Annex to: Derivation of a health-based guidance value for Δ8-tetrahydrocannabinol (Δ8-THC) and its occurrence in food. doi:10.2903/j.efsa.2025.9735

Disclaimer: This Draft Protocol has been approved by the CONTAM Panel during its 147th plenary meeting. It will serve as a basis to conduct the derivation of a health-based guidance value (HBGV) for delta-8-tetrahydrocannabinol (Δ^8-THC) in food with an assessment of the occurrence of Δ^8-THC and the co-occurrence with Δ^9-THC. The Final Protocol will be published as an annex of the final Scientific Opinion. If amendments are made to this Draft Protocol during the course of the risk assessment, these will be reported in Section 9 of the Final Protocol.

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1. Introduction

1.1. Scope of the protocol

The current protocol reports on the problem formulation and approach selected by the Panel on Contaminants in the Food Chain (CONTAM Panel) to elaborate on a scientific opinion related to the risk assessment of Δ^8-tetrahydrocannabinol in food[1].

The protocol is in accordance with the EFSA Guidance on protocol development for EFSA generic scientific assessments (EFSA Scientific Committee, 2023). This guidance foresees that protocols must be adapted to the mandate requirements in order to ensure the delivery of fit-for-purpose and efficient scientific advice. This implies tailoring (i) the level of detail of the protocol and (ii) the approach to publishing and disseminating the protocol to each mandate.

The protocol was developed by the EFSA working group (WG) of experts on Δ^8-THC and EFSA staff in consultation with the mandate requestor and was approved by the CONTAM Panel on 14 November 2024.

Should the need to amend the protocol emerge as the assessment proceeds, such amendments will be documented and justified in section 9.

1.2. Terms of reference of the mandate as provided by the requestor

In accordance with Art. 29 (1) (a) of Regulation (EC) No 178/2002, the Commission asks EFSA for a scientific opinion on the derivation of a health-based guidance value (HBGV) for delta-8-tetrahydrocannabinol (Δ^8-THC) in food with an assessment of the occurrence of Δ^8-THC and the co-occurrence with Δ^9-THC in hemp and hemp derived products. In case a HBGV for Δ^8-THC is derived separately from the HBGV for Δ^9-THC, the scientific opinion should comprise a comprehensive risk assessment on the risks for public health related to the presence of Δ^8-THC in food.The background for the terms of reference can be found under the following link: https://open.efsa.europa.eu/questions/EFSA-Q-2024-00200?search=delta-8

2. Problem formulation

2.1. Objectives of the assessment

The objective of the current assessment is to derive a health-based guidance value (HBGV) for Δ^8-THC and to assess the occurrence of Δ^8-THC in food and its co-occurrence with Δ^9-THC. To that end all evidence on adverse effects on human health of Δ^8-THC as well as recent food occurrence data will be considered. In addition, the adverse health effects of Δ^9-THC as identified in the Scientific Opinion of the CONTAM Panel in 2015 will be compared with the findings on Δ^8-THC.

2.2. Assessment question(s) and sub-questions

The ToRs have been translated into assessment questions (AQs) and sub-questions (SQs) (see Table A1). To aid in the problem formulation, the 2023 EFSA Guidance on Protocol Development proposed the APRIO paradigm (Agent, Pathway, Receptor, Intervention and Output) as a useful tool. In the context of the ToRs for this mandate, the A-P-R-I-O elements were defined as described here below.

[1] https://open.efsa.europa.eu/questions/EFSA-Q-2024-00200?search=delta-8

Agent:

The assessment will focus on Δ^8-THC and its comparison with Δ^9-THC.

Pathway:

The current assessment will be limited to the dietary exposure *to Δ^8-THC via food*.

Receptor:

The target population of the human risk assessment is the European Union population, including specific potentially vulnerable groups (e.g. breastfed infants, pregnant women) and groups with high exposure due to dietary preferences and genetic polymorphism, e.g. *high consumers of Δ^8-THC-containing products*.

Intervention:

Not applicable.

Output:

The hazard assessment will address the adverse health effects to humans associated with the exposure to Δ^8-THC from food, as identified in the hazard identification step.

Assessment questions (AQs) and sub-questions (SQs) were identified for hazard identification, hazard characterisation and occurrence assessment as reported in Table A.1. The AQ and SQs will be answered and combined together to address the mandate ToRs.

Table A.1. AQs and SQs to be answered for the hazard and occurrence assessment of Δ^8-THC in food.

