Statements

Joint position paper from the (ACNFP) & (COT) on establishing a Safe Upper Limit for delta-9-tetrahydrocannabinol (Δ9-THC) and its precursor as contaminants of hemp-derived products including CBD novel foods

Lay Summary

The Lay Summary of establishing a safe level for tetrahydrocannabinol (THC) as a contaminant of cannabidiol (CBD) novel foods and other hemp-derived products.

Executive summary

1. A joint Subgroup of the ACNFP and COT was formed to address a series of over-arching questions in relation to the safety of hemp-derived ingredients and cannabidiol (CBD). The primary aim of the Subgroup is to enable the Food Standards Agency (FSA) to perform risk assessments for CBD and other minor cannabinoids in food. One such minor cannabinoid found within hemp-derived ingredients and CBD novel food products, as an incidental contaminant, is tetrahydrocannabinol (THC), which exists naturally in hemp (*Cannabis sativa Linnaeus*) as various isomers. Concerns have been raised specifically around delta-9-tetrahydrocannabinol (Δ^9-THC) in foods due to its physiological and psychoactive effects, observed after consumption at quite low doses. THC is a controlled substance within the United Kingdom (UK).

2. The presence of Δ^9-THC and its precursor acid form, Δ^9-THCA, as contaminants is unavoidable in CBD novel foods and in other hemp-derived products; this has necessitated consideration of the safety implications for foods containing these

substances as contaminants at low levels. Furthermore, there is a lack of information on the impact different food matrices may have on the bioavailability of Δ^9-THC. In parallel, discussions have been held by the Advisory Council on the Misuse of Drugs (ACMD) on how to manage the contaminant from an illicit substance standpoint in consumer goods, specifically with regards to its psychoactive effects.

3. In-line with the ACNFP and COT joint Subgroup's remit, a review assessing the safety of Δ^9-THC as a contaminant in foods has been carried out with the aim of advising the FSA on establishing a safe upper limit for Δ^9-THC on which maximum oral intake levels of Δ^9-THC may be set. The establishment of a safe upper limit, derived from the evidence base in this independent review, has taken into consideration both the European Food Safety Authority (EFSA) scientific opinion on the risks for human health from the presence of THC in milk and other products of animal origin and the ACMD advice on THC in consumer products. The safe upper limit established by the Subgroup is 1 µg Δ^9-THC/kg bw/day (as the sum of Δ^9-THC + Δ^9-THCA). It is considered that consumers will be protected with intakes at or below the safe upper limit value; no acute or chronic effects are expected to arise.

4. This position paper provides advice on the safety of Δ^9-THC and its precursor Δ^9-THCA, via oral ingestion only, when present at trace levels as contaminants in food products. The safe upper limit may be used as a basis for considering applications for CBD and hemp-derived foods, which may contain Δ^9-THC and its precursor Δ^9-THCA, as contaminants under the Novel Foods Regulation - assimilated regulation (EU) 2015/2283. It is assumed that 100% of Δ^9-THCA could be converted to Δ^9-THC if heated, and therefore safety assessments of food products should consider intake of the sum of Δ^9-THC + Δ^9-THCA relative to the safe upper limit for Δ^9-THC of 1 µg/kg bw/day.

5. In conclusion, THC is a controlled substance within the UK; specifically, Δ^9-THC and its acid precursor, Δ^9-THCA, are found as unavoidable contaminants in CBD novel foods and other hemp-derived products. The Subgroup considered two previous assessments by authoritative bodies – the EFSA CONTAM Panel and the ACMD – and in general agreed with their reasoning and recommendations. The Subgroup concluded that oral exposure to THC (as the sum of Δ^9-THC and Δ^9-THCA) at or below 1 µg/kg bw/day is unlikely to be harmful under appropriate conditions of use.

Background

6. Some parts of the *Cannabis sativa Linnaeus* plant (otherwise known as hemp) have been available for oral consumption within the UK since before 1997 and are therefore not considered to be novel foods. These products include hempseeds and hempseed oils, along with products containing them as ingredients. While there is a history of use in the EU of leaves or flowering parts of the hemp plant, these would be subject to drugs law in the UK, due to the presence of Δ9-THC and related substances. However, in recent years (i.e. since 1997) there has been a rise in popularity of highly refined hemp products and derivatives made from all parts of the plant, containing CBD. In addition to CBD, these products contain a range of other cannabinoids, which are a large group of compounds produced naturally by hemp.

