28 June 2022

Safety of cannabidiol as a novel food: data gaps and uncertainties

Trusted science for safe food

efsa
European Food Safety Authority

Agenda

14:30-15:00	**Connection of participants to the platform**	
15:00-15:10	**Welcome and introduction to the event by the chair**	Ana Afonso (EFSA -NIF)
15:10-16:25	**Status of the safety assessment of CBD as Novel food** **Explanation of the Panel's statement** • **ADME, CBD interaction with drug metabolism (Q&A)** • **Gastrointestinal tract** **Liver** **Neurological, psychiatric and psychologic effects (Q&A)** • **Endocrine and Reprotox (Q&A)** • **Presence of small particles, including nanoparticles, or production of CBD as nanomaterial and CBD nano-formulation (Q&A)**	Annamaria Rossi (EFSA - NIF) Harry McArdle (NDA Panel) Harry McArdle (NDA Panel) Harry McArdle (NDA Panel) Inge Mangelsdorf (NDA Panel) Karen-Ildico Hirsch-Ernst (NDA Panel) Karen-Ildico Hirsch-Ernst (NDA Panel) Jose Vicente Tarazona (EFSA - MESE)
16:25-16:40	**Requirements/instructions for future applications (Q&A)**	Catalina Manieu (EFSA - FDP)
16:40-16:55	**General Q&A**	Chair WG/Panel
16:55-17:00	**Concluding remarks & take-home messages**	Chair WG/Panel

28 June 2022

Status of the Safety Assessment of CBD as Novel Food

Annamaria Rossi

Trusted science for safe food

efsa
European Food Safety Authority

Cannabidiol as Novel Food in EU

EU **Court of Justice** ruled in November 2020:

- CBD cannot be regarded as a "narcotic drug."
- According to the current state of scientific knowledge, unlike THC, the CBD at issue does not seem to have any psychotropic effect

*"Cannabidiol should not be considered as a drug within the meaning of the United Nation Convention Schedule IV of the 1961 Single Convention on Narcotic Drugs. This means that cannabidiol can be **qualified as food**."*

Cannabidiol is qualified as **Novel Food**

Novel Food in the EU

Definition: "novel food" as any food that was not used for human consumption to a significant degree within the EU before 15 May 1997

According to Regulation (EC) No 178/2002 and Regulation (EU) 2015/2283, foods, including NFs, must be safe. Therefore, **the opinions of EFSA are based solely on the analysis of the health risks** and must conclude on that basis alone.

Authorisation procedure

- New applications
- Changes to existing authorisations

9 months (+ stop-the-clock time) from the reception of a valid application

Dossier
- Scientific information

Mandate
- Background
- Terms of reference

Assessment
- Request for additional information
- Technical hearing

Authorisation
- Decision for market authorisation

Additional Data Request

The assessment will be on hold as long as the requested additional information and data are not addressed by the applicant

It is the applicants' responsibility to provide the data requested

EFSA cannot provide scientific advice but the applicant can request a "clarification teleconference" to discuss the data requests

