Statements

Joint position paper from the Advisory Committee on Novel Foods and Processes (ACNFP) & Committee on Toxicity (COT) on establishing a provisional acceptable daily intake (ADI) for pure form (≥98%) cannabidiol (CBD) in foods, based on new evidence.

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Lay Summary

The lay Summary of the Joint Advisory Committee on Novel Foods and Processes (ACNFP) & Committee on Toxicity (COT) Position paper on establishing a provisional acceptable daily intake (ADI) for pure form ≥ 98% CBD in foods based on new evidence.

Summary of status of pure form CBD (≥98% purity) as a novel food.

Following the announcement by the FSA that from 31st March 2021, all CBD products on the market must have their safety assured by companies submitting

a valid safety application, there have been a large number of CBD-related novel food applications. Consequently, a significant level of additional data has become available that requires review.

A joint Subgroup of the ACNFP and COT was formed to address a series of questions in relation to the safety of CBD-containing and hemp-derived ingredients. The overarching aim of the Subgroup is to enable the FSA to perform risk assessments for CBD in food. While there are a number of routes of exposure for CBD, the provisional ADI stated in this paper has been established on the basis of oral exposure.

The objectives of the Subgroup are to:

- Review the new data received from the novel food applications.
- Update previous reviews of CBD safety evidence and provide revised conclusions based on these reviews.
- Provide advice on whether the data available support identification of an Acceptable Daily Intake for CBD as a food ingredient.

1. This joint position paper by the ACNFP and COT is the outcome of discussions as of March 2023, which have focused on the risk assessment of foods and supplements in which the CBD ingredient itself is at least ≥98% purity. The new position described below provides advice on the safety of ingesting products containing at least ≥98% pure CBD via oral administration only and forms a basis for considering the applications under the Novel Foods Regulation. **This advice should not be applied directly to CBD products that are inhaled or applied dermally, nor does it consider exposure from such product types.**

A Statement on a provisional Acceptable Daily Intake (ADI) for Pure Form Cannabidiol (CBD at ≥98% purity) as a Novel Food Ingredient

2. The scientific evidence from human studies and toxicological studies supports a provisional Acceptable Daily Intake (ADI) of 0.15 mg/kg bw/day (equivalent to 10 mg CBD/day for a 70 kg adult) for pure form cannabidiol (CBD) (when used at ≥98% purity) as an ingredient in foods. It is expected that a healthy consumer will not come to harm with this level of intake of pure form CBD (≥98% purity).

A provisional ADI of 10 mg CBD/day for an average 70 kg adult is approximately equivalent to 4-5 drops of an oil-based supplement product containing 5% CBD of ≥98% purity.

Chronic daily lifetime use of Pure Form CBD (≥98% purity) in foods has yet to be fully assessed in a rigorous and scientific way. As a consequence, it cannot be ruled out that long-term daily chronic use of pure form CBD (≥98% purity) at intake levels higher than 10 mg CBD/day could contribute to the development of adverse effects over time, most notably in the liver.

Human evidence suggests that with oral intake levels above 70 mg CBD/day, in some individuals, adverse drug-drug interactions with some medications could occur. A dose of 70 mg CBD/day was the lowest dose evaluated in human studies and drug-drug interactions at doses lower than 70 mg/day cannot be ruled out. It is recommended that consumers do not ingest more than 10 mg CBD in any one day. Currently, somnolence (excessive tiredness) and liver effects are the main effects of concern.

The provisional ADI is recommended subject to the existing advice to consumers that pregnant and breastfeeding women and people taking any prescription medication should avoid the consumption of CBD if possible. Consumers on regular medications should seek advice from a medical professional before using any type of CBD food product. In addition, children, prospective parents trying for a baby and those who are immunosuppressed are advised against consumption of CBD due to remaining data gaps and residual uncertainties concerning the safety of CBD for these groups of consumers.

The provisional ADI of 0.15 mg/kg bw/day (10 mg CBD/day for a 70 kg adult) will act as a basis for risk assessments of novel food products containing Pure Form CBD as an ingredient. Dependent upon the nature of the food type, further considerations and information on bioavailability of CBD in humans in different food matrices may also need to be factored into product specific risk assessments.