AQ 1: What is the health-based guidance value (HBGV) for Δ^8-THC in food?	
1. Hazard identification & characterisation	
SQ 1.1.1	What is the absorption, distribution, metabolism and excretion (ADME) of Δ^8-THC in experimental animal species/strains and how does it compare to the ADME of Δ^9-THC?
SQ 1.1.2	What is the ADME of Δ^8-THC in humans and how does it compare to the ADME of Δ^9-THC?
SQ 1.1.3	What is the difference in ADME of Δ^8-THC between humans and experimental animals?
SQ 1.1.4	Are there biomarkers of exposure to Δ^8-THC that can be detected in human tissues and biological fluids, e.g. blood, urine, breast milk, adipose tissue, placenta? What are the levels of these biomarkers in the European population? Are there appropriate analytical methods? How do they compare to those of Δ^9-THC?
SQ 1.1.5	Is *Δ^8-THC* associated with genotoxic potential, and if so, what is the underlying mechanism?
SQ 1.1.6	Is there evidence of carcinogenicity in experimental animals or humans?
SQ 1.1.7	What adverse outcomes are caused by exposure to Δ^8-THC in experimental animals, what are the critical effects and how do they compare to Δ^9-THC?
SQ 1.1.8	What adverse outcomes are associated with exposure to Δ^8-THC in humans, what are the critical effects and how do they compare to Δ^9-THC?

SQ 1.1.9	What is the dose-response relationship between *Δ^8-THC* and relevant endpoints in experimental animals and how does it compare to that of Δ^9-THC?
SQ 1.1.10	What is the dose-response relationship between Δ^8-THC and relevant endpoints in humans and how does it compare to that of Δ^9-THC?
SQ 1.1.11	What is the modes of action that can explain the observed adverse effects by Δ^8-THC and how do the adverse effects compare to Δ^9-THC? How do the adverse effects compare between humans and experimental animals?
SQ 1.1.12	Is there evidence that allows grouping of Δ^8-THC and Δ^9-THC based on chemical structure, similar pharmacodynamic effects and/or common receptor agonism? If yes, is it possible to proceed with a combined risk assessment?
SQ 1.1.13	What is a health-based guidance value (HBGV) for delta-8-tetrahydrocannabinol (Δ^8-THC) in food?
SQ 1.1.14	What are the uncertainties associated with the hazard identification & characterisation?
AQ 2: What is the occurrence of Δ^8-THC and its co-occurrence with Δ^9-THC in food products?	
2. Assessment of the occurrence data	
SQ 2.2.1	What are the analytical methods used to detect the occurrence of Δ^8-THC in food products and how sensitive are they?
SQ 2.2.2	What is the effect of processing and processing conditions on the levels of Δ^8-THC in food?
SQ 2.2.3	What are the occurrence levesl of *Δ^8 THC* in foodstuffs in Europe?
SQ 2.2.4	What is the co-occurrence of Δ^8-THC and Δ^9-THC in foodstuffs in Europe?
SQ 2.2.5	What are the uncertainties associated with the assessment of the occurrence data?

2.3. Approach for the assessment

Data on both humans and experimental animals as well as in vitro data will be considered for the hazard identification and characterisation. The potential association between the target compound and the endpoints of interest for the human hazard assessment will be evaluated. Dose-response relationship for endpoints relevant to humans and a comparison of the potency between Δ^8-THC and Δ^9-THC will be assessed. The most appropriate endpoint(s) will be used for the identification of a Reference Point and the derivation of a HBGV. An evaluation of possible uncertainties, including for example those derived from consideration of the toxicokinetic and toxicodynamic properties of the target compounds, will be performed. Weight of evidence approach will be used to integrate different lines of evidence (i.e. human, in vivo and in vitro).

The general principles of the hazard identification and characterisation process for chemicals in food as outlined by WHO/IPCS (2020) will be applied. In addition, the following EFSA guidance documents pertaining to hazard and occurrence assessment will be applied as appropriate:

- Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic (EFSA Scientific Committee, 2005);
- Guidance of the Scientific Committee on a request from EFSA related to uncertainties in Dietary Exposure Assessment (EFSA Scientific Committee, 2007);

- Guidance of the Scientific Committee on transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: General principles (EFSA Scientific Committee, 2009);
- Management of left-censored data in dietary exposure assessment of chemical substances (EFSA, 2010a);
- Technical report on handling occurrence data for dietary exposure assessments. (EFSA supporting publication, 2021)
- Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee, 2011);
- Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data (EFSA Scientific Committee, 2012a);
- Scientific Opinion on Risk Assessment terminology (EFSA Scientific Committee, 2012b);
- Scientific Opinion on the guidance on the use of the weight of evidence approach in scientific assessments (EFSA Scientific Committee, 2017b);
- Guidance on the assessment of the biological relevance of data in scientific assessments (EFSA Scientific Committee, 2017c);
- Scientific Committee guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age (EFSA Scientific Committee, 2017c).
- Guidance on Uncertainty Analysis in Scientific Assessments (EFSA Scientific Committee, 2018);
- Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019);
- Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA Scientific Committee, 2019);
- Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals;
- Guidance on Communication of Uncertainty in Scientific Assessments (EFSA, 2019);
- Guidance on the use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2022);
- Guidance of EFSA's Scientific Committee on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments (EFSA Scientific Committee, 2024).

