ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

DRAFT MINUTES OF THE ONE HUNDRED AND FORTY THIRD MEETING HELD ON 10th September 2020

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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 ONE HUNDRED AND FORTY THIRD MEETING OF THE ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES, HELD ON 10th SEPTEMBER 2020, ONLINE USING MICRSOFT TEAMS

ATTENDANCE

Committee	Dr Camilla Alexander-White	**Chair**
	Dr David Mela	**Member**
	Dr Hamid Ghoddusi	**Member**
	Dr Lesley Stanley	**Member**
	Dr Mark Berry	**Member**
	Dr Maureen Wakefield	**Member**
	Dr Rohini Manuel	**Member**
	Dr Rebecca McKenzie	**Member**
	Ms Nichola Lund	**Member**
	Professor Clare Mills	**Member**
	Professor Harry McArdle	**Member**
	Professor Huw Jones	**Member**
	Professor Paul Fraser	**Member**
	Professor Susan-Fairweather-Tait	**Member**
	Professor Wendy Harwood	**Member**
Apologies	Dr Anton Alldrick	**Member**
	Professor Susan Duthie	**Member**
Assessor	Ms Karen O'Connor	**Senior Novel Foods Policy Advisor**
Observers (FSA)	Dr Chun-Han Chun	**Head of Science Strategy Assurance**
	Dr Paul Turner	**Science Council Representative**
	Dr Sabrina Roberts	**Senior GM Policy Advisor**
	Mr Hoa Chang	**GM Policy Advisor**
	Dr Amie Adkin	**Head of Risk Assessment**
	Ms Georgina Finch	**Food Standards Scotland**
	Ms Siobhan Watt	**Food Standards Scotland**
	Mr Adam McDowell	**Policy Advisor FSA Wales**
	Mr Andrew Dodd	**Novel Foods Policy Officer**
	Ms Kerry Gribbin	**Senior Policy Advisor**
	Ms Lisa Nelson	**Senior Communications Manager**
	Dr Olivia Osborne	**Toxicological Risk Assessor FSA**
	Professor Alan Boobis	**Chair Committee of Toxicity (COT)**
	Professor Robin May	**FSA Chief Scientific Advisor**

Secretariat	Mrs Frances Hill	**Technical Secretary**
	Mrs Erin Oliver	**Senior Secretariat**
	Mr Richard Uchotski	**Secretariat**
	Mr Francisco Matilla-Garcia	**Secretariat**
	Ms Beth Rendle	**Secretariat Administrative Hub**

Glossary of Terms

ACNFP- Advisory Committee on Novel Foods & Processes
ADME- Absorption, Distribution, Metabolism, Excretion
CBD- Cannabidiol
COM- Committee on Mutagenicity
CoP- Code of Practice
COT- Committee of Toxicity
EFSA- European Food Safety Authority
EU- European Union
FAIM- Food Additives Intake Model
FSA- Food Standards Agency
GM- Genetically Modified
HPLC- High Performance Liquid Chromatography
NDNS- National Diet & Nutrition Survey
NOAEL- No Observed Adverse Effect
SACS- Scientific Advisory Committees
THC- Tetrahydrocannabinol
TMC- Total Microbial Count
TYMC- Total combined Yeasts and Moulds count
UK- United Kingdom

1. Apologies and announcements

Apologies have been received by Professor Susan Duthie.

Dr Anton Alldrick declined to participate in this meeting due to interests brought to the Secretariat's attention ahead of the meeting: a personal interest and in relation to the interests of his employer regarding Cannabidiol (CBD) products. He did not attend any part of the meeting, participate in any discussions and did not have sight of the papers being discussed. It was raised by the committee that Dr Alldrick was an expert in this area and his knowledge would be valuable to the committee, but the committee felt that it was entirely appropriate for Dr Alldrick not to be privy to any commercial dossiers and to not influence any advice on how CBD should be assessed. They asked whether it would be possible for Dr Alldrick to offer advice on the more general aspects of CBD safety assessment e.g. the publicly available COT paper.

Paul Tossell, who usually acts as our FSA Assessor, gave his apologies. Karen O'Connor from our Policy team acted as Assessor in his place.

2. Meeting Minutes for 142nd Meeting ACNFP/142/MINS

The Committee agreed that the minutes were a true record of the 142nd meeting of the ACNFP held on 23rd June 2020, except for one substantive correction that was requested, to make it clear that the discussion around the relevance of 90-day studies in GM safety guidance, was specifically in relation to whole GM food.