Background

3. Cannabidiol (CBD) has, for several years, been investigated and researched for potential medical applications, including the treatment of epilepsy and seizures. However, CBD has now entered the food sector. These products include beverages (beer, spirits, wine, coffee and soda-style drinks), edible oils as food supplements (tinctures, drops, syrup, olive oils infused with CBD), chewables and

confectionary. These products were confirmed as novel foods in January 2019, which means that there was no significant history of consumption in the EU before May 1997 and they now need to be evaluated and authorised before they can be legally placed on the market.

4. In February 2020, the FSA published consumer advice on the safety of CBD food products. The analysis by the COT was limited by the available data and was largely based on a comprehensive literature review looking for safety data on CBD and pivotal evidence available in the public domain at that time from human studies on a medicine, Epidiolex®, which contained ≥98% pure CBD.

5. The FSA noted that signs of adverse effects on the liver were observed at doses of CBD at 5 mg/kg bw/day in patients and healthy human volunteers; this dose is equivalent to 350 mg in a 70 kg adult. The data in the literature also suggested that humans might be more sensitive to the adverse effects of CBD in the liver than laboratory animals.

6. Somnolence effects were noted at doses ≤10 mg/kg bw/day in human studies. Inhibitory drug-drug interactions have also been observed with some medications when CBD is co-administered at doses of 1 mg/kg bw/day (equivalent to 70 mg in a 70 kg adult); the likelihood of effects at lower doses had not been determined. Some of these interactions, in particular those involving tacrolimus and warfarin, have been attributed to inhibition of the hepatic P450 enzymes, CYP3A4 and CYP2C9. Based on the COT assessment, therefore, the FSA concluded in February 2020 that 1 mg/kg bw/day, or 70 mg in a 70 kg adult, of CBD represented a pragmatic upper level of intake above which there would be clear concerns about safety, until further data are available.

7. The FSA recommended that healthy adults do not take more than 70 mg of CBD per day. This applies to a person having an average body weight of 70kg; those having lower body weights should reduce their intake accordingly, so that it is not more than 1 mg/kg bw/day. Furthermore, this advice does not mean that 70 mg/day is safe, but that there is evidence adverse health effects could occur in some individuals in a general population at intakes above this level.

8. As a precaution, the current advice does not recommend a provisional acceptable daily intake (ADI) of CBD for people in vulnerable groups, unless under medical direction. These include pregnant and breastfeeding women, children, prospective parents and those taking any prescription medication.

Focus of the subgroup’s work – post-FSA call for data

9. Since the work of the COT, the FSA has sought further toxicological data from applicants seeking authorisation for CBD as a novel food. A substantial number (hundreds) of applications for CBD use in novel foods have now been received. The new safety data on CBD in food has required the formation of a joint ACNFP and COT Subgroup to perform a review of new CBD evidence.

10. In considering the new studies, the Subgroup organised the data based on the ingredients’ composition, which comprised three groups:

- Group A: those ingredients using ≥98% pure CBD only and no other cannabinoids (derived from either plant-based extraction or synthetic chemistry sources);
- Group B: those ingredients using CBD and a mixture of cannabinoids (derived from either plant-based extraction or synthetic chemistry sources);
- Group C: natural hemp or hemp-based extract ingredients containing a range of cannabinoids.

11. For ≥98% pure CBD ingredients where the remaining 2% of the composition is known, it was found that there is now sufficient toxicological and human study evidence to perform a human health risk assessment, seeking to establish an acceptable daily intake (ADI) for ≥98% pure CBD. It was not possible to establish a full ADI, due to data gaps, but the Subgroup were able to establish a provisional ADI. The intention is that this provisional ADI will form a safe intake level at which it can be expected that consumers will come to no harm, with due consideration of uncertainties in its derivation.

12. In line with the requirements of the novel food regulation, the scientific evidence for each novel food dossier will be assessed to ensure the safety of the ingredient has been demonstrated. This provisional ADI will form part of the evidence base for risk managers and risk communication for the individual dossiers and advice to the public on the consumption of pure-form CBD in food. The Subgroup will continue to work through the data for the other two Groups B and C to establish to what extent read across between groups is possible, to inform further advice to the FSA on these products.