3. Method for answering sub-questions (SQs) related to hazard identification and characterisation

The evidence needed to address the ToR are lines of evidence on any health-related effect associated with dietary intake of Δ^8-THC reported in the peer reviewed literature. Therefore, a narrative review methodology and the Weight of Evidence approach for assembling, integrating and weighing the evidence (EFSA Scientific Committee, 2017) will be applied.

Table A.2. Overview of the methods that will be applied for answering the various assessment questions and sub-questions

Assessment question(s) and/or sub-questions[1]		Methods foreseen
1.	**SQ 1.1.1. – 1.1.14** **(Hazard assessment)**	**Using evidence from scientific literature:** • **Data collection: extensive literature searches and structured screening process using expert judgement** • **Evidence appraisal: use of expert judgement** • **Evidence synthesis: use of expert judgement**
2.	**1.2.3. – 1.2.5.** **(Occurrence and co-occurrence assessment)**	**Using:** • **Occurrence data of Δ^8-THC and co-occurrence data in food submitted to EFSA and if applicable from selected studies in the public literature**

[1]AQ/SQ number as defined in the problem formulation section

3.1. Evidence retrieval

The AQs and SQs related to the hazard identification and characterisation and the occurrence assessment formulated in Table A.1 will be answered using evidence from scientific literature following an Extensive Literature Search (ELS) without time limit.

A literature search will be performed to identify primary research studies as well as systematic reviews and meta-analysis relevant to the sub-questions formulated. In addition, the bibliography of the key full text papers will be checked for further potentially relevant studies. The expertise of the working group will be used in deciding whether to pursue these further to complement the evidence collection.

3.1.1. Sources of evidence

The ELSs will be performed searching the bibliographic databases or scientific citation research platforms summarised in Table A.3.:

Table A.3. Bibliographic databases used in searches.

Database	Platform	Dates
Web of Science Core Collection	Web of Science	1975-present
CAB Abstracts	Web of Science	1910-present
Current Contents Connect	Web of Science	1998 -present
FSTA	Web of Science	1969-present
Medline	Web of Science	1991-present
ProQuest Dissertations &Thesis	Web of Science	1637-present
BIOSIS Citation Index Web of Science 1926-present	Web of Science	1926-present
PubMed	NLM	1946-present
Embase	Embase.com	inception-present
Scopus	Scopus.com	inception-present

The literature searches will be performed by EFSA supported by the Working Group.

The output from the searched databases, i.e. the bibliographic references including relevant information (e.g. title, authors, abstract) will be exported into separate Endnote 21 files, allowing a count of the individual hits per database. Files will then be combined and duplicate records removed.

The files obtained will be transferred into the web-based systematic review software DistillerSR® (Evidence Partners, Ottawa, Canada), for the study selection procedure.

3.1.2. Eligibility criteria for study selection

To inform the sub-question related to the hazard identification and characterisation, all retrieved studies reporting associations of exposure to Δ^8-THC with effects in humans (e.g. epidemiological studies), as well as experimental animal and in vitro studies reporting effects after exposure to Δ^8-THC will be considered. The eligibility criteria related to the report characteristic are listed in Table A.4 and apply to all sub-questions. The eligibility criteria related to study characteristics are listed in Tables A.5 for human studies, Table A.6 for experimental animal and in vitro studies, and Table A.7 for toxicokinetic studies. The relevant studies will be discussed in the corresponding section of the Opinion.

The selection of the scientific studies for inclusion or exclusion will be done by the relevant domain experts from the CONTAM WG on Δ^8-THC and/or CONTAM Panel. It will be based on consideration of the extent to which the study is relevant to the assessment.

Table A.4. General eligibility criteria related to report characteristics (all sub-questions)

Language	In	English [(a)]
Time	In	No time limit
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data), systematic reviews, reviews, meta-analyses, PhD Theses
	Out	Editorials, letters to the editor, abstracts, conference proceedings/ Δ^8-THC analogues or derivatives

(a): Studies in European languages other than English might also be cited if considered relevant by the experts from the CONTAM WG on Δ^8-THC or CONTAM Panel.