7. Since January 2019, it has been clarified that CBD products are considered as novel foods within the UK and have required evaluation and subsequent authorisation prior to being legally placed on the market. During evaluation of CBD novel food products by the FSA and through a review of the legal status of CBD novel food products containing Δ^9-THC by the ACMD, it was determined that cannabinoids other than CBD may be present within these novel foods as contaminants and may pose a risk to human health. Notably, Δ^9-THC is a common and unavoidable contaminant of CBD novel foods and other hemp-derived products.

8. The physiological and psychoactive effects of Δ^9-THC include tachycardia, effects on blood pressure and changes in appetite, mood, cognition, memory, and perception; in addition, Δ^9-THC exhibits a high potential for abuse. Consequently, it is listed as a controlled substance in the UK. The effects caused by consumption of Δ^9-THC are thus of concern when the compound is ingested within the context of food. Therefore, its potential effects require due consideration by the Subgroup to inform assessments of CBD and other hemp-derived products.

9. Outside the realm of food, some medications containing CBD and Δ^9-THC (Epidiolex and Sativex, respectively) are based on the neurological effects of these cannabinoids and are currently authorised for use within the UK, primarily for the treatment of muscle spasticity or chronic pain. Information obtained from their development for such uses helped inform this assessment.

10. THC exists as multiple isomers, which include, but are not limited to, Δ^8-THC and Δ^9-THC, and these can be present in the carboxylated (acid) and decarboxylated state. Δ^9-THC commonly occurs within industrial hemp, the variety used for foods, as does its acid precursor Δ^9-THCA, which may contribute to total Δ^9-THC in foods. The abbreviation “THC” in this statement is used to refer

to Δ^9-THC and its precursor acid unless otherwise stated.

11. Other cannabinoids occur naturally within the *Cannabis sativa Linnaeus* plant, although research is limited primarily to Δ^9-THC and its precursor Δ^9-THCA, and to CBD. The focus of this statement is pertinent to total Δ^9-THC, which is defined as the sum of Δ^9-THC and its precursor Δ^9-THCA; the latter of which undergoes conversion to Δ^9-THC through non-enzymatic decarboxylation pathways such as heating. This approach, considering total Δ^9-THC, is scientifically consistent with the review of Δ^9-THC (and total THC) in CBD consumer products by the ACMD in the UK.

12. In principle, any suggested safe upper limit for Δ^9-THC could also be applied pragmatically to other controlled cannabinoids (such as the isomer Δ^8-THC, which is of similar of less potency than Δ^9-THC) when setting maximum permitted levels within consumer products, where there is an absence of specific safety data relating to those cannabinoids.

13. No safe upper level of intake has been established previously for Δ^9-THC as a contaminant of food products within the UK. Products with detectable Δ^9-THC would currently be managed under the Misuse of Drugs Act. The current exempt product definition within the Misuse of Drugs Act and associated guidance includes reference to products containing no more than 1 mg of THC per container. However, in October 2023 the ACMD provided advice on a potential updated maximum permitted level for Δ^9-THC and other controlled cannabinoids in CBD-containing consumer products (including novel foods) for the purposes of drugs law. The recommended maximum permitted level was 50 µg per controlled cannabinoid, per unit of consumption of CBD consumer products; where in this instance, a unit of consumption or “single serving” is defined as the typical quantity of a CBD product consumed on one occasion. This recommended maximum permitted level is based on an amount which is both reasonably detectable within CBD novel foods and falls below the level at which it is thought Δ^9-THC produces psychoactive effects in humans.

14. In-line with the conclusions of the ACMD, consideration has now been given more broadly to the overall safety of Δ^9-THC when consumed as a contaminant in foods, where it is more challenging to define a unit of consumption. The question was asked: Is it possible to define an oral intake level of consumption of Δ^9-THC as a contaminant in foods that is not expected to result in adverse psychological effects such as altered cognitive function or adverse physiological effects such as tachycardia and hypotension.

Remit for the Subgroup's position on Δ^9-THC as a contaminant in CBD novel food products and other hemp-derived products intended for oral consumption.