Consortia or joint effort to provide the data requested are encouraged

Scientific Guidance

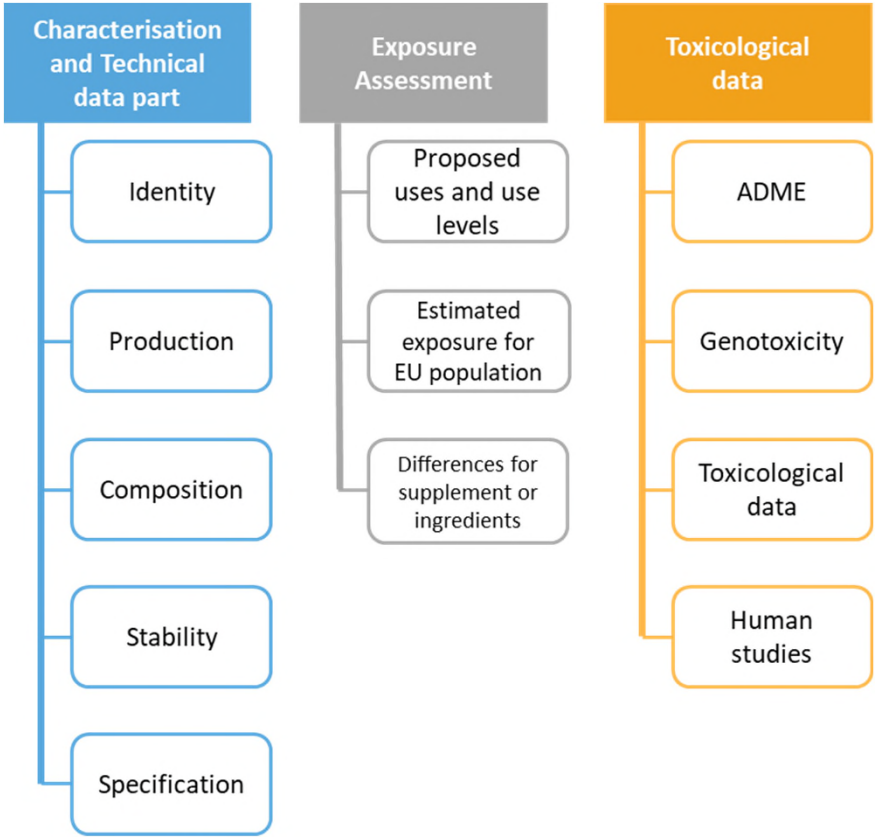
GUIDANCE

EFSA Journal

doi:10.2903/j.efsa.2021.6555

Guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283[1] (Revision 1)[2]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA),[3]
Dominique Turck, Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grazyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Marco Vinceti, Peter Willatts, Karl-Heinz Engel, Rosangela Marchelli, Annette Pöting, Morten Poulsen, Seppo Salminen, Josef Schlatter, Davide Arcella, Wolfgang Gelbmann, Agnès de Sesmaisons-Lecarré, Hans Verhagen and Hendrik van Loveren

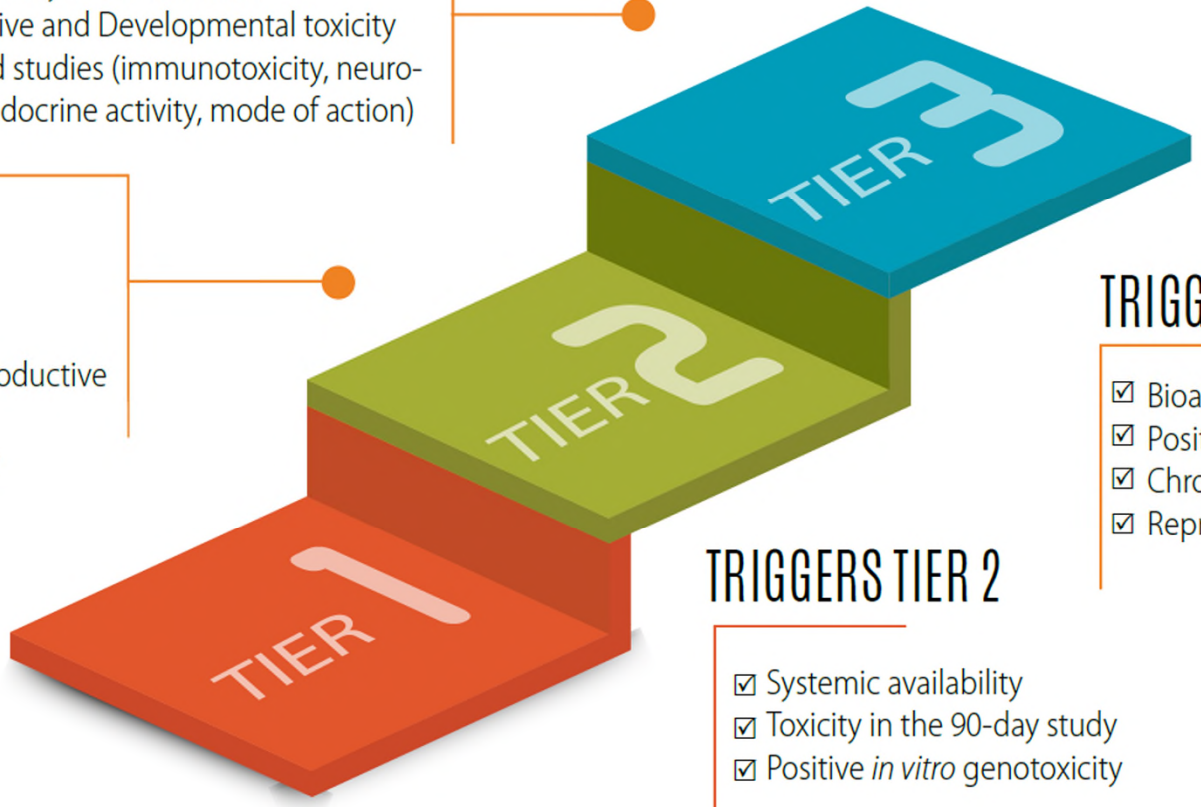


Scientific Guidance

- ADME: repeated dose, volunteer studies
- Carcinogenicity: *Mode of Action*
- Reproductive and Developmental toxicity
- Specialised studies (immunotoxicity, neuro-toxicity, endocrine activity, mode of action)

- ADME: single dose
- Genotoxity (*in vivo*)
- Chronic toxicity
- Carcinogenicity
- Extended One-Generation Reproductive Toxicity Study (EOGRTS)
- Prenatal developmental toxicity

