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Does cannabidiol (CBD) in food supplements pose a serious health risk? Consequences of the EFSA clock stop regarding novel food authorisation

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Baden-Württemberg

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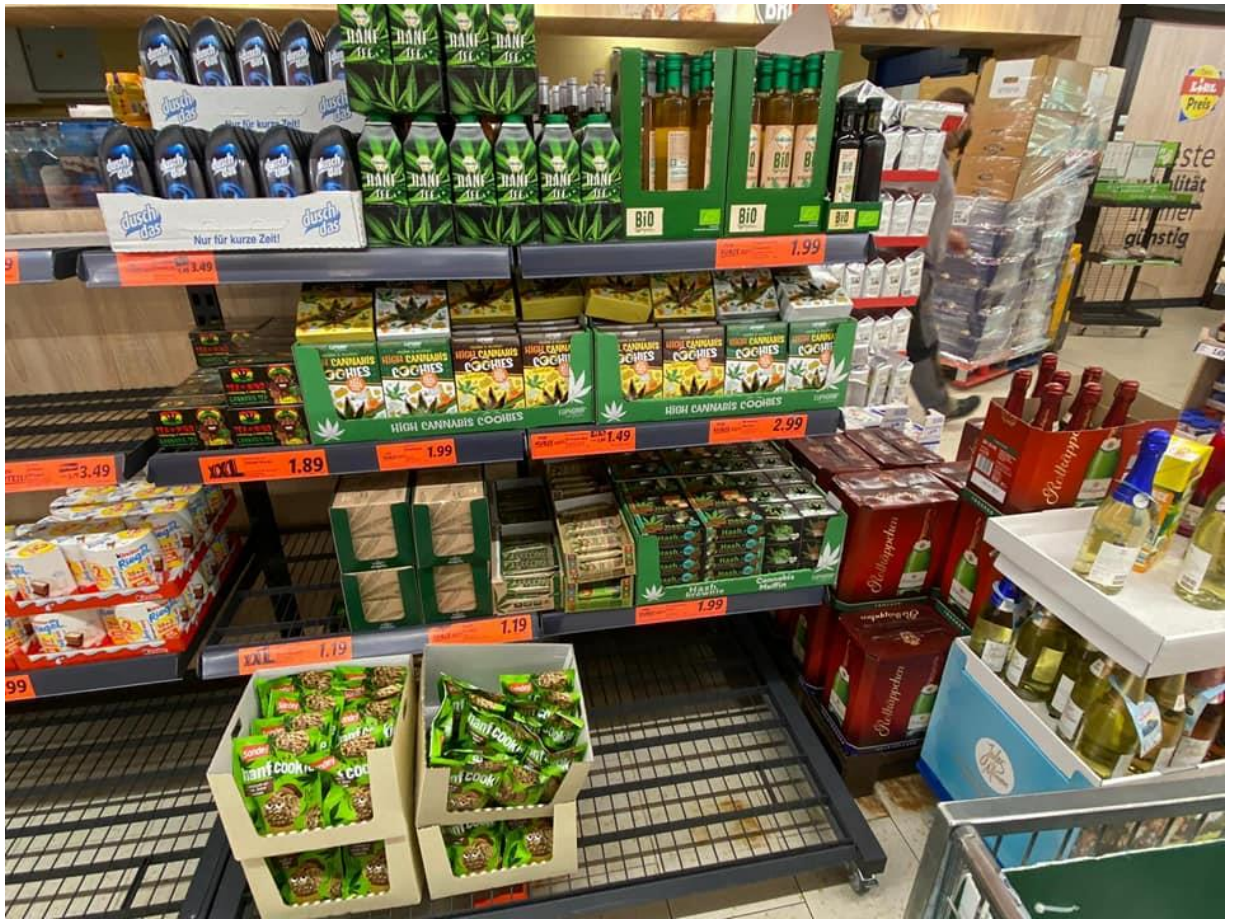
Foods 2022 –
Live Session 2 - "Food Toxicology and Food Safety"

Hemp and CBD arrived in the mainstream of EU food markets…



Lidl Aktionssortiment, 13.8.2021. Bildquelle: Facebook

Problems regarding food policy in the EU

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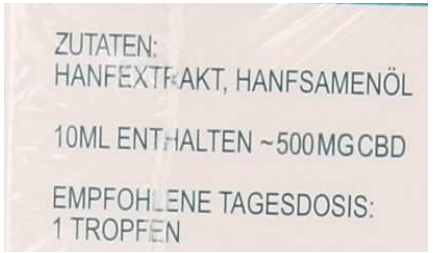
- CBD products (typically 5-20% CBD in oil matrix) are regularly marketed as „food supplement“ or similar products
- THC level needs to be safe according to food requirements (and safe is not 0.2%!)
- Extracts need novel food approval (several applications but none approved yet)
- Advertisement with health and disease related claims is forbidden