15. The objectives of the Subgroup were to:

- Review the data from the public literature considered by the Food Standards Agency on Δ^9-THC safety after oral ingestion.
- Provide conclusions on the safety of Δ^9-THC based on the available data and how these fit within the current UK legislation.
- Provide advice on whether the data available support the establishment of a safe upper limit as an intake value for Δ^9-THC as a contaminant in foods.

Evidence considered in establishing a safe upper limit for Δ^9-THC as a contaminant in food.

16. A search of the published literature was conducted to assess the safety of THC (specifically Δ^9-THC) when consumed as a contaminant of foods. The search was performed using Google Scholar, PubMed Central, and Science Direct databases using the keywords: THC, tetrahydrocannabinol, oral toxicity, 90-day study, THC safety and THC pharmacokinetics. All literature published up to November 2023 was considered. Literature on toxicological studies that considered routes of administration other than the oral route have limited relevance to the present assessment and were, therefore, not considered in this review. Literature addressing recreational use of marijuana (*Cannabis sativa*) was not considered in this review due to the use of experimental doses higher than those expected at contaminant level consumption as a component of foods and uncertainty about the composition of the substance used. Both experimental animal data and human clinical data were considered as part of the review.

Toxicological data

17. A scientific opinion published by the European Food Safety Authority on the risks for human health related to the presence of THC in milk and other food of animal origin was identified as part of the literature search. This EFSA review of Δ^9-THC toxicity is considered pertinent to the safety of consumption of Δ^9-THC as a contaminant of CBD and hemp-derived products for the following reasons: the review considers oral consumption as a route of exposure, within the context of food, and at dose levels similar to those expected when THC is present as a contaminant in CBD products. Additionally, the risks of combined consumption

with other cannabinoids and isomers have been considered.

18. Experimental animal data are considered, covering acute toxicity and long-term, repeated dose toxicity in a range of animal models and over timeframes of up to 2 years. Human adverse effects data have also been considered in the review and conclusions have been drawn on acute and repeated-dose toxicity. Additionally, the opinion reviews a range of other information and data surrounding THC safety and toxicity. A lowest observed adverse effect level (LOAEL) and an acute reference dose (ARfD) for Δ^9-THC are noted as outcomes of the EFSA opinion.

19. Two narrative reviews summarised the available information concerning potential therapeutic uses and possible side effects of Δ^9-THC: Ben Amar (2006) reviewed clinical trial data between 1975 to June 2005 while Hazekamp and Grotenhermen (2010) considered clinical trial data between July 2005 and 2009. Both reviews considered the adverse effects of Δ^9-THC in humans after both acute and repeated exposure.

20. The substantive review of Δ^9-THC toxicity by the EFSA-CONTAM Panel, along with the additional clinical trial data, helped in establishing the Subgroup's position on Δ^9-THC safety.

21. The Subgroup agreed with the LOAEL for Δ^9-THC, as reported by EFSA, which was 2.5 mg/day for a 70 kg adult - equivalent to 0.036 mg/kg bw/day. In identifying the LOAEL, the EFSA-CONTAM Panel considered a range of animal data covering acute and long term, repeated dose toxicity, along with the human clinical trial data from between 1975 and 2009.

22. Three clinical studies have considered the effects of Δ^9-THC. Ballard and de Wit (2011) evaluated the effects of Δ^9-THC in 11 healthy volunteers (6 male and 5 female, aged 21-35). In this double-blind, within-subject crossover study, a single dose of Δ^9-THC (2.5 mg) or placebo was administered with or without a concurrent low dose of ethanol (0.1 or 0.2 g/kg). Heart rate, blood pressure and various behavioural and subjective parameters related to mood, working memory and reaction time were assessed 2-3 hours after oral consumption of Δ^9-THC. The effects of Δ^9-THC were described as "modest"; they included increased sedation, reduced scores for "vigor" and "friendliness" in the Profile of Mood States test and slightly impaired cognitive function. Diastolic blood pressure also fell in response to a single dose of 2.5 mg Δ^9-THC. The results of this study were consistent with those of two clinical trials in AIDS patients by Beal et al, 1995.

23. The first of these (Beal et al., 1995) was a six-week multicentre, double-blind, placebo-controlled parallel group trial in which patients were offered 2.5 mg THC (branded as Dronabinol) twice daily. This was reduced to one dose daily if the patient could not tolerate the double dose. The therapeutic aim of this study was to enhance appetite and stabilise patients' body weight. During the study 6/72 Dronabinol-treated patients withdrew due to perceived drug toxicity (compared with 3/67 on placebo) and 11 reduced their dose because of side effects. Adverse effects were reported by 43% of treated patients (compared with 13% of controls) and included central nervous system (CNS) effects such as euphoria, dizziness, "thinking abnormalities" and somnolence. These effects were generally mild and were not related to urinary cannabinoid levels.

