Cannabis in the food sector: a toxicological perspective

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1. Content

- 1. **Regulatory Toxicology (an introduction)**
- **2. CBD as Novel Food**
- **3. Toxicological information available**
- **4. EIHA strategy**
- **5. Conclusions**

1. Science of toxicology

Different Branches

- Experimental toxicology
- Molecular toxicology
- **Regulatory toxicology**
- Forensic toxicology
- Clinical toxicology
- Food and nutritional toxicology
- Industrial toxicology
- Environmental toxicology (eco-toxicology and environmental fate)

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1. SCIENCE OF TOXICOLOGY

Evaluation the following endpoints

- Acute toxicological profiling (oral, dermal, inhalation)
- Local effects (irritation, corrosion, eye and skin)
- Sensitisation effects (skin, inhalation)
- Target Organ Toxicity (repeated toxicity up to chronic)
- Genotoxicity (mutagenicity + clastogenicity) with MoA assessment
- Reproductive toxicity (fertility + development)
- Carcinogenicity studies (one/two species)
- Special end-points (e.g. EDS), studies with specific analysis (hormone levels)
- ADME studies (Adsorbtion, Distribution, Metabolism, Excrection)

All studies/tests must be carried out under GLP (Good Laboratory Practices) and following OECD (Organisation for Economic Co-operation and Development) Guidances

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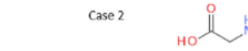
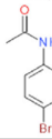
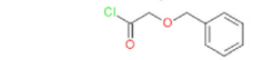
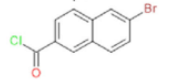
1. SCIENCE OF TOXICOLOGY

ALTERNATIVE METHODS

Information on intrinsic properties may be generated by means **other than vertebrate animal testing with:**

a) "*in vitro* methods"
b) Qualitative or Quantitative Structure Activity Relationshio (Q-SAR)
c) Structurally related substances (grouping or read across)
d) Intelligent Testing with suitable justification for certain end-points

TARGET= reduce the number of testing vertebrate animals

Case Study	Compound	(Q)SAR Prediction			Expert Review
		Derek	Sarah	Nexus	
Case 1	Compound 19 	Inactive (contains unclassified features)	Outside domain	Outside domain	Class 3
Case 2	Compound 11 	Equivocal	Negative	Positive	Class 3
Case 3	Compound 1 	Plausible	Negative	Positive	Class 5
Case 4	Compound 4 	Inactive (contains misclassified features)	Positive	Positive	Class 5
Case 5	Compound 6 	Equivocal	Negative	Positive	Unassigned
	Compound 9 	Equivocal	Positive	Positive	Unassigned
	Compound 16 	Equivocal	Negative	Positive	Unassigned

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2. CBD as Novel Food

- ***Cannabis Sativa* L.** = plant (generic name = all varieties)
- **Hemp (industrial hemp)** = allowed Cannabis varieties with low THC level (0.2%), allowed in Europe and listed in the EU Plant variety database
- **Hemp food products** = Hemp seeds, Hemp seed oil, Hemp seed flour
- **Hemp Extracts**
- **Cannabidiol (CBD)**

} **Defined Novel Foods in January 2019**

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2. CBD AS NOVEL FOOD

WHAT'S A NOVEL FOOD?

Novel Food is defined as food that **had not been consumed to a significant degree by humans in the EU before 15 May 1997**, when the first Regulation on novel food came into force (Regulation(EC) No 258/97)

'Novel Food' can be newly developed, innovative food, food produced using **new technologies and production processes** , as well as food which is or has been traditionally eaten outside of the EU.

The underlying principles underpinning Novel Food in the European Union are that Novel Foods must be:

NF MUST BE

- Safe for consumers
- Properly labelled, so as not to mislead consumers
- If novel food is intended to replace another food, it must not differ in a way that the consumption of the Novel Food would be nutritionally disadvantageous for the consumer.

Notes: *Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001*

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2. CBD AS NOVEL FOOD: SAFETY

NOVEL FOOD DOSSIER REQUIREMENTS

1. Identity of the novel food
2. Production process
3. Compositional data (5-batch and stability test)
4. Specifications
5. History of use of the novel food
6. Proposed uses and use levels and anticipated intake
7. **ADME (Adsorption, Distribution, Metabolism, Excretion)**
8. Nutritional information
9. **Toxicological information (Genotoxicity, 90-day study)**
10. Allergenicity

Derive a safe life-long (daily) intake

Safety ⟷ Toxicological data

Toxicological information on the substance

3. TOXICOLOGICAL INFORMATION AVAILABLE

AVAILABLE DATA FROM LITERATURE

- Information from the studies of the drug Epidiolex (CBD based)
- A number of pharmacological studies on humans
- Experimental studies on animals
- Some epidemiologic information