Establishment of a provisional Acceptable Daily Intake (ADI) for CBD (≥98% purity)

Determining a Point of Departure for use in risk assessment

13. The Subgroup was provided with an update of toxicological study data for both hemp derived and synthetic CBD of ≥98% composition. Due to the high levels of CBD, and in turn the low levels of impurities and other cannabinoids, data presented for both hemp-derived and synthetic CBD of ≥98% purity were deemed pertinent. Both categories of data were considered together.

14. These datasets add to the body of existing evidence for CBD, incorporating new information provided by applicants. Members reviewed each new study considering the information on the toxicological parameters. It was considered whether the whole body of evidence would allow a toxicological Point of Departure (POD) to be identified, for which effects and whether there were any outstanding data gaps. Three 90-day studies were deemed suitable by the Subgroup as providing quantitative data as a basis for determining a reliable POD and ultimately, for establishing a provisional ADI.

15. When identifying an appropriate POD to use in the novel foods risk assessment, members agreed that to provide a definitive conclusion from the main studies presented, a POD for each would need to be identified, which was in the form of a No Observed Adverse Effect Level (NOAEL) for the most sensitive, human-relevant, adverse effects in rodents. The POD results from all three studies were then considered, to determine the critical POD on which to establish the provisional ADI.

16. The Subgroup noted that the NOAELs from the three studies were 72, 50 and 25 mg/kg bw/day, respectively, and that in each case the NOAEL could form a POD for use in risk assessment.

17. However, when considering that the dosing vehicle in all three studies was a simple carrier oil and not a complex food matrix, appropriate uncertainty factors may need to be considered in novel foods risk assessments to account for any potential differences in bioavailability of the CBD. This is due to evidence from human studies that a high-fat meal can increase bioavailability by 4-fold.

18. It was agreed that the standard 100-fold uncertainty factor to account for toxicokinetic and toxicodynamic differences between species and individuals

should be applied to the POD. As is common in authoritative body risk assessments internationally, an additional uncertainty factor of 3 was used to allow for possible increased sensitivity on chronic exposure and for other data gaps the studies could not cover adequately.

Consequence of using the Point of Departure for the three main studies as the basis of the provisional ADI

Study 1

19. The standard 100-fold uncertainty factor was applied to the 72 mg/kg bw/day POD alongside the additional uncertainty factor of 3, giving an overall UF of 300-fold which, when applied to the POD, would result in a putative ADI of 0.24 mg/kg bw (72 mg/kg bw/day POD / (10 x 10 x 3)). For a 70 kg adult, 0.24 mg/kg bw x 70 kg would lead to an ADI of 17 mg/person.

Study 2

20. The standard 100-fold uncertainty factor was applied to the 50 mg/kg bw/day POD alongside the additional uncertainty factor of 3, giving an overall UF of 300-fold which when applied to the POD would result in a putative ADI of 0.17 mg/kg bw (50 mg/kg bw/day POD / (10 x 10 x 3)). For a 70 kg adult, 0.17 mg/kg bw x 70 kg would lead to an ADI of 12 mg/person.

Study 3

21. The standard 100-fold uncertainty factor was applied to the 25 mg/kg bw/day POD alongside the additional uncertainty factor of 3, giving an overall UF of 300-fold which when applied to the POD would result in a putative ADI of 0.08mg/kg bw (25 mg/kg bw/day POD / (10 x 10 x 3)). For a 70 kg adult, 0.08 mg/kg bw x 70 kg would lead to an ADI of 5.6 mg/person.

22. This toxicological evaluation of all three supporting studies corroborates, and is largely consistent with, the conclusions of the COT Opinion in February 2020 (updated in July 2021). Data from human studies were used by the COT as the basis of a provisional risk assessment, suggesting that the maximum Health Based Guidance Value (HBGV) that could be supported was 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. However, the COT was unable to finalise the establishment of a HBGV due to the deficiencies in the data available at that time.