24. Similar adverse effects were reported in the follow up, open-label study (Beal et al, 1997), in which all patients from the first trial were offered Dronabinol (2.5 mg once or twice daily) for up to 12 months; in addition, 19 of the 93 patients who started the trial experienced perceived toxicity serious enough to merit study withdrawal. The reported reasons for withdrawal included CNS effects, weakness, palpitations, tachycardia and alcohol intolerance.

25. At an intake level of 2.5 mg per day and above in human studies, therefore, adverse psychological effects such as altered cognitive function and physiological effects including tachycardia and hypotension, were observed. It was noted that adverse effects on the CNS, such as altered mood and sedation are the most sensitive endpoints in humans. However, it should be noted that 2.5 mg/day was the lowest dose administered in human studies and as such effects at lower doses could not be excluded. Further evaluation at lower doses would be needed to determine a no observed adverse effect level (NOAEL) for Δ^9-THC based on these most sensitive effects.

26. Due to the most sensitive effects occurring within hours after administration, the EFSA-CONTAM Panel decided to establish an ARfD for Δ^9-THC using the 2.5 mg/day per person LOAEL (0.036 mg/kg bw/day) identified from the review of human studies. Subsequently, after applying appropriate safety factors (3 for extrapolation from a LOAEL to a NOAEL x 10 for interindividual variability = 30), an ARfD for Δ^9-THC was established at 1 µg/kg bw. The EFSA-CONTAM Panel commented that from animal toxicity data it is expected that this intake would also be protective of any systemic chronic effects.

27. Further data on the toxicology and pharmacokinetics obtained from the publicly available literature as Δ^9-THC have been evaluated extensively within a pharmaceutical context. However, it must be noted that information from the oral

consumption of Δ^9-THC as a pharmaceutical constituent to assess its potential therapeutic benefit does not directly equate with an understanding of the safety of Δ^9-THC as an incidental and undesirable contaminant in food. Therefore, while it provides useful information, this has less pertinence to this review, which is focused on the adverse effects that occur from the dietary consumption of the substance in foods.

Absorption, distribution, metabolism and excretion (ADME) data

28. Pharmacokinetic data were also obtained from the publicly available literature. The data suggested low oral bioavailability of Δ^9-THC with some variability due to differences in route of exposure, combinations with other cannabinoids, and other dietary factors. It is suggested that bioavailability is a low as between 4% and 12% when ingested orally. Although oral bioavailability of Δ^9-THC is low, some variation due to food matrix formulation may occur.

29. After oral ingestion, Δ^9-THC is metabolised primarily in the liver by P450 enzymes (CYP2C9, CYP2C19 and CYP3A4), undergoing extensive hepatic first-pass metabolism by microsomal hydroxylation and yielding both active and inactive metabolites. Specifically, Δ^9-THC is metabolised into two main products: 11-hydroxy-THC (11-OH-THC) and 11-carboxy-THC (11-COOH-THC), the first of which is usually present in plasma in concentrations equal to those of THC. 11-hydroxy-THC has also been reported to elicit psychoactive effects in comparative pharmacological studies.

Mechanism of action and pharmacodynamic data

30. Δ^9-THC interacts with a number of different endocannabinoid receptors within the body - especially those localised in the brain. The complex CNS and pharmacological effects of Δ^9-THC are achieved through partial agonism of the cannabinoid 1 receptor (CB1R) localised primarily within the brain, and cannabinoid 2 receptor (CB2R) which is mainly found throughout the immune system and lymphoid organs. It is primarily through activation of CB1R that Δ^9-THC produces a range of psychological effects.

31. The effects of Δ^9-THC (as Dronabinol formulated in the drug MARINOL) have been observed to occur between thirty minutes and one hour after ingestion, with peak effects occurring between 2 and 4 hours. Psychoactive effects are reported to last between 4 and 6 hours and are dependent on dosage. Concentrations of

both Δ^9-THC and metabolites peak at approximately 0.5 to 4 hours after oral dosing and decline over several days. Values for clearance average about 0.2 L/kg-hr but are highly variable. After absorption, excretion is through the faecal and urinary routes, where biliary excretion is the major route of elimination.