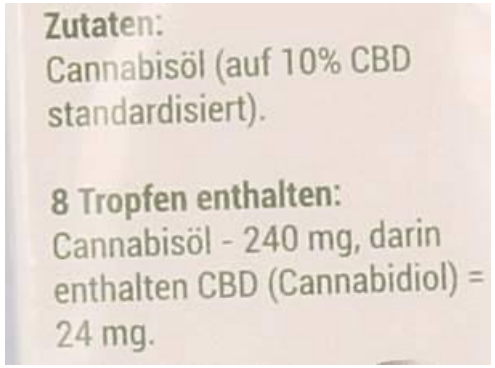
CBD-Extracts

- CBD-Oil ≠ Hemp oil
  - Hemp oil = Hemp seed oil
  - CBD-Oil = Hemp extract in edible oil
- Extract of complete plant incl. flower (e.g. using supercritical CO_2, ethanol, propanol)
- Typically „Full spectrum extracts“ on the market including THC and other cannbinoids, but also isolates and synthetic CBD

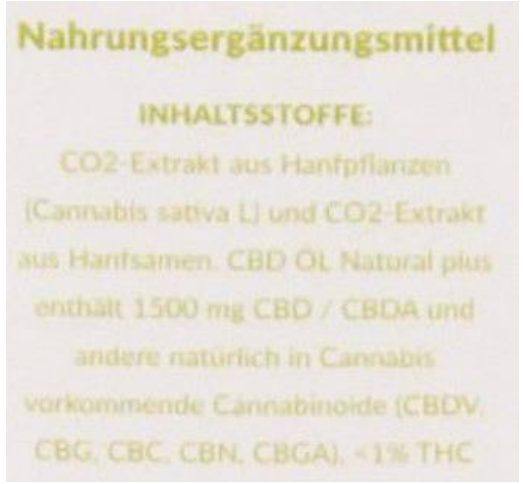

ZUTATEN:
HANFEXTRAKT, HANFSAMENÖL

10ML ENTHALTEN ~500MG CBD

EMPFOHLENE TAGESDOSIS:
1 TROPFEN


Zutaten:
Cannabisöl (auf 10% CBD standardisiert).

8 Tropfen enthalten:
Cannabisöl - 240 mg, darin enthalten CBD (Cannabidiol) = 24 mg.


Nahrungsergänzungsmittel

INHALTSSTOFFE:
CO2-Extrakt aus Hanfpflanzen (Cannabis sativa L) und CO2-Extrakt aus Hanfsamen. CBD ÖL Natural plus enthält 1500 mg CBD / CBDA und andere natürlich in Cannabis vorkommende Cannabinoide (CBDV, CBG, CBC, CBN, CBGA), <1% THC

CBD-Stores

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Hemp as „Novel Food“

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- Traditional hemp food products are not „novel“ (i.e. seeds and leaves and derived products)
- Other plant parts including inflorescences are questionable (used only for „beer flavouring“ before 1997 but not consumed as such)
- Oils enriched with CBD or hemp extracts are evaluated as being „novel“ (no sufficient history of consumption demonstrated by industry)
- Novel foods need safety assessment by EFSA and approval by the EU commission (implementing regulation) before placing on the market
- Enforcement of novel food regulation is obviously insufficent