- Absorption
- Genotoxicity (*in vitro*)
- Extended 90-day toxicity study (*in vivo*)



TRIGGERS TIER 3

- ☑ Bioaccumulation
- ☑ Positive *in vivo* genotoxicity
- ☑ Chronic carcinogenicity
- ☑ Repro and developmental toxicity

TRIGGERS TIER 2

- ☑ Systemic availability
- ☑ Toxicity in the 90-day study
- ☑ Positive *in vitro* genotoxicity

Trusted science for safe food

28 June 2022

NDA Panel's statement

Harry McArdle

efsa
European Food Safety Authority

The CBD Statement

EFSA Journal

STATEMENT

ADOPTED: 26 April 2022

doi: 10.2903/j.efsa.2022.7322

Statement on safety of cannabidiol as a novel food: data gaps and uncertainties

EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA),
Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, Stefaan De Henauw,
Karen Ildico Hirsch-Ernst, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle,
Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies,
Sophia Tsabouri, Marco Vinceti, Francesco Cubadda, Thomas Frenzel, Marina Heinonen,
Rosangela Marchelli, Monika Neuhäuser-Berthold, Morten Poulsen, Miguel Prieto Maradona,
Josef Rudolf Schlatter, Viviana Trezza, Henk van Loveren, Océane Albert, Céline Dumas,
Andrea Germini, Wolfgang Gelbmann, Georges Kass, Eirini Kouloura,
Estefania Noriega Fernandez, Annamaria Rossi and Helle Katrine Knutsen

Scope

Identify the hazards of CBD and how they relate to physical, chemical and pharmacological properties when used as food supplement and/or food ingredient.

Provide an overview of the uncertainties and data gaps that need to be addressed before the safety assessment of applications for CBD as a NF can be concluded.

Development of the CBD Statement

Literature search of available scientific literature:

- Animal studies
- Human studies focusing on data provided for pure CBD

Limitation of available studies

- Toxicology studies are with very varied mixtures
- The content of other components and their identity are rarely described
- In humans, many studies have involved patients that required concomitant use of other medications
- Most human data refer to the efficacy of Epidyolex® at therapeutic doses, at which adverse effects were sometimes observed ➔ no NOAEL could be identified

28 June 2022

ADME, CBD interaction with drug metabolism

Harry McArdle

Trusted science for safe food

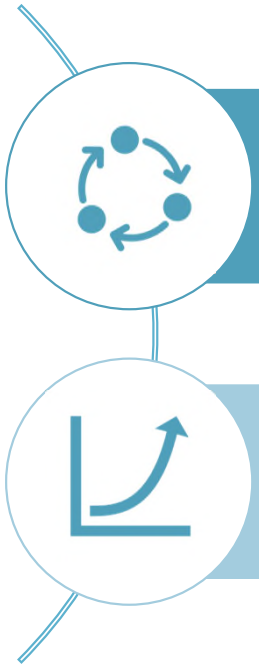
European Food Safety Authority

ADME: available data

Statement

- This section briefly describes summarises the absorption, distribution, metabolism and excretion of CBD
- Different aspects will be examined in more detail in the relevant sections later

ADME: data gaps



The matrix used, the form of the CBD and the food consumed at the same time could affect bioavailability

Animal studies suggest accumulation of CBD with time: does this happen at lower doses in humans and do the harmful effects also increase?

CBD interaction with drug metabolism

Statement

- Interactions between CBD and neurological drugs have been demonstrated
- CBD interacts with a wide range of CYP enzymes and the concentrations at which these interactions manifest is not clear. This means CBD affects metabolism of other foods and drugs and vice versa.