3. Matters Arising from the last meeting. ACNFP/143/MA

3.1 The Committee reviewed a future way of working- GM Guidance document and considered approaches for the risk assessment of GM safety information. In general, the Committee expressed a view that the EFSA guidance documents discussed were comprehensive and appropriate for a UK system. However, Members acknowledged that specific areas could be updated in light of new scientific developments and new safety information, and this has been noted.

3.2 The Committee reviewed the revised Code of Practice (CoP) from the SACS and provided comment. Amendments have been made based on suggestions received. The CoP was discussed again by the Committee for clearance in Item 8. On the issue of communication and collaboration with

other Committees which was discussed, this has been raised with the SACS co-ordination team and is now an agenda item at the upcoming joint-SACS meeting.

3.3 The Committee discussed the Food Standards Agency (FSA's) position statement on the safety of genome editing technologies. Comments on changes to the statement were provided and the document shared with relevant parts of the FSA.

3.4 The Committee discussed a Novel Food Guidance Paper regarding the EU guidance on Novel Foods. The members reviewed the guidance to check its applicability for future use in the safety assessment of novel foods. The Secretariat thank Members for their comments. These have been taken on board and will be considered in any updates to the novel foods guidance.

4. Committee on Toxicity Position Statement ACNFP/143/01

The Committee on Toxicity (COT) has recently published a position paper on the potential risk of CBD in food products to summarise several discussions that have been held by COT (and in consultation with the Committee on Mutagenicity (COM) on matters relating to genetic toxicology) on the safety of selective cannabidiol (CBD) extracts when used as a food product. These meetings largely reviewed the publicly available safety data on CBD especially in relation to toxicological and genotoxicity data. Given that the ACNFP will be reviewing CBD dossiers from applicants soon, the ACNFP reviewed this paper and held an overall discussion on the paper and any issues it may raise. The Chair of the Committee on Toxicity, Professor Alan Boobis, was also present at the meeting to address any questions directly that the ANCFP raised.

Firstly, the ACNFP gave overarching comments on the paper. The paper looks solely at CBD and not at other cannabinoids or contaminants that may be present in the CBD-based novel foods. The Committee noted that the main health concerns highlighted by the Committee on Toxicology were hepatotoxicity, immunotoxicity, reproductive toxicity and drug metabolism interactions.

The Committee commended the COT on the position statement, stating overall that the paper is a useful document for helping the committee to understand the current knowledge on the toxicity of CBD.

1. The Committee noted that the primary source of current toxicology data is from studies to support the authorisation of >98% pure CBD as a medicine, with brand name Epidiolex. This is a CBD-based medicine licenced to treat certain forms of epilepsy. The Committee noted that medical trials are not designed to support the safety of food products as exposure patterns, co-consumption, purity of the CBD and recorded outcomes differ and therefore results from these studies may only be useful in supporting novel food applications for CBD in certain circumstances. The ACNFP noted that there are still gaps in the toxicological data package around systemic toxicity and human bioavailability.
2. The Committee noted that there will likely be variation between the purity of the extracts destined for use in foods and proportions of minor components present between different novel food applications and therefore product specific

characterisation data will be important. Members also noted that bioavailability is likely to vary considerably between CBD in different matrices or co-consumed with foods and data to support the properties and human systemic exposure from each product will be important.

3. The Committee noted the data indicating that CBD may be hepatotoxic. Liver effects have been observed in patients when using Epidiolex and in animal studies and the mechanism is unknown. Furthermore, COT stated that in the case of liver toxicity it is often difficult to set a NOAEL as such effects could be adaptive rather than an adverse effect.

4. The Committee highlighted that adverse effects had been observed at the lowest doses tested in the available studies. It is also possible that humans may be more sensitive than animals to CBD. Therefore, it is not possible to set a level at which no effects have been observed. This makes a traditional risk assessment, based on the concept of minimal risk, difficult to perform.

5. In relation to human studies, members noted that liver injury has been observed at exposures greater than 5 mg/kg bw/day, interactions with medication have been observed at exposures of 1 mg/kg bw/day and effects on somnolence (sleepiness) have occurred at levels of 10 mg/kg bw/day although this is likely to exceed exposures that may be achieved through food uses.