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3. TOXICOLOGICAL INFORMATION AVAILABLE

LIMITS

- Information from the studies of the drug Epidiolex (CBD based)
  - Ratio benefits : risks
  - Data partially available (pharma owns the data)
  - High (therapeutic) doses
  - Co-administration with other drugs
- A number of pharmacological studies on humans
  - Co-administration with other drugs
  - Searching for beneficial/therapeutic effects (efficacy)
  - Studies carried out on patients (food sector target is general heathy population)
- Experimental studies on animals
  - No NOAEL available
  - Tested item unclear (extracts with no detail and/or doses very low to meet the intended market)
  - No GLP laboratories (university studies mostly)
  - Unclear endpoints
  - No GLP 90-day study or chronic exposure data
- Some epidemiologic information
  - Fragmented information (doses, formulation, person condition or comorbidity)

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3. TOXICOLOGICAL INFORMATION AVAILABLE

LIMITS

Literature is vast but lacks of ***specificity*** and ***useful toxicological endpoints*** for assessing CBD (or hemp extracts) in their intended use in the food sector (food supplement and/or food ingredient).

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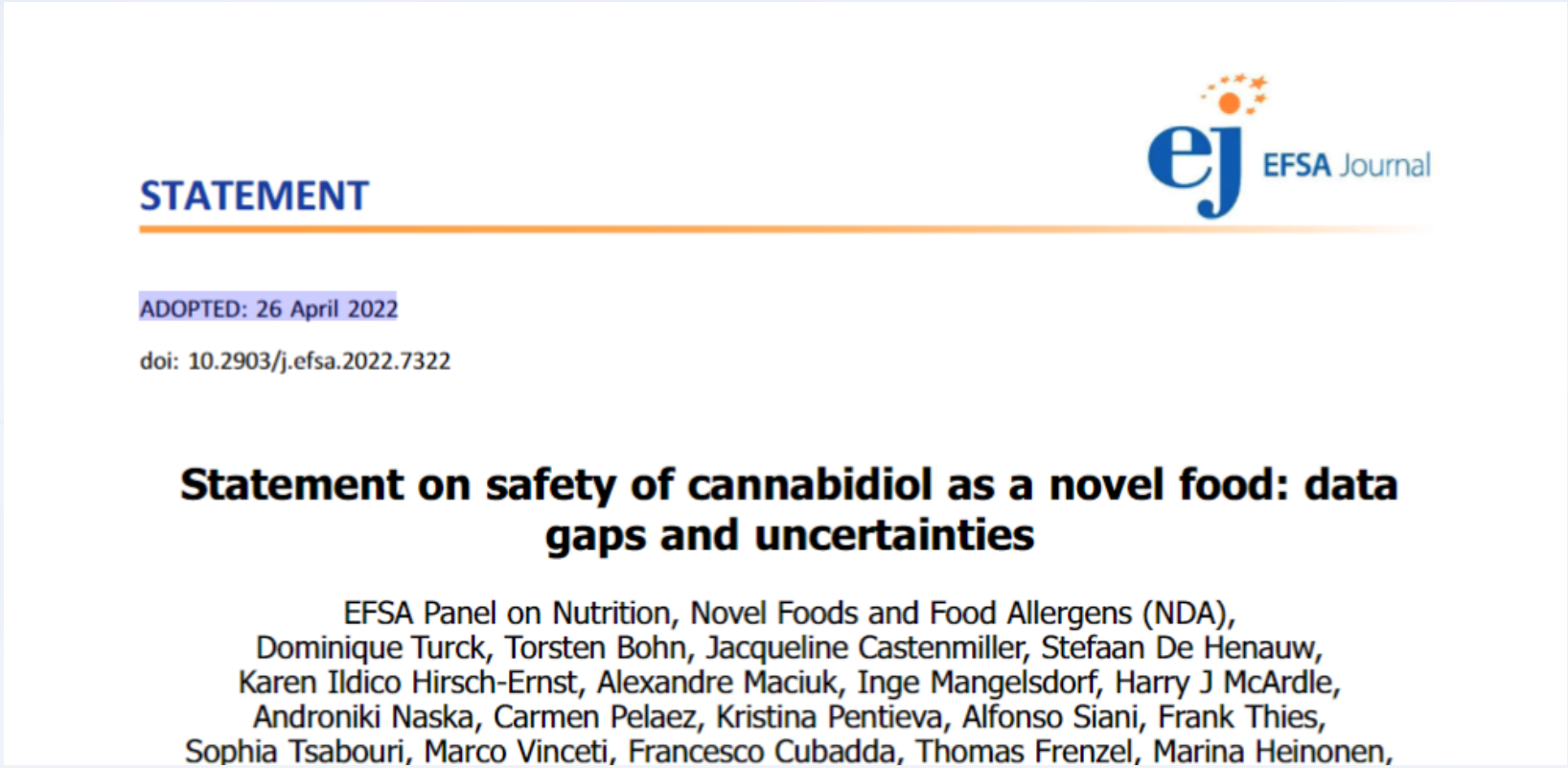
3. TOXICOLOGICAL INFORMATION AVAILABLE