Q&A

Trusted science for safe food

28 June 2022

Gastrointestinal tract

Harry McArdle

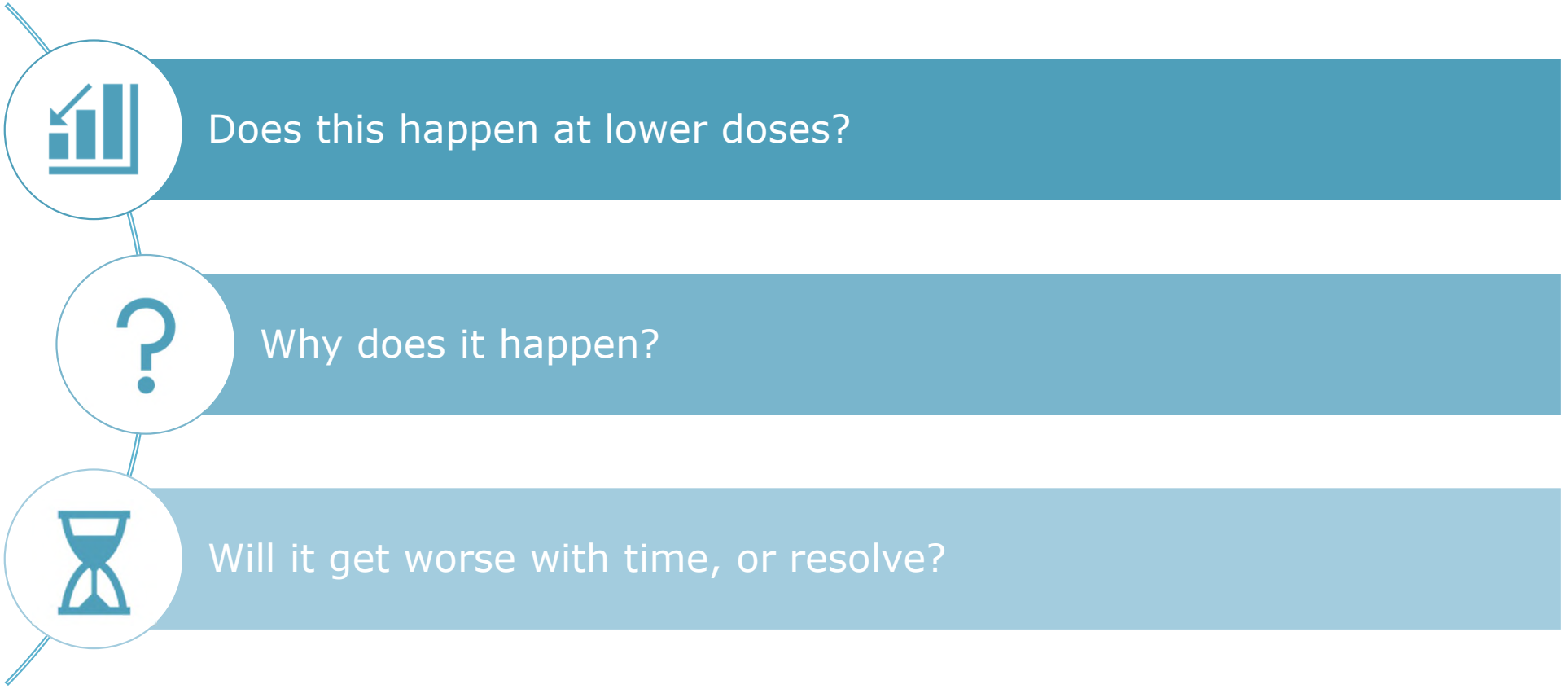
efsa
European Food Safety Authority

Gastrointestinal effect: available data

Statement

- The main problem with CBD is diarrhoea occurs as side effect of CBD consumption

Gastrointestinal effects: data gaps



Trusted science for safe food

28 June 2022

Liver

Inge Mangelsdorf

efsa
European Food Safety Authority

Liver: available data in experimental animals

Experimental animals

- Rats
- Mice
- Dogs
- Rhesus monkeys

Exposure duration

- Up to 39 weeks

Observed adverse effects

- ↑ liver weight
- ↑ liver enzyme levels (ALT, AST, ALP, GGT)
- ↑ bilirubin
- liver cell hypertrophy

Derived reference point

- LOAEL*: 10 mg/kg body weight
- NOAEL**: not identified

* Lowest observed adverse effect level
** No observed adverse effect level

Liver: available data in humans

Subjects

- Healthy volunteers
- Health care workers
- Patients (epilepsy, Crohn's disease, Type II diabetes)

Adverse effects (after 2-4 weeks)

- ↑ liver enzyme levels (ALT, AST, ALP, GGT)
- ↑ bilirubin

Derived reference point

- LOAEL: 4.3 mg/kg body weight
- No reliable NOAEL

Correlation between species

- Similar effects as in animal studies

Liver: mechanistic study

Experimental animals

- Mice

Observed adverse effects

- ↑ liver weight
- liver cell hypertrophy
- ↑ ALT, AST
- ↑ bilirubin

Gene expression

>50 differentially regulated genes related to:

- general liver toxicity
- oxidative stress
- lipid metabolism
- metabolising enzymes (cypP450, UGT)

Liver: central role of toxicity of CBD

Liver toxicity

Interaction with endogenous metabolism

- Hepatic metabolism of steroids
- Thyroid hormone metabolism

Interaction with metabolism of drugs

- Ethanol, caffeine, bupropion, clobazam, cyclophosphamide, ketamine, propofol

Liver: data gaps

Trusted science for safe food

28 June 2022

Neurological, psychiatric and psychologic effects

Karen-Ildico Hirsch-Ernst

efsa
European Food Safety Authority

Neurological, psychiatric and psychologic effects: available data in humans

Subjects

- Clinical trials with Epidyolex® as adjunctive antiepileptic drug (in combination with other drugs) for treatment of patients (Lennox-Gastaut or Dravet syndrome)

Doses

- 5, 10, 20 mg/kg bw per day

Adverse effects

- somnolence
- sedation
- lethargy
- ataxia
- abnormal coordination
- aggression
- sleep disorders