6. The COT identified a pragmatic upper level of intake for a 70kg adult at 1 mg/kg bw/day above which there would be clear concerns about safety, until further data are available. As the COT did not have access to all of the animal data, as some studies are commercially sensitive, and specific conditions of human exposure from food exposure are, at the present time, unknown, they could not do a margin of safety evaluation. Therefore, the 1mg/kg level that the COT has identified is pragmatic as being unlikely to cause harm on the basis of current information but does not reflect a guaranteed safe level on the basis of minimal risk. .

Action: To incorporate the knowledge shared by the COT into the future assessment of CBD Novel Food Applications

5. CBD Applications (Reserved Business) ACNFP/143/02

Selective extracts of cannabidiol (CBD) in food products and beverages have been formally classified as Novel Foods by the European Commission. At the end of the EU Exit transition period, the ACNFP will be responsible for reviewing the risk assessment of novel foods for the UK market, which will include the assessment of CBD novel food products. As a training exercise for the Committee and to prepare both members and the secretariat for assessing CBD applications following the end of the transition period, the Committee reviewed two CBD dossiers that have been informally submitted to the FSA.

The Committee commented that by providing all the sections of the report as individual PDF files it made reading rather cumbersome. The Committee stated that they would prefer to have one large collated PDF file made available containing all the sections of the application.

General

In both dossiers it is not clear how the evidence has been gathered. For example, was a peer review literature search performed and how; were studies designed as part of an overall safety strategy. The authors should be able to present the data in a convincing way so as to provide assurance that all relevant data and studies (published and commercial) are included in the dossier.

Lack of Product Relevant data

The Committee was concerned that both applications used data from the Epidiolex submission to support the safety of their product but did not provide safety data on their specific product. As noted in the previous item, the purity of the CBD used for medical trials may not fully reflect CBD in food use. Therefore, the Committee agreed that applicants should carry out their own toxicological data where their CBD substance differed from medical grade or provide bridging studies to make sure the toxicology data being used to assure safety was relevant for the purity and composition of their CBD product.

Processing, Composition and Specifications

The Committee commended the level of detail on the production process in one of the applications, as a good example. This application clearly described the steps, listed the amounts and the processing that occurred, the proportions in which the chemicals where used, listed timings, and the chemicals used at each stage and had some food safety plans associated to the production process. The Committee also commended the description of the processing at each stage and suggested that more applications should strive for the detail outlined in this application.

The Committee commented that more detailed chemical analysis was required in both applications. They noted that there was no consideration of the different stereoisomers of CBD. Further, the impact of processing on the chemical structure of CBD was not considered. This is important as a small chemical change can in principle induce a large biological effect.

One applicant had used unvalidated in-house methodologies for chemical analysis of the raw plant materials and CBD content. The Committee highlighted that they were unable to gauge how effective such methods would be for different matrices. They noted that one method used to characterise the plant material was based on HPLC and did not appear to incorporate bivariate analysis or additional mass spectrometry.

The Committee considered that the microbiological tests carried out were not adequate, and the proposed limits for TMC and TYMC were not standard acceptable limits, and that the acceptance criteria was unclear.

The Committee noted that in both applications, the starting materials were not well defined. When considering chemical synthesis, it was unclear where the starting material was sourced from. When using plant material, the cultivation and agriculture of the plants were not defined, the pesticides used were not listed, the genetic variety of the plants and the variation in metabolites in different plants were not considered.

The Committee commented that just classifying CBD plan sources by their low THC content was not adequate to account for the difference in composition of the raw materials, such as variety in terpenes and secondary metabolites.

For one application, the Committee questioned the provision of two different production processes in one application. Although, this is permitted by the regulations, the Committee noted that two different production process will have two different sets

of safety concerns that needed to be clearly separated, with the differences between the two processes and the subsequent difference in the two final forms of CBD explained.

The Committee suggested that there was limited, or no information provided on the chemicals used in relation to the contaminants in the process.

History of Use

The Committee were content that there was no established history of use of selective CBD extracts as food products.

Proposed Uses

The Committee noted the wide range of final foods proposed by one of the applicants whilst the other intended to use the CBD only as a supplement. The committee considered that the food matrix would impact the bioavailability, but the applicants did not provide data to support the use of CBD in different food stuffs. The committee also highlighted that likely consumption figures would need to be included in each dossier and that the two examples had not attempted to model potential exposure to CBD from their products, with no mention of FAIM or use of UK NDNS data. The use of CBD in many different food products would require full justification and clear evidence to demonstrate safety. The committee noted that it may be easier to demonstrate the safety of CBD in supplements alone at a specific intake, compared to incorporation or multiple intakes from a range of foodstuffs.

