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 3rd CBD Meeting held on the 30th of November 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 3rd 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 30th of November 2022, online using Microsoft Teams.

Attendance

Committee Chair

Professor Alan Boobis - Chair of COT

Committee Members

Dr Camilla Alexander-White - Chair of ACNFP

Mrs Alison Austin - ACNFP

Dr Cheryl Scudamore - COT

Dr Stella Cochrane - 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

Professor Gunter Kuhnle - COT

Dr Olivia Osborne - COT Secretariat

Mrs Ruth Willis - Technical Secretary ACNFP

Observers (FSA)

Mr. Will Smith - ACNFP Secretariat

Mr. Shaun Jacobs - ACNFP Secretariat

Observers BEIS

Ms. Frances Hill

Secretariat

Mr Ben Haynes - Lead Secretariat for Subgroup

Dr Tahmina Khan - ACNFP Secretariat

Mrs Afielia Choudhry - ACNFP Secretariat

Dr Cath Mulholland - Technical Secretary COT

Executive summary

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 a data update on the ACI Consortium of CBD applications during their meeting on 30th November 2022. They identified several issues that need to be addressed in order to proceed with the safety assessment of CBD Novel Food applications.

1. Apologies and Announcements

Apologies were received from Prof. Gary Hutchinson, Prof. Gunter Kuhnle, Dr. James Coulson, Mrs Ruth Willis and Dr. Olivia Osborne.

2. Minutes from the 1st and 2nd meetings

CBD/01/02/MINS

The Chair welcomed the members, representatives from the FSA, the observers and the Secretariat team. The Chair noted that the status of minutes from the previous subgroup meetings was to be addressed by the lead Secretariat.

The lead Secretariat thanked the members for their continued patience whilst awaiting the package containing the of minutes which had been reviewed by FSA staff. The Secretariat explained that the package was circulated earlier that morning and was therefore available to subcommittee members for comment. The Secretariat explained the intent to have both sets of the previous minutes commented on and finalised by subcommittee members within the 2-week deadline provided.

3. ACI Consortium CBD Update Paper (Reserved Business) CBD/03

Detailed review of the updated data package.

The subcommittee were provided with an update of toxicological study data for the ACI Consortium of CBD applications, which adds to the body of existing evidence for both CBD isolate and Broad-Spectrum products, incorporating new information as provided by the applicants.

The identification of the reserved ADI for isolates by the subcommittee during the previous subgroup meeting allowed the group to make some initial conclusions and build upon the advice already provided to consumers. For this meeting the FSA provided the consortium data package from one applicant to confirm whether it would support the reserved ADI based on the body of toxicological evidence. The FSA also requested that the subcommittee provide an indication as to whether on its own, the data package could support further data read across to the wide number of applications seeking to use it.

Members reviewed each new study considering the information on the toxicological parameters and whether the whole body of evidence would provide further support for the previously derived toxicological point of departure, for which toxicological effects/endpoints and whether there were any outstanding evidence gaps. Considerations were made by the subcommittee on the new study data as follows:

Liver Observations

Members agreed that the effects reported in the liver provided in the new consortium 90-day study were consistent with the findings discussed in previous meetings, with a large increase in liver weight being the predominant observation (2.5 times the size reported in the control). Members could not dismiss this effect as it depicted a high volume of liver enlargement for this particular package, and it was consistent with observations for other CBD test materials. Furthermore, as observations of this increase in liver weight were seen at the lower dose, the subgroup concluded that the hepatotoxic effects of CBD in animal toxicology studies cannot be ignored. The liver as a target organ continues to be the main effect observed after CBD administration that may also be relevant to humans. It was noted that there was no accompanying elevation in liver enzymes and no other changes that warranted any toxicological significance in the study being reviewed. Members concluded that these effects may be adaptive in the new 90-day study but as there was no recovery period then it is unclear.

Haematological findings

The sub-group noted that the haematological findings from the consortium 90-day study presented significant toxicological observations for females administered the high dose, albeit some observations of alterations began at the low dose but were not deemed a significant toxicological effect.

Locomotor activity

Discussion turned to the locomotor activity observations reported in the consortium study, where alterations in 2 females and a third of males were noted in the high dose. The significance of these results was debated further as there were some observations in females at the low dose. The sub-group further considered the relationship of these observations reported in the rodents to potential somnolence and finally, extrapolation to humans. It was concluded that these results could potentially put greater weight on the human data available which considers the neurological effects of CBD administration in humans.

Male reproductive effects

The subcommittee reviewed the potential male reproductive effects reported in the consortium 90-day study, where a 36% alteration in sperm count was noted at the highest dose. Members concluded that this result highlighted some concern but would not reduce the POD established from evidence previously considered.

Conclusions reached for the consortium at this stage.

When considering a NOAEL to use in novel foods risk assessment for the consortium and its products alone, members agreed that a dosage of 50 mg/kg/day to support this Group B CBD isolate mix could be appropriate in this case. By utilising the same uncertainty factor (UF) of 1000 as was defined in the September 2022 CBD subcommittee meeting for pure form CBD considering the evidence, this may lead to an ADI of 3.5 mg/day for this tested product mix only. The constituents of the mix were known, however the potency of cannabinoids other than CBD is not known, reading across to other CBD mixtures without compositional data is challenging due to the lack of toxicity data on other cannabinoids. It was concluded that for those products that are >98% CBD, the ADI of 10 mg/day was still supported.