Derived reference point

- Observed already at 5 mg/kg bw per day
- No reliable NOAEL

Neurological, psychiatric and psychologic effects: available data in humans

Subjects

- Healthy volunteers

Duration of the studies

- Often involve only single administration of CBD
- or are of short-term duration

Adverse effects

- different adverse events have been observed (e.g. headaches or somnolence)

Derived reference point

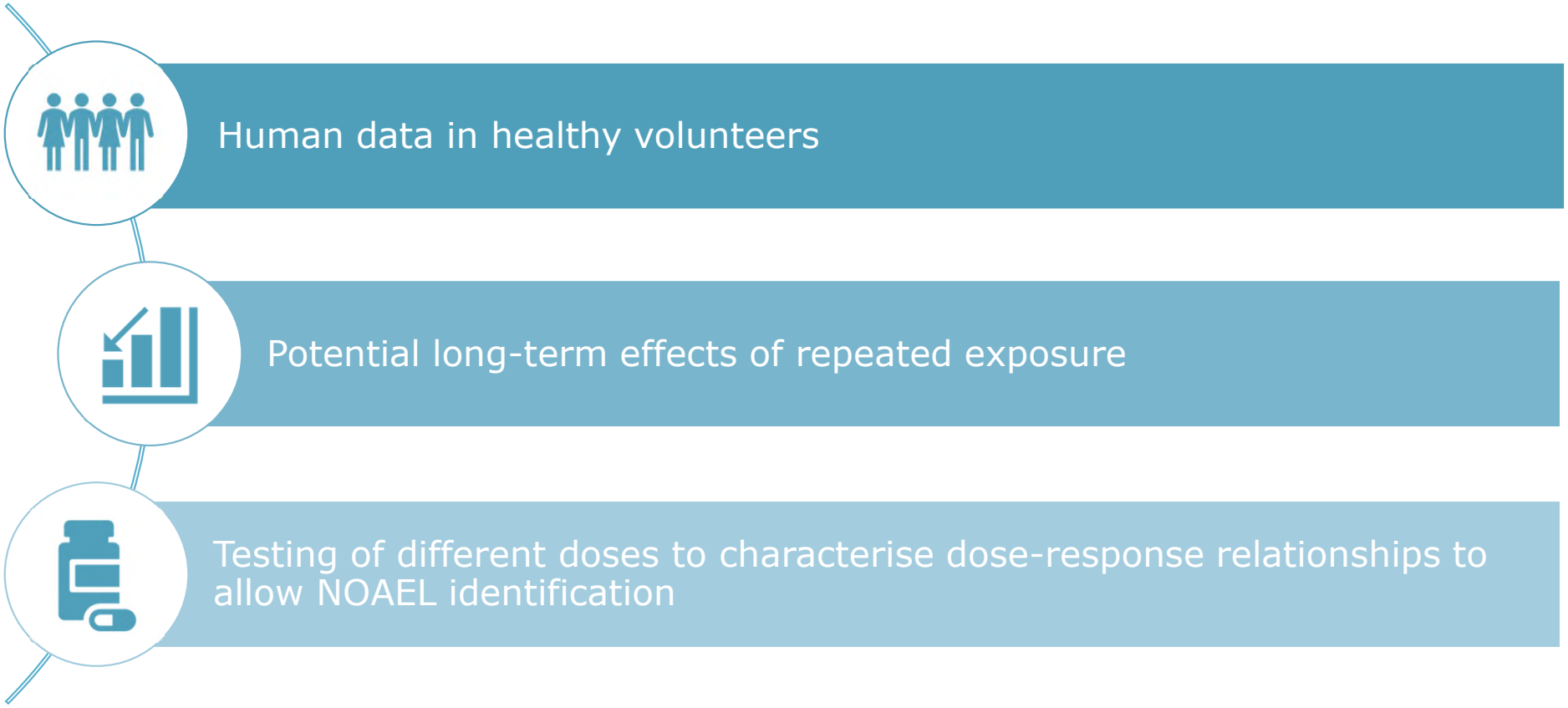
- reliable dose–response relationships for neurological effects of CBD have not been established

Neurological, psychiatric and psychologic effects: considerations

Mechanistic information:

- Numerous potential targets of CBD, including CB1- or CB2-receptors, GABAA-, 5HT1A- or D2-receptors, are expressed in the nervous system
- The extent of any effect of CBD will depend among others on the interplay between target receptors, CBD dose and the duration/time frame of use

Neurological, psychiatric and psychologic effects: data gaps



Q&A

28 June 2022

Endocrine and Reproductive system

Karen-Ildico Hirsch-Ernst

Trusted science for safe food

efsa
European Food Safety Authority

Endocrine system: available evidence

Thyroid and thyroid hormone system

- Rat 26-week oral toxicity study: dose-dependent T4 decrease, TSH increase, thyroid follicular hypertrophy (EMA, 2019)
- Rhesus monkey, subchronic study: changes in relative thyroid weight