Establishment of a provisional ADI for pure form CBD (≥98% purity).

23. It was concluded that based upon the body of evidence from animals and humans to date, a provisional ADI can be established of 10 mg/day for a 70 kg healthy adult, obtained by averaging the putative ADIs based on the three pivotal studies (0.16 mg/kg bw x 70 kg, rounded to one significant figure) and supported by the available human data. As important data gaps and uncertainties remain for pure-form CBD products, however, the subgroup concluded that in the absence of evidence, a cautionary approach should be applied to the current position until human-based data and evidence are provided which justify a change in that position. Therefore, the subgroup has chosen to settle on a 'body of evidence approach' to arrive at a provisional ADI of 10 mg/day (0.15 mg/kg bw/day) to take account of the lack of human-based long-term evidence and evidence regarding potentially vulnerable groups.

24. This value is based on observations of adverse effects in the liver that are relevant in humans and the working position, based on the evidence available from existing studies, that reproductive or developmental effects are not likely to be the most sensitive effects compared to the effects observed in the liver. If further toxicological or human evidence becomes available, e.g., information on long term exposure through post-marketing surveillance, this could help in reducing uncertainty and as such, the uncertainty factors and provisional ADI would be revised accordingly if new data supported such a change.

Uncertainties

Overall data gaps and resulting uncertainty areas for pure form CBD

25. Based on the studies made available for pure-form CBD products, there are several areas of uncertainty from the data received from the novel food applications. These were also identified in the COT position paper in 2020. These relate to the severity of the adverse effects in the liver in humans, the bioavailability of pure form CBD, effects of chronic life-time use, vulnerable

groups, CBD – drug interactions and the remaining data gaps for reproductive toxicity and immunotoxicity.

Uncertainties for the bioavailability of pure form CBD products

26. The Subgroup agrees that it will be most straightforward to apply the provisional ADI established for pure-form (≥98%) CBD in the risk assessments of pure CBD in simple oil supplements. Further consideration of CBD bioavailability is necessary for the evaluation of ≥98% pure CBD when used as an ingredient in a more complex novel food matrix. This is because the food matrix is expected to influence the uptake and action of CBD, potentially increasing its effect.

27. The subgroup also concluded that additional pharmacokinetic bioavailability studies in rats and mice would not be informative in relation to these substances and the ways by which this type of study in humans can now be conducted outweighs the need for further animal pharmacokinetic studies. Bioavailability remains a considerable source of uncertainty due to the lack of supporting human-based data focusing on the pharmacokinetic (PK) characteristics and resulting bioavailability of pure-form CBD when administered orally in normal use.

Uncertainties for chronic lifetime use of pure form CBD of ≥ 98% purity

28. The Subgroup highlighted that the studies used in risk assessment were sub-chronic in design and relatively short-term in relation to the potential for chronic lifetime exposure, particularly given possible accumulation of CBD in the body. This remains an uncertainty and has led the Subgroup to recommend the establishment of a provisional, rather than a full, ADI. If further data were to become available that could impact on the provisional ADI, then it could be revisited in the future.

Uncertainties and data gaps in immunotoxicity evidence

29. Members agreed that recent clinical literature provides evidence that CBD is immunosuppressive at the level at which the novel food is being administered. In particular, there are significant data gaps surrounding immunosuppression in children, where potential subtle changes in vaccination responses would be a cause for concern. The lack of human-based information on the possibly of immunotoxic effects of CBD is a significant data gap.

30. It was recommended that in individuals who are at increased risk of infection or are currently immunosuppressed, CBD usage be avoided as this may further impact their immune response.

Uncertainties for vulnerable groups and CBD

31. Due to lack of data, key uncertainties remain as to the effect of CBD when used by pregnant women, breast feeding women and also by children. These should be regarded as potentially vulnerable groups, and their risk managed accordingly.

Drug interactions

32. The interactions between CBD and other medicines are also an area of high uncertainty due to lack of data. Pre-existing evidence of drug-drug interactions at a level of 1 mg/kg/day (70 mg/day), with no information below this level, has been taken into consideration in establishing a provisional ADI at 10 mg/day.