Defining a safe upper limit for Δ^9-THC as a contaminant of food

32. The joint ACNFP and COT Subgroup reviewed the information from the literature and considered a point of departure identified from the EFSA opinion on the same question (EFSA, 2015). The critical point of departure was a LOAEL of 0.036 mg/kg bw/day from sensitive individuals and was the lowest dose tested in the human clinical studies reviewed. This value is consistent with the data used to form the ACMD advice on consumer CBD products, where single oral doses of 2.5 – 5 mg of Δ^9-THC produced psychoactive effects (Ballard et al., 2011).

33. Within the scientific opinion published by the EFSA-CONTAM Panel, it was stated that:

“The CONTAM Panel noted that a difference of approximately 700 times [higher] is present between the chronic Reference Point (RP) calculated from experimental animal studies and the established ARfD of 1 µg Δ^9-THC/kg bw. Therefore, the CONTAM Panel concluded that ensuring exposure is below the ARfD would also protect against possible effects of repeated exposure and establishing a Tolerable Daily Intake (TDI) was not necessary.”

34. The joint ACNFP and COT Subgroup agreed with the statement made by the EFSA-CONTAM panel. Based on a review of the data from the animal studies within the publicly available literature, the Subgroup concluded that the ARfD would be sufficiently protective for long-term safety in humans.

35. Uncertainty factors, including a factor of 3 to extrapolate from a LOAEL to a NOAEL, were applied to the LOAEL identified. This was considered appropriate as the effects are mild to moderate in severity. A further factor of 10 was applied for interindividual variability, resulting in a total uncertainty factor of 30. The factor of 30 applied to the 0.036 mg/kg/bw/day LOAEL results in a level of 1 µg/kg bw for consumed Δ^9-THC as a contaminant in food - (equivalent to 0.07 mg Δ^9-THC for a 70 kg adult). This was established as an ARfD (EFSA, 2015).

36. The Subgroup agreed that the ARfD for Δ^9-THC would be sufficiently protective to apply to the UK population. Furthermore, the ARfD is considered to

be sufficiently protective of the most sensitive adverse effects (altered cognitive function) observed during human studies with single doses of 2.5 mg of Δ^9-THC per day. As such it can be assumed that acute or chronic adverse effects are unlikely to occur at and below this intake. In the absence of any recent (post-2015) contradictory data being identified in the literature review, the joint ACNFP and COT Subgroup agreed that this ARfD value is appropriate for use as a pragmatic safe upper limit for use in both the acute and chronic risk assessments of foods within the UK.

37. This value should apply to the sum of Δ^9-THC and its precursor acid form (Δ^9-THCA), the latter of which is converted into to Δ^9-THC when heated through processes such as cooking. The presence of Δ^9-THC precursors was discussed in the ACMD report, which considers the potential Δ^9-THC within a product to be the sum of both Δ^9-THC and its precursor, Δ^9-THCA. When setting limits, it is suggested that they may be applied with this considered. This is drawn from the definition in US Federal law on the domestic production of hemp (US Federal Law, 2018).

38. In conclusion, the Subgroup proposes that the ARfD identified in the literature of 1 µg Δ^9-THC/kg bw/day be used as a pragmatic safe upper limit value to use for the safety evaluation of Δ^9-THC as a contaminant in foods. To be consistent with the ACMD report on 'Consumer Cannabidiol (CBD) Products), the established safe upper limit should be applied to the total potential Δ^9-THC within a food, which would include that as derived from its acid precursor - Δ^9-THCA. In addition, the safe upper limit should be applied in a way which considers exposure through consumption of multiple sources of contaminant Δ^9-THC in the daily diet.

Position of the safe upper limit established in relation to recommendations by the Advisory Council on the Misuse of Drugs on THC in Consumer Cannabidiol (CBD) products

39. The recommendation by the ACMD for setting a legal limit of 50 µg per controlled cannabinoid, per unit of consumption, took into consideration safety of oral consumption of Δ^9-THC, as well as the capability and reliability of measuring cannabinoids, when deciding on an upper limit. The ACMD considerations are made in respect of the dose at which psychoactive effects are likely to be seen. This recommendation of the ACMD was evaluated by the Subgroup in the context of the safe upper limit of 1 µg Δ^9-THC/kg bw/day (equivalent to 70 µg/day for a

healthy 70 kg adult) that it had established.