Hypothalamo-pituitary gonadal axis

- In rodent and simian models, potential of CBD to affect levels of:
  - Gonadotropins (LH, FSH)
  - Sex hormones, including testosterone, oestradiol and progesterone

Endocrine effects in humans have not been investigated

Reproductive system: Available animal data

Developmental toxicity

- *In utero* exposure to Epidyolex®: litter loss, supernumerary liver lobe (rats); reduced fetal weights (rabbits)

Reproductive tract toxicity

- Alterations of reproductive organ weights and size (simian and rodent models)
- Impairment of spermatogenesis
- Histopathological changes (testes, ovaries)

Fertility (investigated in males)

- Decrease in sperm quality at ≥ 15 mg/kg bw/day (murine and simian models); decreases in male fertility rate, impregnation rate, number of litters, live pups (mice)
- Potential effects on sexual behaviour, e.g. latency to first mount (mice)

Reproductive system: data gaps

Q&A

28 June 2022

Presence of small particles, including nanoparticles, or production of CBD as nanomaterial and CBD nanoformulation

Jose Vicente Tarazona

Trusted science for safe food

efsa
European Food Safety Authority

EFSA 2021 Nano Guidances overview

European Food Safety Authority

Guidance on Technical Requirements (TR)

GUIDANCE

New!

EFSA Journal

ADOPTED: 30 June 2021

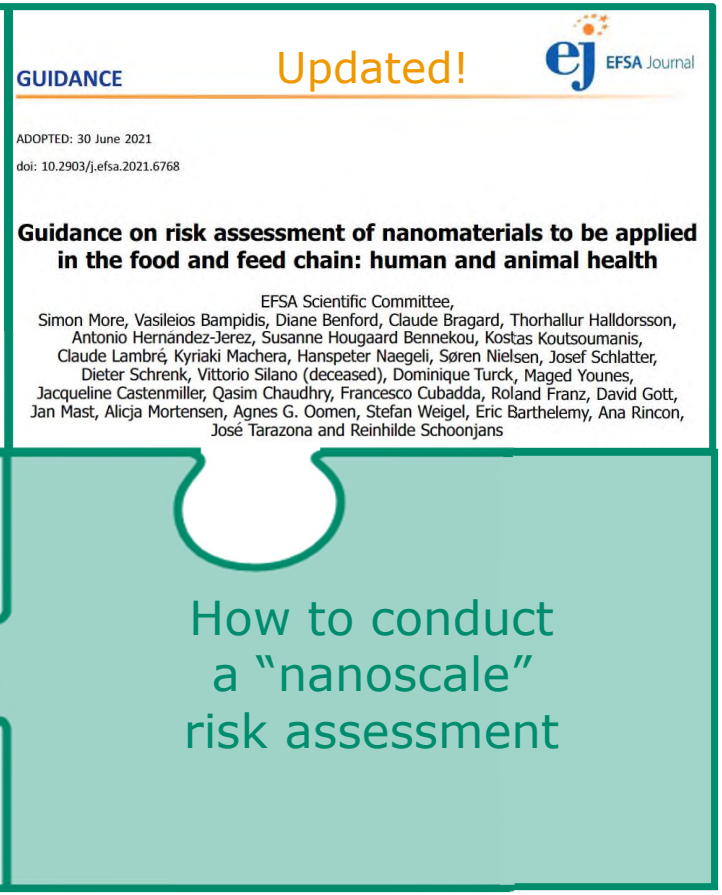
doi: 10.2903/j.efsa.2021.6769

Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles

EFSA Scientific Committee,
Simon More, Vasileios Bampidis, Diane Benford, Claude Bragard, Thorhallur Halldorsson, Antonio Hernández-Jerez, Susanne Hougaard Ben… …tas Koutsoumanis, Claude Lambré, Kyriaki Machera, Hanspeter Na… …Josef Schlatter, Dieter Schrenk, Vittorio Silano (deceased) … …ed Younes, Jacqueline Castenmiller, Qasim Chaudhry, Franc… …ranz, David Gott, Jan Mast, Alicja Mortensen, Agnes G. Oomen, S… …lemy, Ana Rincon, Jose Tarazona and Reini…

Are "nanoscale considerations" needed for the risk assessment?

Guidance on Nano - Risk Assessment (RA)



GUIDANCE

Updated!

