. The Secretariat explained the intent to have both the previous and current minutes to be circulated together as one package.

3. CBD isolate and Synthetic CBD update paper (Reserved Business)

Detailed review of the updated data package

The current COT Opinion from February 2022 suggests that a health-based guidance value (HBGV) can be derived using a LOAEL of 5 mg/kg bw/day from human studies on Epidiolex. There are caveats to the applicability of this HBGV to susceptible sub-groups (e.g. pregnant women) and to its application for the safety evaluation of CBD as a novel food/supplement. However, in 2020, the body of toxicological evidence was not comprehensive or robust enough in terms of study design and outcomes to derive a toxicological point of departure (POD) for use in a guideline risk assessment. Since 2020, new studies have become available, and the subgroup were asked to review the data and suggest whether a point of

departure could be derived.

The subgroup were provided with an update of toxicological study data for the pure form of CBD, which adds to the body of existing evidence for CBD, incorporating new information as provided by applicants. Following the proposed recommendations by the subgroup during the previous meeting, to improve analysis of the data package on CBD isolates, the FSA provided a revised table format to support a scientific review of the body of toxicological evidence.

Members reviewed each new study considering the information on the toxicological parameters and whether the full body of evidence would allow for a toxicological point of departure to be derived, for which effects and whether there were any outstanding evidence gaps. Considerations were made by the subgroup as follows:

Behavioural parameters

The subgroup further considered if the behavioural and functional responses (e.g. salivation, somnolence) that were reported in the rodents were relevant to humans. As somnolence has been established in human data for CBD and is considered one of the most common side effects reported in human studies, the rodent observations could not be dismissed as also being relevant to humans.

Members agreed that CBD is not psychoactive, and this type of effect is more consistent with other cannabinoids similar to THC. It was concluded that the pharmacology of CBD or the putative benefits as a supplement are still not fully understood.

Liver observations

Members agreed that effects in liver are a consistent observation for CBD in both animal and human studies. Some of the hepatic changes observed in animal toxicology studies appeared relatively consistent with the adaptive hypertrophic response that are widely regarded as rodent specific, though not all. Members discussed observations on elevated liver enzymes and histopathology of the liver that could not fully be dismissed as rodent specific.

The subgroup discussed the typical observations in the liver data seen in humans, compared to rodents and all members agreed they were less consistent with an adaptive response. This suggests humans and rats may respond to CBD in a different way and this should be taken into account in interpreting the

toxicological data for risk assessment. Effects on the liver are key end effects for CBD, and selecting an appropriate point of departure was discussed in this context from the available data.

Thyroid parameters

Discussion turned to the thyroid and the liver- axis. The subgroup discussed the changes observed in the rodent toxicological data at relatively high doses compared to those used in the context of CBD in novel foods. It was agreed that the effects seen on thyroid hormones and thyroid histopathology are likely to be related to an indirect effect that is a rodent specific effect and was concluded to be adaptive and not adverse. A point of departure should not be based around observations on thyroid hormone modulations in rodent studies as it is not considered relevant to humans.

Reproductive parameters

The subgroup reviewed whether there was any new evidence on reproductive and developmental effects identified in the studies. Members agreed that any additional data provided since the previous COT review did not provide conclusive data on the impact of CBD on reproductive/developmental systems and so the data gap remained. The outcome of the COT Opinion in Feb 2022 recommended that CBD containing foods should not be used by pregnant women. This was supported by the subgroup and it was recognised reproductive and developmental toxicity remains an ongoing area of uncertainty, based upon some existing evidence in the peer-review literature from the FSA comprehensive literature review, continuing to give cause for concern.

The subgroup recognised the lack of available guideline study data but concluded that the new 90-day study data did suggest that sperm evaluation is a parameter that is not consistently observed in all studies. Given there was not a consistent effect seen in the data and that observations were at higher doses that those being considered for the liver effects; it was suggested that additional animal studies were not required to complete the toxicological review of the data currently.