40. The Subgroup noted that the evidence-based intake established as a safe upper limit of 70 µg/day is consistent with the recommendation by the ACMD (50 µg/unit of consumption) with respect to safety of Δ^9-THC consumption. Adverse effects from oral consumption of Δ^9-THC as a contaminant of CBD novel foods and hemp-derived products are not expected to occur if the recommendation of the ACMD on the legal limits of controlled cannabinoids is implemented. However, this would only be sufficiently protective under certain conditions of dietary exposure.

41. It is expected that, for example, when CBD in novel foods is consumed at or below the FSA's provisional Acceptable Daily Intake (ADI) of 10 mg CBD/day, the contaminant level of THC, which is unavoidable, should stay below the safe upper limit established here. However, intakes of food products vary over a day and additional consideration must be given to the specific product intakes within the context of consuming Δ^9-THC as a contaminant in food products per day. A 'unit of consumption' as per the ACMD is difficult to define for foods, *i.e.* the FSA considers safety within the context of food, any limits on safety must be applied in a way which would consider multiple and repeat exposures and the possibility of consuming multiple units of CBD novel foods and other hemp-derived products.

42. CBD is proposed for use in a range of consumer products, some of which are not intended to be consumed as a single portion/unit of consumption per day. In addition, consumers may choose to consume a range of products on multiple occasions throughout the day remaining within the 10 mg recommended maximum intake of CBD but being exposed to increased levels of the contaminant Δ^9-THC. Such products may be prone to both accidental and purposeful misuse, leading to consumption of Δ^9-THC at levels above the safe upper limit.

43. As Δ^9-THC is always present as a contaminant of CBD and hemp-derived products, any regulatory limit for THC in a CBD novel food product should be proportional to both the CBD content and to a 'unit of consumption' of the product. One 'unit of consumption' of 10 mg/day of CBD, should not result in intake of more than 70 µg/day total THC in the CBD ingredient specification. Hence, total THC intake should not exceed 0.7% of the mass of CBD in any defined unit of consumption, up to a maximum of 0.7% of the 10 mg/day provisional ADI for CBD.

44. In summary, for CBD products, the ACMD recommendation would be sufficiently protective of safety under the condition that a single 'unit of

consumption’ is taken once daily. The recommendation would not be protective if more than one ‘unit of consumption’ of CBD is taken per day - such as where multiple units of consumption are a typical way to intake a product - even if the total CBD intake per day remains below its provisional ADI established by the FSA. As a result, the Subgroup recommends that the safe upper limit be used to determine appropriate regulatory limits, or safe intake limits for Δ^9-THC (and its precursor - Δ^9-THCA) in foods, given the potential sources of exposure. For CBD products, intakes will need to be considered on an individual product basis, where considering the level of Δ^9-THC in relation to exposure to CBD will be helpful in setting levels for individual products.

Overall data gaps and resulting uncertainty areas for Δ^9-THC as a contaminant of food

45. Several uncertainties were identified in the evidence package supporting the Subgroup’s advice on the safety of consuming food products containing trace levels of Δ^9-THC and its precursor via oral ingestion. These were considered in selecting the safety factor of 30 which was applied in determining an acceptable level for total daily oral consumption of Δ^9-THC as a contaminant in foods.

46. The uncertainties identified were as follows:

- Regarding observed effects on humans:
    - The study which identified a LOAEL in healthy young adults was small; 11 subjects.
    - The study supporting a lack of additional adverse effects in vulnerable individuals was conducted in a very specific group of patients, adults experiencing weight loss due to AIDS. In addition, the adverse effects itemized in this study were self-reported by the participants rather than being measured in the clinic.
    - No studies addressing adverse effects in pregnant women, unborn children, neonates, infants or children were available in formulating this advice.
    - Human evidence is mostly limited to clinical trial and efficacy data for pure Δ^9-THC oral medication or therapies. The data suggest that with acute oral intake levels above 2.5 mg Δ^9-THC/day, adverse CNS effects such as changes in cognitive function, and changes in diastolic blood pressure could occur.