EFSA Journal

ADOPTED: 30 June 2021

doi: 10.2903/j.efsa.2021.6768

Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health

EFSA Scientific Committee,
Simon More, Vasileios Bampidis, Diane Benford, Claude Bragard, Thorhallur Halldorsson, Antonio Hernández-Jerez, Susanne Hougaard Bennekou, Kostas Koutsoumanis, Claude Lambré, Kyriaki Machera, Hanspeter Naegeli, Søren Nielsen, Josef Schlatter, Dieter Schrenk, Vittorio Silano (deceased), Dominique Turck, Maged Younes, Jacqueline Castenmiller, Qasim Chaudhry, Francesco Cubadda, Roland Franz, David Gott, Jan Mast, Alicja Mortensen, Agnes G. Oomen, Stefan Weigel, Eric Barthelemy, Ana Rincon, José Tarazona and Reinhilde Schoonjans

How to conduct a "nanoscale" risk assessment

Guidance on Particles: Technical Requirements
Proposed appraisal routes

S.2	Solubility	**Aim**: demonstrate that consumers will not be exposed to small particles
S.2	Dissolution rate	
S.3	Screening particle size	**Aim**: demonstrate absence or quantity of small particles in properly dispersed samples
S.3	Quantification particle size	
S.4	Coverage by existing studies	**Aim**: demonstrate that the fraction of small particles is properly covered by existing safety studies

Each appraisal route and the underlying principles are extensively described in the dedicated Sections

Addressing small lipophilic organic particles

Novel food: presence of lipophilic nanoparticles. If marketed in lipophilic media solubilisation must be demonstrated

GI tract: may dissolve in the GI tract and/or reach the human intestine as particles

Intestinal epithelial cells: GI uptake may be through conventional processes for lipophilic molecules, and/or uptake as particles

Systemic distribution: internalised nanoparticles may partition to physiological hydrophobic environments and/or been distributed as particles

If cell/systemic internalisation as particles

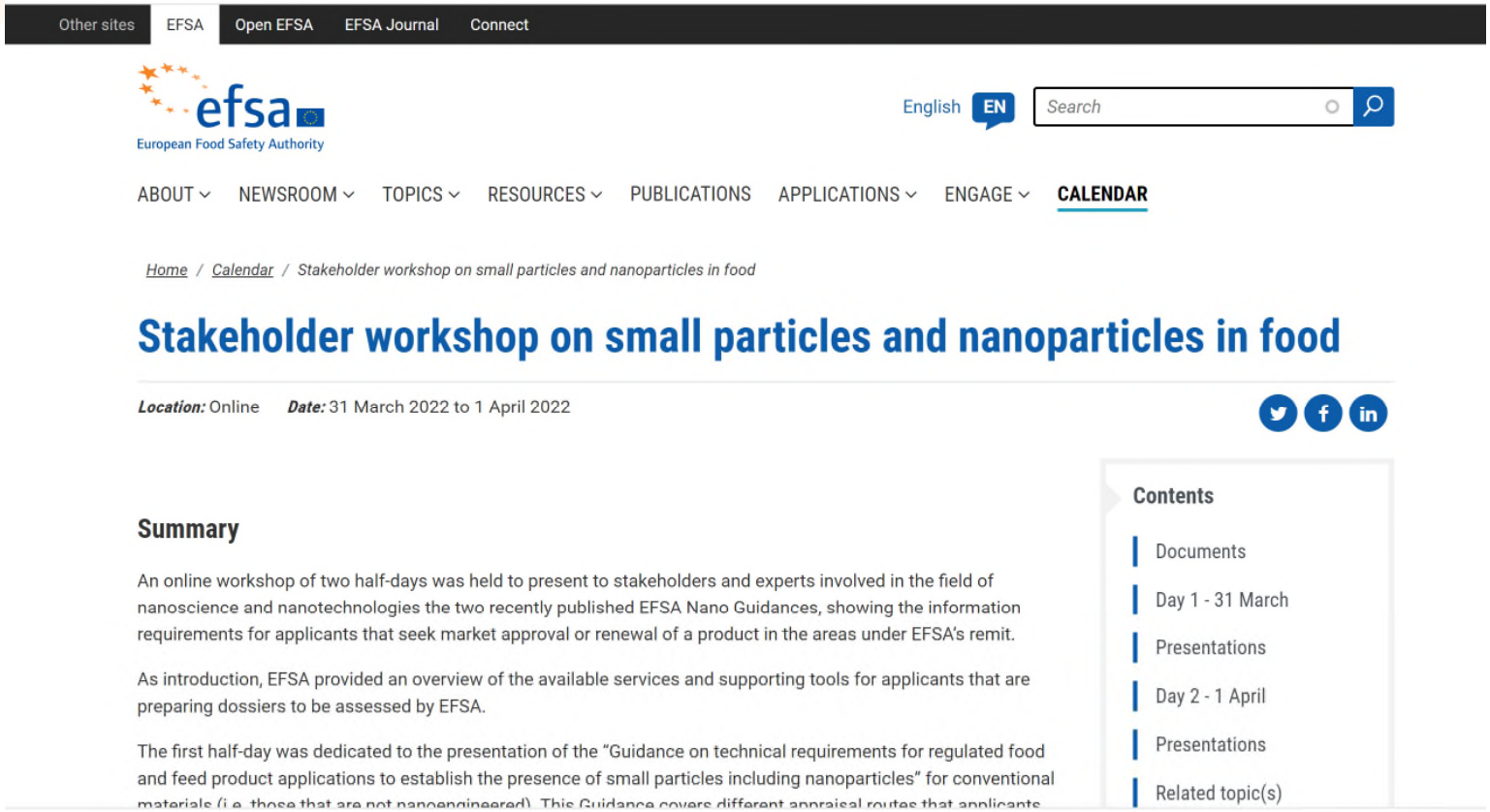
Safety assessments must consider and integrate nanoparticle related aspects