For those products in the 80-98% CBD group and where other cannabinoids are present, the subcommittee agreed that they need to get a better understanding whether the ‘other cannabinoids’ are likely to be more or less potent than the >80% CBD in terms of liver effects, psychoactivity or other effects that can be reasonably predicted. It was concluded that the subcommittee should look at cannabigerol (CBG) at the next opportunity and discuss a review of the data for product mixtures where CBG is a significant component e.g., more than 1%. This will allow an understanding of the contribution of the other cannabinoids make to

the toxicological effects noted. It will also allow an opportunity to understand what if any read across to other cannabinoid mixtures can be made from the dataset.

Future considerations for the ACNFP/COT subcommittee reviews

A key issue is that effects of many of the hundreds of other cannabinoid constituents are unknown at this time, with some knowledge about cannabigerol (CBG) emerging in the literature.

The members discussed the potential benefits of future reviews surrounding the compositional analyses of applicants' CBD products. It was suggested that grouping the CBD novel foods into three separate groups according to composition was a sensible approach. For Group A Pure form >98% CBD, the priority going forward should now be given to generating and collating more human evidence in the form of PK data and adverse events data in human studies. It was agreed that no more 90-day repeat-dose toxicity studies were needed on pure form CBD applications to inform the ADI.

Based on the body of evidence from human data principally, and as supported by the animal data, an ADI for Group A can be set at 10 mg/day. Members agreed that if there are PK datasets to suggest that human bioavailability is lower than in the available study evidence, then that could be used to reduce the toxicokinetic uncertainty factor. However, it was discussed that the intent of a manufacturer is to have as much bioavailability as possible to have a useful product, so it is unlikely that vehicle effects or bioavailability data would serve to increase this ADI.

The subcommittee discussed the potential of a combined reproductive study in the context of addressing the remaining uncertainties. It was concluded that if a reproductive/development study were to be done, it should be done by a consortium covering pure form CBD products only. However, the purpose should be clear, as it is unlikely to increase the ADI. Product labelling is expected to be done at the moment and CBD is not to be used by those intending to get pregnant. Members determined that if there were no reproductive/developmental effects seen in a potential study, then the labelling could be removed but there are still UFs of 1000 needed for the liver effects on the ADI of 10 mg/day derived from toxicological data. It was concluded that the purpose of doing a reproductive/developmental study would be to avoid labelling by performing a study that showed no effects.

For the future, Group B, which would encompass products containing 80-98% CBD , and it was concluded that all manufacturers should characterise their products ideally in a consistent manner, using standardised analytical methods, so the FSA can develop a database over the years ahead. A question was put forward to the Secretariat as to whether a template database in Microsoft Excel could be built by the FSA to include all of the expected cannabinoids and ‘impurities’ in the test items and the product being defended, vehicles used and basic requirements of 90-day studies etc.

The database was further considered where each manufacturer would have to complete the characterisation data file detailing which cannabinoids are in their product and send it back to the FSA, so FSA can build up a database of Group B product mixes on the market with any 90-day studies the manufacturers have done.

Additionally, members agreed that if manufacturers submitted 90-day studies on their specific Group B CBD and ‘other cannabinoids’ mix products, the ACNFP can look at their data in the context of their specific product approval to cover the unknown effects on the ‘other cannabinoids in the mix’. The subgroup’s main concern regarding the Secretariat’s question for potential read across using just one broad-spectrum 90-day study over the entire consortium is that they do not have enough data to develop a body of evidence on which to develop generic criteria for a Group B product at the moment, with respect to ‘other cannabinoids’. However a case by case approach can be taken depending on the constituent levels in the mix.

Overall, over time further data will be gathered and properties may start to emerge in an observational way with various product mixes as they are tested. Meanwhile, the FSA could look at research on the toxicity of ‘other cannabinoids’ in the Group B mixes. This could be done using NAMs in principle for a range of expected effects e.g., in liver. As reproductive/developmental effects are not well characterised it is advised that those women of childbearing potential, intending to get pregnant do not take Group B mix substances as for pure CBD and that children under the age of 18 should not be given these products.

Further Considerations

The subcommittee debated that the main focus going forward would be to concentrate on the analysis of ‘other cannabinoids’ for the eventual Group B cannabinoid mixtures, given the known uncertainties surrounding additional cannabinoids and their potentially toxic effects on the human body which has

been highlighted in emerging literature data.

Considering the current context that additional cannabinoids should not exceed the thresholds set by the FSA, yet numerous applicants are providing products with supporting compositional analyses that suggest higher levels of cannabinoids, development of a generic specification detailing the CBD is at 80% in a product may need to be considered.

It was agreed amongst members that deducing the likelihood that the remaining 20% of constituents in Group B products (which contain 80% CBD) can cause harm should be explored further. The FSA/Subgroup already has a

Given the current residual uncertainties of CBD in the context of novel foods use, the subcommittee suggested that the FSA ensures that all the available human and volunteer studies on CBD are made available to the subgroup in order to better understand the kinetics, fate and behaviour of CBD in humans. It was suggested amongst members that as a whole, human studies on somnolence for CBD products, human evidence on drug-drug interactions and CBD and cannabinoids in breast milk and development be reviewed further, to aid the FSA in developing appropriate risk management strategies. Particular emphasis on the importance of future reviewing of human immunotoxicology data made apparent by the immunotoxicology specialists was agreed upon by the Chair and Subcommittee members.

However, the current human evidence (as reviewed by the COT February 2020) and subsequent animal toxicology evidence is concordant in being able to generate an ADI of 10 mg/day for pure form >98% CBD.

4. Date of the next meeting

The next meeting is scheduled for Tuesday 17th January 2023. It will be held online via Microsoft Teams.