Table A.5. Eligibility criteria for the selection of human studies

Sub-questions		
Study design	In	Cross-sectional studies Cohort studies Case-control studies Case series/Case reports Clinical trials Experimental studies (randomised and non-randomised interventions)
	Out	Animal studies

		In vitro studies
Study characteristics:	In	Any study duration Any number of subjects
	Out	/
Population	In	All populations groups, all ages, males and females Study location: all countries
	Out	/
Exposure/ intervention	In	Exposure: - Studies in which levels of Δ^8-THC have been measured in human tissues and human biological fluids - Studies in which the dietary exposure to Δ^8-THC has been estimated (including transplacental exposure)
	Out	Dermal, inhalation, iv route
Specific outcome of interest	In	All endpoints
	Out	/

Table A.6. Eligibility criteria for the selection of toxicological studies in experimental animals and *in vitro* studies

Sub-question		
Study design	In	Experimental animal studies *In vitro* studies in relevant systems (mammalian (including human) primary cells and cell lines, subcellular fraction and bacterial cell lines used in genotoxicity studies)
	Out	Human studies, studies in non-relevant species
Study characteristics:	In	Any study duration Any number of animals Any cell culture/models Dose groups: ≥ 1 dose group + control group
	Out	/
Population	In	Any age, males and females, in utero
	Out	/
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies), s*c.*, *i.p.*, *i.v.* Compounds: Δ^8-THC OR Estimated exposure validated Number of doses: single or repeated administration Dose groups: ≥ 1 dose groups + control group
	Out	Inhalation, dermal application, Experimental studies on combined exposure
Specific outcome of interest	In	All endpoints
	Out	/

Table A.7. Eligibility criteria for the studies on toxicokinetics

Sub-questions		
Study design / Test system	In	*In vivo* studies in humans *In vivo* studies in experimental animals *In vitro* studies in tissue preparations, cell cultures/models etc.
	Out	
Exposure/ intervention	In	Routes of administration: all except inhalation
	Out	/inhalation
Specific outcome of interest	In	Any outcome related to the absorption, distribution, metabolism and elimination of the target compound

3.1.3. Data extraction from included studies

The details of the selected studies will be reported in tables and discussed in the corresponding section of the Opinion, and will include: populations under study, compound(s) analysed, doses (or dietary exposure), direct or indirect (during gestation) exposure, tissue concentrations, end-point(s).

3.2. Evidence appraisal

The appraisal of the studies in terms of reliability and relevance for this assessment will be based on expert knowledge and judgement taking into consideration the study characteristics (e.g., study design, methodology, endpoint, dosing).

3.3. Evidence synthesis / integration

The final critical endpoints will be identified by integrating evidence from both human experimental animal and in vitro lines of evidence considering the respective level of confidence. For weighing the evidence, relevance and reliability will be assessed across all human studies and animal studies reporting on adverse health outcomes, toxicokinetics and ADME as well as studies (in vivo and in vitro) informing on the mode of action.

A dose-response assessment will be performed on relevant adverse effects for the identification of chronic Reference Points, e.g. no-observed-adverse-effect levels (NOAEL) or benchmark doses (BMD) and its lower confidence limits (BMDL) for a particular incidence of effect. The lowest relevant Reference Point will be considered for the possible derivation of an HBGV.

Data on the toxicokinetics (ADME and toxicokinetic modelling) will support the extrapolation of results from experimental animal studies, human and in vitro studies to the general population. This information is also important to determine which uncertainty factors related to inter-species difference and inter-individual variability need to be taken into account when establishing an HBGV.

Information on mode of action will also support this step, as mode of action can describe the key events and the relationships required for the various adverse outcomes as a result of exposure to Δ^8-THC and inform the human relevance of effects observed in *in vivo* and *in vitro* experimental models. In this specific assessment, the mode of action could also support the comparison between Δ^8-THC and Δ^9-THC and the eventual calculation of a potency factor.

4. Method for answering SQs related to hazard identification and characterisation

For SQs 1.1.1-1.1.13, the general principles of the hazard identification and characterisation for chemicals in food will be applied. Namely, the general principles as described by WHO/IPCS (2020) as well as the different EFSA guidance documents relevant to this step of the risk assessment, e.g. the Guidance on transparency in the scientific aspects of risk assessments (EFSA, 2009), the Management of left-censored data in dietary exposure assessment (EFSA, 2010a), Guidance on selected default values (EFSA Scientific Committee, 2012a).