Conclusions reached at this stage

When considering a POD to use in novel foods risk assessment, members agreed that from the studies presented; a POD of 150 mg/kg bw/day could be established as a No Observed Adverse Effect Level (NOAEL) for the most sensitive effects of

liver observations in rodents that could not be discounted as relevant to humans.

Members agreed and confirmed that as the POD from the data package was 150mg/kg bw/day and this was a NOAEL not a LOAEL, hence no additional uncertainty factor of 3 was needed.

Taking into account the context that the dosing vehicles in all studies were in a simple carrier oil and not a novel food matrix, appropriate uncertainty factors may need to be considered in novel foods risk assessment to account for any differences potentially in bioavailability.

It was agreed that the standard 100-fold uncertainty factor accounted for toxicokinetic and toxicodynamic differences between species and individuals and should be applied to the POD.

The subgroup explored the need for additional uncertainty factors to account for the lack of bioavailability data and the fact that human sensitivity could be greater than rodents regarding the liver effects. The lack of metabolic knowledge on CBD in humans compared to rodents, alongside gaps in reproductive and immunomodulatory endpoints suggests an additional UF should be added. On that basis it was concluded that an additional uncertainty factor of 10, making it 1000-fold UF in total, could be applied to the POD to derive a putative ADI. i.e. 150mg/kg bw/day POD – divided by (10 x10 x10) = 0.15mg/kg bw/day.

For a 70kg adult = 0.15 mg/kg bw/day x 70 kg would lead to an ADI of 10mg/day This toxicological evaluation corroborates, and is largely consistent with, the conclusions of the COT Opinion in Feb 2022, where data from human studies were used to set a HBGV of 11.7 mg/day or more conservatively (considering the potentially more chronic nature of using CBD as a food in a general population vs a medicine), a 3-fold lower value of 4 mg/day.

The concerns surrounding pregnancy and CBD-drug interactions would still apply and may require risk management measures. The conclusion made at this point in the discussion was that based upon the body of evidence from animal studies, a reserve ADI can be set at 10 mg/day. This value is based on observations in the liver and the working position based on evidence to date that reproductive or developmental effects are not likely to be the most sensitive effects compared to those effects observed and considered on the liver, If further toxicological or human evidence becomes available e.g. a lower POD is observed for more sensitive effects, or that reproductive effects are more sensitive the ADI may change upon further review of new evidence and uncertainty evaluation.

Other considerations for risk management

The subgroup advised that warning labels should be carried on products in relation to taking CBD when trying to get pregnant, given the concerns highlighted from literature data and the current data gaps in reproductive/developmental toxicity.

Warning labels may also be advised due to the effects of somnolence seen in both animals and humans.

Overall, a large caveat in using human study data for Novel Foods context going forward is the lack of bioavailability data and the impact this has on extrapolating the effects seen in oil formulations to the variety of products and formulations applicants are wishing to market. The importance of considering the composition uncertainty, as recent UK data suggested that most CBD products are lower than the claimed 98% purity of CBD suggesting that analytical methods may not yet be consistent and repeatable, or the product has a degree of instability in its cannabinoid content.

The human extrapolation uncertainties should encompass certain sensitive subgroups, populations and their lifestyles – age (children vs adults), ethnicity, diet and food combinations and interactions, herbal products, other CBD use (cosmetics), alcohol consumption, vaping, smoking, acute vs chronic exposure (not enough chronic data), pregnancy and lactation.

The context of how the Novel Foods products is used and whether drug-drug interactions are possible was also considered important in terms of risk management. The subgroup recognised the potential for significant foreseeable misuse or overdose even if an ADI was specified on products, and as such self-induced accidental overdose occurring is something that should be monitored. The members identified that in the context of deriving a new reserve ADI of 10 mg/day, data and evidence gaps remain, largely around the impact of food matrix on bioavailability, a lack of data on reproductive/developmental toxicity endpoints, and potential for drug-drug interactions.

4. Date of the next meeting

The next meeting is scheduled for Wednesday 30th November 2022. It will be held online via Microsoft Teams.