The EFSA released a gap analysis on CBD safety data and the concerns can be summarized in

- Effects on liver (drug-drug interactions; CBD metabolism)
- Effect on the gastrointestinal tract (e.g. diarrhea)
- Effects on the endocrine system (e.g. hormones, reduce male fertility)
- Nervous system (e.g sedation effects)
- No NOAEL available where to start from



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,

Source: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2022.7322

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4. EIHA PROJECTS GMBH STRATEGY

For **both** **Isolated CBD** (>98%) and **Hemp Extract** a package of studies

- Genotoxicity
  - Bacterial Reverse Mutation Test (OECD 471)
  - *In Vitro* Mammalian Cell Micronucleus Test (OECD 487)

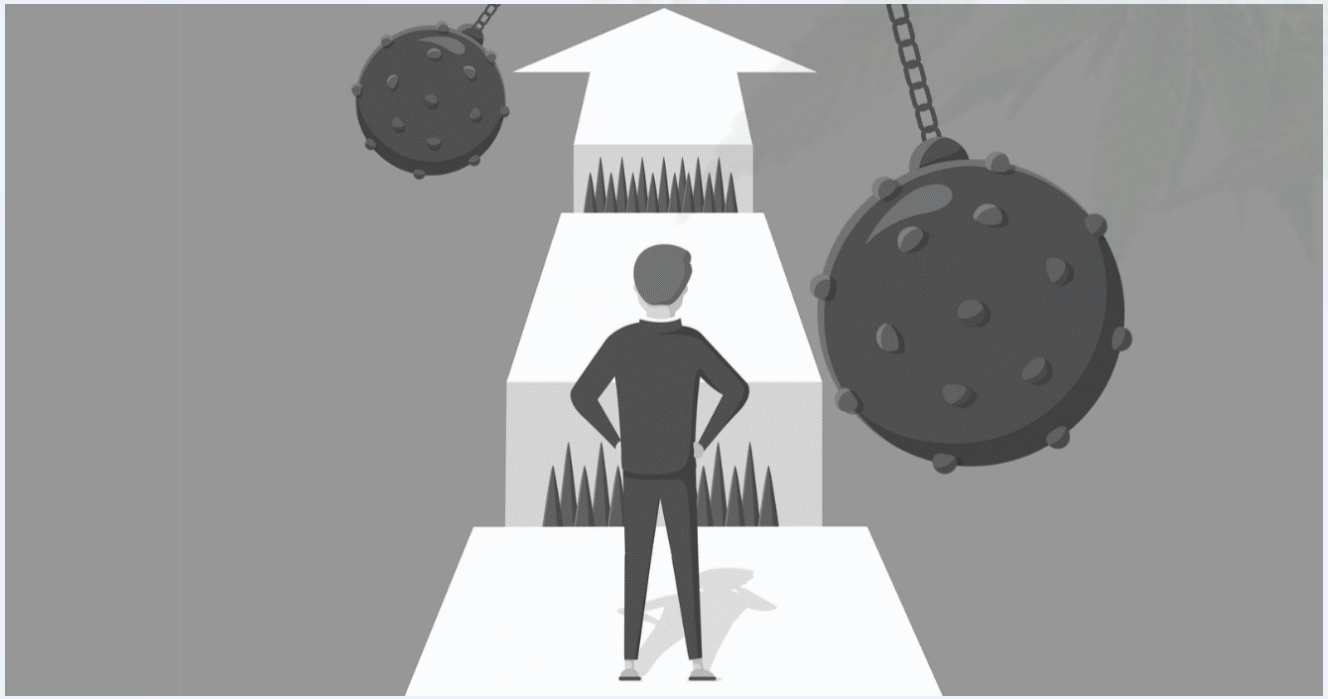
- Sub-chronic toxicity
  - 90-day study with 28 days of Recovery Period (OECD 408)
    - *Options included*: hormones evaluation and reproductive organs analysis

Outcomes

- A **NOEL/NOAEL** will be obtained
- Organs will be evaluated after repeated treatment (liver, reproductive ones, etc) and after suspension (recovery period)
- Biochemistry parameters checked during and at the end of the exposure (e.g. Hepatic enzymes, etc)
- Interference with the hormonal system evaluated (Hormones analysis)
- Toxicokinetic evaluation (absorption and distribution)

5. Conclusions

CBD and Hemp products are a SCIENTIFIC challenge!



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