Overall, the following approach will be used for evidence collected from scientific literature and food composition databases:

Data collection: as described in section 3.1.

Evidence appraisal: as described in section 3.2.

Evidence synthesis: as described in section 3.3.

5. Method for answering SQs related to occurrence and co-occurrence assessment

To answer SQ 2.1.1-2.1.4 and to assess the concentration of Δ^8-THC in food and its co-occurrence with Δ^9-THC in European countries, a structured approach will be followed.

The available occurrence data on Δ^8-THC in food will be extracted from the EFSA database. Following a mandate from the European Commission to EFSA, a call for annual collection of chemical contaminant occurrence data in food was issued by the former EFSA Dietary and Chemical Monitoring Unit (now iDATA Unit) in December 2010. Since then, data have been submitted every year by national food authorities, research institutions, academia, food business operators and other stakeholders by a deadline agreed with the EFSA Scientific Network on Chemical Monitoring Data collection[2].

The data submission to EFSA follows the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed (EFSA, 2010a) and the EFSA Guidance on Standard Sample Description 2 (EFSA, 2013). Occurrence data are managed following the EFSA standard operational procedures (SOPs) on 'Data collection and validation' and on 'Data analysis of food consumption and occurrence data'. For these risk assessments all occurrence data on Δ^8-THC received since the previous Opinions and by a certain deadline will be considered.

Following the EFSA's Technical report on handling of occurrence data for dietary exposure assessment (EFSA, 2021) to guarantee an appropriate quality of the data used, the initial dataset extracted from EFSA occurrence database will be evaluated by applying several data cleaning and validation steps. Special attention will be paid to the identification of duplicates and to the accuracy of different parameters, such as 'Sampling strategy', 'Sampling year', 'Sampling country', 'Analytical methods', 'Result express', 'Reporting unit', 'Limit of detection/quantification', and the codification of food categories.

[2]Current call: https://www.efsa.europa.eu/en/call/call-continuous-collection-chemical-contaminants-occurrence-data-food-and-feed-2023

Since 2018, all occurrence data submitted to EFSA have been codified according to the FoodEx2 classification system (EFSA, 2015). The FoodEx2 classification system consists of a large number of standardised basic food items aggregated into broader food categories in a hierarchical parent-child relationship. Additional descriptors, called facets, are used to provide additional information about the codified foods (e.g. information on food processing and packaging material).

In addition, evidence from the literature will be considered.

Overall, the following approach is used for evidence both from scientific literature and food composition databases:

- Data collection: occurrence data of the EFSA database and extensive literature searches for studies following as much as possible the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed as described in section 3.1.
- Evidence appraisal: as described in EFSA's Technical report (EFSA, 2021).
- Evidence synthesis: the method will be defined based on the amount and heterogeneity of the data.

6. Method to address the overall uncertainty in the risk assessment

The evaluation of the inherent uncertainties in the assessment of Δ^8-THC will be performed based on the EFSA Guidance on uncertainties of the EFSA Scientific Committee (EFSA Scientific Committee, 2018) and the EFSA Guidance on communication of uncertainty in scientific assessments (EFSA, 2019).Recommendations will be included in the Scientific Opinion for the generation of additional data that could decrease the impact of the identified uncertainties on the conclusions of the risk assessment, where relevant.

7. Public consultation

In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key issues. Accordingly, the draft Opinion on Δ^8-THC that will be developed will be subject to public consultation before its final adoption by the CONTAM Panel.

The comments received will be evaluated by the WG on Δ^8-THC in food and by the CONTAM Panel and when applicable will be taken into account for finalisation of the draft Opinion.

8. Plans for updating the literature searches

The literature searches performed as detailed in Sections 3 will be repeated approximately four months before the planned date of endorsement of the draft Opinion by the CONTAM Panel.

9. Amendments to the protocol

Only editorial amendments to the protocol were introduced before final adoption of the draft Opinion.

Abbreviation

ADME	Absorption, distribution, metabolism and excretion
APRIO	Agent, Pathway, Receptor, Intervention and Output
AQ	Assessment question
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
EFSA	European Food Safety Authority
ELS	Extensive Literature Search
EU	European Union
HBGV	Health-based guidance value
ip	Intraperitoneal
iv	Intravenus
LB	Lower bound
LOQ	Limit of quantification
NOAEL	No-observed-adverse-effect level
sc	Subcutaneous
SOP	Standard operational procedures
SQs	Sub-questions
Δ8-THC	Delta-8-tetracannabinol
TORs	Terms of reference
UB	Upper bound
WG	Working group
WHO	World Health Organisation

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