EFSA Scientific Committee "Nano" Guidances must be followed

Toxicity testing approaches, require specific adaptations:

- negative AMES test results are not sufficient to exclude genotoxicity concerns: two complementary mammalian cell lines *in vitro* studies must be provided
- ADME studies should be conducted according to EFSA Guidance
- other OECD Test Guidelines must be adapted according to EFSA Guidance
- toxicity tests with the substance dissolved in a lipid matrix inform on the toxicity of the chemical but not on the nano-specific considerations
- Integrated Approaches to Testing and Assessment and the use of New Approach Methodologies may minimise the need for animal testing

For more information



- Presentations
- Video recordings
- FAQ

https://www.efsa.europa.eu/en/events/stakeholder-workshop-small-particles-and-nanoparticles-food

Q&A

Trusted science for safe food

28 June 2022

Experiences from suitability check and web-queries on CBD applications as novel foods

Catalina Manieu

Scientific officer

Front-Desk & Workforce planning (FDP) unit

efsa
European Food Safety Authority

Suitability check

Ensure the information and data comprised in the application is in accordance with the specific requirements laid down in the relevant legislation and EFSA's administrative and scientific guidelines

First stage of the lifecycle of the application, before the risk assessment phase starts

During risk assessment phase the information of the application will be scrutinized by experts, who will provide scientific advice to risk managers, for taking the final decision on the authorization of the novel food

Suitability check

EFSA has 30 WDs for providing its views on the suitability of the application to the EC

EC will contact the applicant upon EFSA provides the suitability check outcome

Additional (new) checks:

- Administrative confidentiality check
- Verification of notification of studies obligations


Technical report | Open Access

Administrative guidance for the preparation of applications on novel foods pursuant to Article 10 of Regulation (EU) 2015/2283

European Food Safety Authority (EFSA)

First published: 12 March 2021 | https://doi.org/10.2903/sp.efsa.2021.EN-


Transparency Regulation: Practical Arrangements

Published: 11 January 2021

Novel food: main findings

Identity

- It is key to clearly indicate the novel food to be placed in the EU market
- NF
- Raw material

Production process

- Detailed description
- Raw material – chemical synthesis
- Purification process
- Solvents – reagents

Compositional data

- Main components
- Stability
- Shelf life
- Presence of small particles

Specifications

Proposed uses

Confidentiality

Ask a Question: recurrent queries

How can I get an authorisation for a NF?

Is my product, containing CBD, a novel food?

- Extremely important to clearly define which is the novel food itself
- Regulatory question that should be addressed to the European Commission

EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products

Pre-submission phase

- General Pre-submission advice
- Ask a Question (EFSA webform)
- Administrative support to SMEs on applications

Suitability check phase

- Clarification teleconference during suitability check
- Monitoring of applications submitted by SMEs

Support to applicants

Join our new LinkedIn group: "EFSA support to applicants"

A space where you will find:

- Information and support materials
- Updates on the developments and progresses of IT tools and platforms
- Alerts on new training material and upcoming events
- Answers to the most frequently asked questions
- Clarification from your peers

https://www.linkedin.com/groups/9083910/

Q&A

Information from the infosession

Post event documents

A Q&A - 'FAQ' document, the summary of the event, the presentation slides and the recording will be published on the EFSA website shortly

Feedback

Thank you for attending our information session

Please take a few minutes to fill out our survey
(the link will be sent you via email)
Your feedback is essential to improve our future events!

Stay connected

Subscribe to

efsa.europa.eu/en/news/newsletters
efsa.europa.eu/en/rss

Receive job alerts

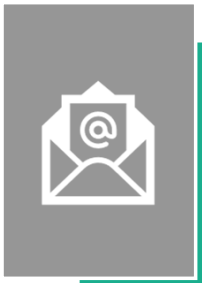
careers.efsa.europa.eu – job alerts

Follow us on Twitter

@efsa_eu
@plants_efsa
@methods_efsa
@animals_efsa

Follow us Linked in

Linkedin.com/company/efsa



Contact us

efsa.europa.eu/en/contact/askefsa