The role of further studies and utilising the provisional ADI in addressing the data gaps and uncertainties associated with pure-form CBD intake.

Statement on addressing uncertainties and data gaps.

33. The Subgroup’s review of the available data indicates that important data gaps and/or uncertainties remain for reproductive and developmental toxicity, immunotoxicity, bioavailability of CBD and CBD–drug interactions. These uncertainties have been addressed by the use of an additional uncertainty factor and the establishment of a provisional, rather than a full, ADI.

34. **The information now available from guideline toxicology studies is sufficient to enable adequate hazard characterisation of systemic toxicity from sub-chronic oral exposure to pure-form CBD of >98% purity. Hence, further sub-chronic toxicity studies would be an unnecessary use of animals, and applicants are encouraged to find alternative means of providing new evidence in support of applications for pure-form CBD of >98% purity. The Subgroup was of the view that**

the data gap on the consequences of chronic exposure to CBD on a daily basis might best be addressed by post-marketing surveillance, and that lifetime studies in animals would not be helpful.

35. Additionally, the Subgroup encourages applicants seeking to provide additional toxicological data for CBD ingredients to act collaboratively where scientifically appropriate, to generate robust evidence while minimising the use of animal testing.

36. For orally ingested pure form CBD of ≥98% purity, the Subgroup is aware that reproductive/development toxicity studies have been conducted in support of the drug Epidiolex (CBD > 98% purity extracted from *Cannabis sativa).* It did not, however, have access to the original study reports. Summary information available from the EMA and the FDA indicated that some developmental effects were observed at high doses. This was taken into consideration when establishing the provisional ADI.

37. In considering the need for additional reproductive/developmental toxicity studies, the availability and suitability of these studies should be addressed before embarking on new studies. The Subgroup recommended that any additional studies should be undertaken by a collaborative consortium rather than many companies performing many separate studies. The purpose of these studies should be clear: to address existing data gaps in order to enable appropriate advice to be provided to pregnant or breastfeeding women.

38. Members agreed that if human PK data showing that human bioavailability is lower than that used in the current risk assessment, this evidence could be used to refine the uncertainty factors applied in establishing a provisional ADI.

39. New PK data should focus on the different product matrices which may affect CBD absorption as relevant to humans. Where appropriate, *in vitro* and *in silico* studies supporting the prediction of human *in vivo* bioavailability would further the evidence on this point.

40. The lack of bioavailability data for CBD as delivered systemically via ingestion from specific food matrices is a source of significant uncertainty. This will be taken into account in reviewing novel food applications and the intended uses requested by applicants.

Conclusion

41. This position paper outlines the new provisional ADI established for pure-form CBD (≥98% purity) ingested via oral administration only. This fulfils the initial aim of the Subgroup to enable the FSA to perform risk assessments for CBD in orally ingested food products submitted for novel foods authorisation.

42. The updated advice is based on points of departure (PODs) from three pivotal 90-day repeat dose toxicology studies. These allow identification of No Observed Adverse Effect Levels (NOAELs) for effects on the liver in rodents that were considered as relevant to humans. In establishing the provisional ADI, the POD is divided by the standard uncertainty factor of 100, covering the potential for toxicokinetic and toxicodynamic differences (10-fold for interspecies differences and 10-fold for interindividual differences). In this case, an additional uncertainty factor of 3 is applied, as the studies were sub-chronic in design. The POD was divided by a total Uncertainty Factor of 300 in each of the assessments, using the three pivotal toxicology studies to derive daily intake values that could be considered as acceptable and not lead to consumer harm. Based on the values obtained from toxicological risk assessment, a provisional ADI is advised at 10 mg CBD/day (0.15 mg/kg bw/day).

43. Due to critical data gaps and uncertainties in the scientific evidence, the FSA applied a cautionary approach in 2020 and recommended that CBD should not be consumed by pregnant or breastfeeding women, children, prospective parents trying for a baby or by people taking medication. There is no new evidence that would justify a change in this position and as such, these groups should be regarded as potentially vulnerable groups. Overall, from the 2020-2023 call for novel food applications and associated toxicological evidence for pure form CBD ingredients, the toxicological data continues to support the current FSA position: ‘as a precaution, FSA recommends that CBD should not be consumed by pregnant or breastfeeding women, children or prospective parents trying for a baby or by people taking medication’. To this should be added, those who are immunosuppressed.