The Committee noted that if approval was granted to a company who sells the oil to be added to other foods by other companies, then there may be concerns over traceability and how they could limit the final uses and intakes. It would also be difficult for these companies to demonstrate the safety of the final products when they may not know what these are at the application stage.

ADME (Absorption, Distribution, Metabolism, Excretion)

The Committee was concerned that the ADME data showed that absorption of CBD is variable. It is metabolised by a variety of cytochrome P450s that are expressed at variable levels in the population. The phase 2 metabolism is poorly understood. Further, it accumulates in fatty tissues in human and rates of turnover are not clearly defined. It is not fully known how the compound is excreted in humans or what the turnover might be.

It is also noted that CBD interacts with enzymes that are involved in the metabolism of drugs and that co-consumption with other medication could be a risk factor to some consumers.

Nutritional Information

The Committee were content that CBD is not replacing other foods in the diet.

Toxicology

Overall, it was deemed by the Committee that the toxicology data was not adequately described for assuring the safety of the substances being reviewed in these dossiers and that there are still data gaps as noted by the COT position paper.

Allergy

The Committee stated that it was unlikely that CBD products would be allergenic. However, the evidence of immunomodulation may be a concern although these data are extremely limited.

Conclusions

The Committee concluded that both applications were lacking in multiple areas and did not supply adequate safety data to demonstrate the safety of their products. The Committee concluded that for both applications they would stop the clock and request that the applicants generated data to address their safety concerns.

ACTION: These comments have been collated and will be used to assist in future appraisals of CBD applications.

7. Request for Advice for CBD Applicants ACNFP/143/03

A number of small and medium sized companies applying for approval of their CBD products on the UK market are aiming to work together to plan and execute a joint package of toxicology data that could in principle be used for multiple products. Whilst each manufacturer is planning to submit individual manufacturing processes and composition analyses, they propose to share results from the relevant toxicology studies to prove the safety of CBD-based novel food products. Applicants of small and medium-sized companies have also requested a reference range of acceptable levels of cannabinoids and other components of their products to account for variability between company's batches. The Committee discussed if it was willing to follow such a proposition, and whether it is willing to provide referential values.

Members generally considered that separate applications should be submitted for each product, but they could share study data and evidence between them if the use of such data can be scientifically justified as part of their risk assessment. Therefore, a shared package of toxicology studies would be acceptable in circumstances that could be scientifically justified.

Members highlighted that in this situation, bridging studies are likely to be necessary for each application. These could include studies on bioavailability and analytical data to show how similar the product is to that used in the toxicology or pharmacokinetics studies i.e. to show the data in the toxicology studies are relevant to their product specification.

Members were very wary of setting numerical limits for tolerances. The database as it currently stands, does not provide enough information for the committee to be able to do this. Each product will be different. The applicants know the details of their product and the onus is on them to be able to scientifically justify the information they have provided.

Each CBD ingredient will require analytical data including an impurity profile, cannabinoids etc. Data will also need to be provided on the bioavailability of the ingredient in any proposed food matrices or carrier oils.

Action: This information will be disseminated as required.

8. The Code of Practice **ACNFP/143/04**

The Code of Practice (CoP) has been updated since November 2019, with the Committee considering in several meetings the updates that have been made. The CoP was last discussed at the June 2020 meeting where further areas for improvement and clarity were provided and acted upon by the Secretariat. The Committee discussed these additions made since the June 2020 meeting. In addition to this, a Statement of Indemnity for all FSA Scientific Advisory Committees (SACS) has also been created by the SACS co-ordination team which is referred to within the Code of Practice. The Committee also reviewed this statement. A couple of points for clarification were raised.

Members discussed various sections of the Code of Practise and updated the text in including plans for if the Chair was unavailable and interaction between other government departments. There was also a discussion on how a final decision on a dossier should be completed and if there should be a formal agreement from all members at the end of the discussion or during the process of producing an opinion. The Secretariat agreed to take this forward with the Chair.

Action: To raise points made about the Statement of Indemnity with the SACS co-ordination team and consider formal agreement process for opinions.

9. Items for Information

9.1 Novel Food Policy Update **Written**

The Committee was provided with a written update on the issues under consideration in the EU on novel foods.

9.2 GM Policy Update **Written**

The Committee was provided with a written update on the issues under consideration in the EU of GM issues.

10. Date of next meeting:

The next meeting is scheduled for 25th November 2020. The meeting will be online due to concerns surrounding Covid-19.