- Regarding gaps in the scientific evidence:

    - The disposition of Δ^9-THC has not been fully characterized; in particular, its half-life in humans following oral ingestion has not been reported.
    - Possible matrix/formulation effects on absorption and disposition have not been fully investigated.
    - Data gaps remain concerning the potential for reproductive toxicity and effects on the immune system.

- Regarding assumptions made in this evaluation:
    - This advice on an acceptable level for regular oral consumption is based on an ARfD, assuming that repeated exposure will not lead to effects at lower levels.

47. The subgroup considers that a safety factor of 30 provides sufficient reassurance in the light of these remaining uncertainties.

A statement on a safe upper limit for Δ^9-THC (and its precursor, Δ^9-THCA) as a contaminant in foods

48. The scientific evidence within publicly available literature (which includes human clinical studies and animal toxicological studies) supports a safe upper limit of 1 µg/kg bw/day (equivalent to 0.07 mg/day Δ^9-THC for a 70 kg adult) for total daily oral Δ^9-THC (including its precursor Δ^9-THCA) consumption as a contaminant in foods. Following a scientific review of the data, the Subgroup recommend this as a safe upper limit for application in the risk assessment of novel foods contaminated with Δ9-THC. The safe upper limit can work alongside the legal limits recommended by the ACMD.

49. The Subgroup recommends that the safe upper limit should be used to define a maximum amount of Δ^9-THC permitted in CBD novel foods. The amount of THC in a food should be no more than 0.7% (w/w) of its CBD content. At this level, consumption of CBD novel foods and other hemp-derived products within the provisional ADI (10 mg CBD/day) will deliver up to 70 µg/day of the contaminant Δ^9-THC. This is compliant with the safe upper limit of 1 µg Δ^9-THC/kg bw/day for a 70 kg adult.

50. With a maximum permitted level of 0.7% of the CBD content, consumption of Δ^9-THC as a contaminant of CBD novel foods and other hemp-derived products will be below the safe upper limit for Δ^9-THC of 1 µg/kg bw/day. It is expected that a healthy consumer will not come to harm with this level of intake of Δ^9-THC. The

safe upper limit is considered to also pragmatically cover chronic daily lifetime consumption of Δ^9-THC as a contaminant in foods.

51. The safe upper limit of 1 µg/kg bw/day (0.07 mg/day Δ^9-THC for a 70 kg adult) should be used as a health-based guidance value in the risk assessments of CBD novel food products and other hemp-derived products containing Δ^9-THC (and its precursor Δ^9-THCA) as a contaminant. Dependent upon the nature of the food type, further consideration and information on bioavailability of Δ^9-THC in humans in different food matrices may also need to be factored into product specific risk assessments.

52. Application of the safe upper limit for Δ^9-THC is subject to advice that adverse effects in sensitive populations would require further consideration. The Subgroup advise that prospective parents trying for a baby, including pregnant and breastfeeding women, should avoid consumption of foods containing Δ^9-THC as a contaminant. The reproductive toxicity of Δ^9-THC when consumed as a contaminant of food has not been extensively explored and consequently, adverse reproductive effects cannot be ruled out.

53. It is also advised that consumers on regular medications should seek advice from a medical professional before consuming any food product containing Δ^9-THC as a contaminant. In addition, children and those who are immunosuppressed are advised against consumption of Δ^9-THC due to known toxicity and remaining data gaps and residual uncertainties concerning the safety of Δ^9-THC within these groups of consumers.

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Abbreviations

ACNFP	Advisory Committee on Novel Foods and Processes

ACMD	Advisory Council on the Misuse of Drugs
ARfD	Acute Reference Dose
BMD	Benchmark Dose
bw	Body Weight
CBD	Cannabidiol
CNS	Central Nervous System
COT	Committee on Toxicology
CONTAM	Panel on Contaminants in the Food Chain
EFSA	European Food Safety Authority
FSA	Food Standards Agency
kg	Kilograms
mg	Milligrams
µg	Micrograms
PoD	Point of Departure
RP	Reference Point
Safe Upper Limit	The upper threshold of intake below which no acute or chronic adverse effects are expected to occur

TDI	Tolerable Daily Intake
Δ^8-THC	Delta-8-tetrahydrocannabinol
Δ^9-THC	Delta-9-tetrahydrocannabinol
THC	Tetrahydrocannabinol (includes Δ^9-THC and its precursors)
THCA	Tetrahydrocannabinolic Acid
UK	United Kingdom