44. The potential for interactions between CBD and other medicines and the bioavailability of CBD are areas of high uncertainty. Existing human evidence of drug-drug interactions at 1 mg/kg/day (70 mg/day) has been considered in establishing a provisional ADI at 10 mg/day.

45. Furthermore, evidence in humans suggests that they may be of similar or even greater sensitivity than rodents to the hepatotoxic effects of CBD. There was evidence for effects on the liver in some healthy subjects at doses as low as 5 mg/kg bw/day (NOAELs in the 90-day studies in rats of 72, 50 and 25 mg/kg

bw/day). The response at lower doses has not been well characterised. This area of uncertainty was considered when establishing a provisional ADI based on toxicological data from experimental animals by taking account the body of human data for Epidiolex in the overall weight of evidence in establishing a provisional ADI for CBD. There are some indications that a small number of individuals may be susceptible to idiosyncratic immune-mediated liver toxicity on exposure to CBD, and the lowest dose at which this might occur is not known. How this is addressed is a risk management decision.

46. To note, conflicts of interest were received from members of both parent committees. From the ACNFP, these conflicts of interest were obtained from Dr. Anton Alldrick and Emeritus Professor Harry McArdle who are involved with CBD-related works and ultimately chose not to be present during the discussions of the statement. From the COT, these conflicts of interest were obtained from Professor Alan Boobis and Dr. Stella Cochrane both of whom declared conflicts of interest related to having connections with those undertaking CBD projects of interest but were not involved with them directly. As such, both COT members declared having nothing to do with the aforementioned projects and therefore they continued to play an active role in Subgroup discussions.

Statement on a provisional Acceptable Daily Intake (ADI) for Pure Form Cannabidiol (CBD at ≥98% purity) as a Novel Food Ingredient

The scientific evidence from human studies and toxicological studies supports a provisional Acceptable Daily Intake (ADI) of 0.15 mg/kg bw/day (equivalent to 10 mg CBD/day for a 70kg adult) for pure form cannabidiol (CBD) (when used at ≥98% purity) as an ingredient in foods. It is expected that a healthy consumer will not come to harm with this level of intake of pure form CBD (≥98% purity).

A provisional ADI of 10 mg CBD/day for an average 70 kg adult is approximately equivalent to 4-5 drops of an oil-based supplement product containing 5% CBD of ≥98% purity.

Chronic daily lifetime use of Pure Form CBD (≥98% purity) in foods has yet to be fully assessed in a rigorous and scientific way. As a consequence, it cannot be ruled out that long-term daily chronic use of pure form CBD (≥98% purity) at intake levels higher than 10 mg CBD/day could contribute to the development of adverse effects over time, most notably in the liver.

Human evidence suggests that with oral intake levels above 70 mg CBD/day, in some individuals, adverse drug-drug interactions with some medications could occur. A dose of 70 mg CBD/day was the lowest dose evaluated in human studies and drug-drug interactions at doses lower than 70 mg/day cannot be ruled out. It is recommended that consumers do not ingest more than 10 mg CBD in any one day. Currently, somnolence (excessive tiredness) and liver effects are the main effects of concern.

The provisional ADI is recommended, subject to the existing advice to consumers that pregnant and breastfeeding women and people taking any prescription medication should avoid the consumption of CBD if possible. Consumers on regular medications should seek advice from a medical professional before using any type of CBD food product. In addition, children and prospective parents trying for a baby are advised against consumption of CBD, as are those who are immunosuppressed, due to remaining data gaps and residual uncertainties concerning the safety of CBD for these groups of consumers.

The provisional ADI of 0.15 mg/kg bw/day (10 mg CBD/day for a 70kg adult) will act as a basis for risk assessments of novel food products containing Pure Form CBD as an ingredient. Dependent upon the nature of the food type, further considerations and information on bioavailability of CBD in humans in different food matrices may also need to be factored into product specific risk assessments.