Novel Food Catalogue

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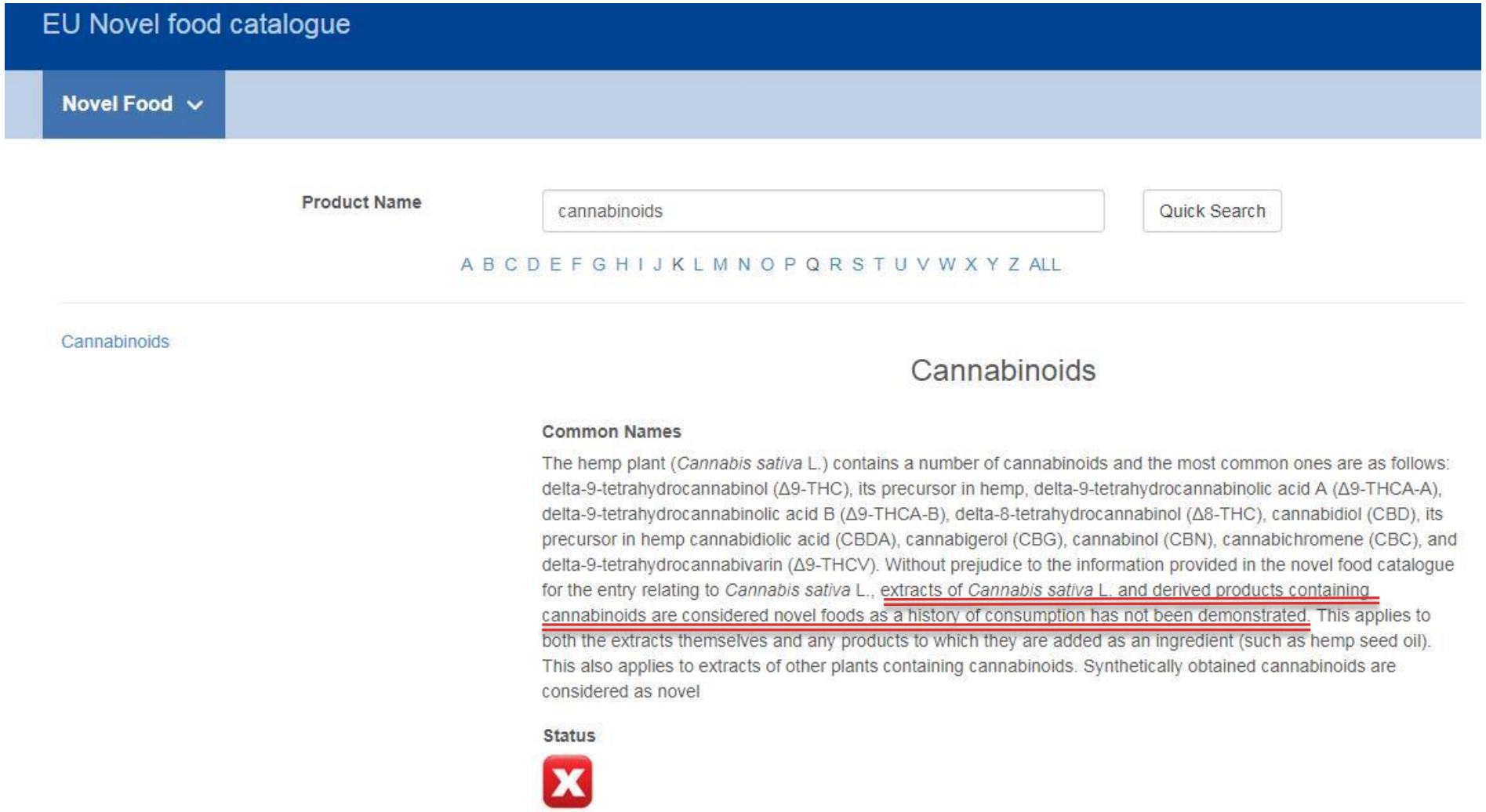

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EFSA CBD Statement

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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),
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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

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EFSA CBD Statement

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Abstract

The European Commission has determined that cannabidiol (CBD) can be considered as a novel food (NF), and currently, 19 applications are under assessment at EFSA. While assessing these, it has become clear that there are knowledge gaps that need to be addressed before a conclusion on the safety of CBD can be reached. Consequently, EFSA has issued this statement, summarising the state of knowledge on the safety of CBD consumption and highlighting areas where more data are needed. Literature searches for both animal and human studies have been conducted to identify safety concerns. Many human studies have been carried out with Epidyolex®, a CBD drug authorised to treat refractory epilepsies. In the context of medical conditions, adverse effects are tolerated if the benefit outweighs the adverse effect. This is, however, not acceptable when considering CBD as a NF. Furthermore, most of the human data referred to in the CBD applications investigated the efficacy of Epidyolex (or CBD) at therapeutic doses. No NOAEL could be identified from these studies. Given the complexity and importance of CBD receptors and pathways, interactions need to be taken into account when considering CBD as a NF. The effects on drug metabolism need to be clarified. Toxicokinetics in different matrices, the half-life and accumulation need to be examined. The effect of CBD on liver, gastrointestinal tract, endocrine system, nervous system and on psychological function needs to be clarified. Studies in animals show significant reproductive toxicity, and the extent to which this occurs in humans generally and in women of child-bearing age specifically needs to be assessed. Considering the significant uncertainties and data gaps, the Panel concludes that the safety of CBD as a NF cannot currently be established.

Animal bioassay data, BMD modelling

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Study, animal model	Study design, CBD doses	Endpoint	Sex	Model	p-value	BMD (mg/kg bw/day)	BMDL (mg/kg bw/day)
GWTX1412, rats	26-week oral at doses of 0, 15, 50, and 150 mg/kg bw/day (n=15/sex/group)	Liver, centrilobular hypertrophy	Males + females combined	Dichotomous Hill	0.9989	41	20
GWTX1413, dogs	39-week oral at doses of 0, 10, 50, and 100 mg/kg bw/day (n=4/sex/group)	Liver, hepatocyte hypertrophy	Males + females combined	Log-Probit	0.5771	(3)	(2)
Marx et al., rats	90-day oral at doses of 0, 25, 90, and 180 mg/kg bw/day (n=10/sex/group)	Liver weight	Males	Exponential 2	0.5235	(52)	(43)
			Females	Polynomial 3	0.9771	(52)	(34)
Dziwenka et al., rats	90-day oral at doses of 0, 6.3, 22.7 and 81.6 mg/kg bw/day (n=10/sex/group)	Relative liver weight	Females	Exponential 2	0.1941	(39)	(26)

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BMD modellig 26-w oral study in rats

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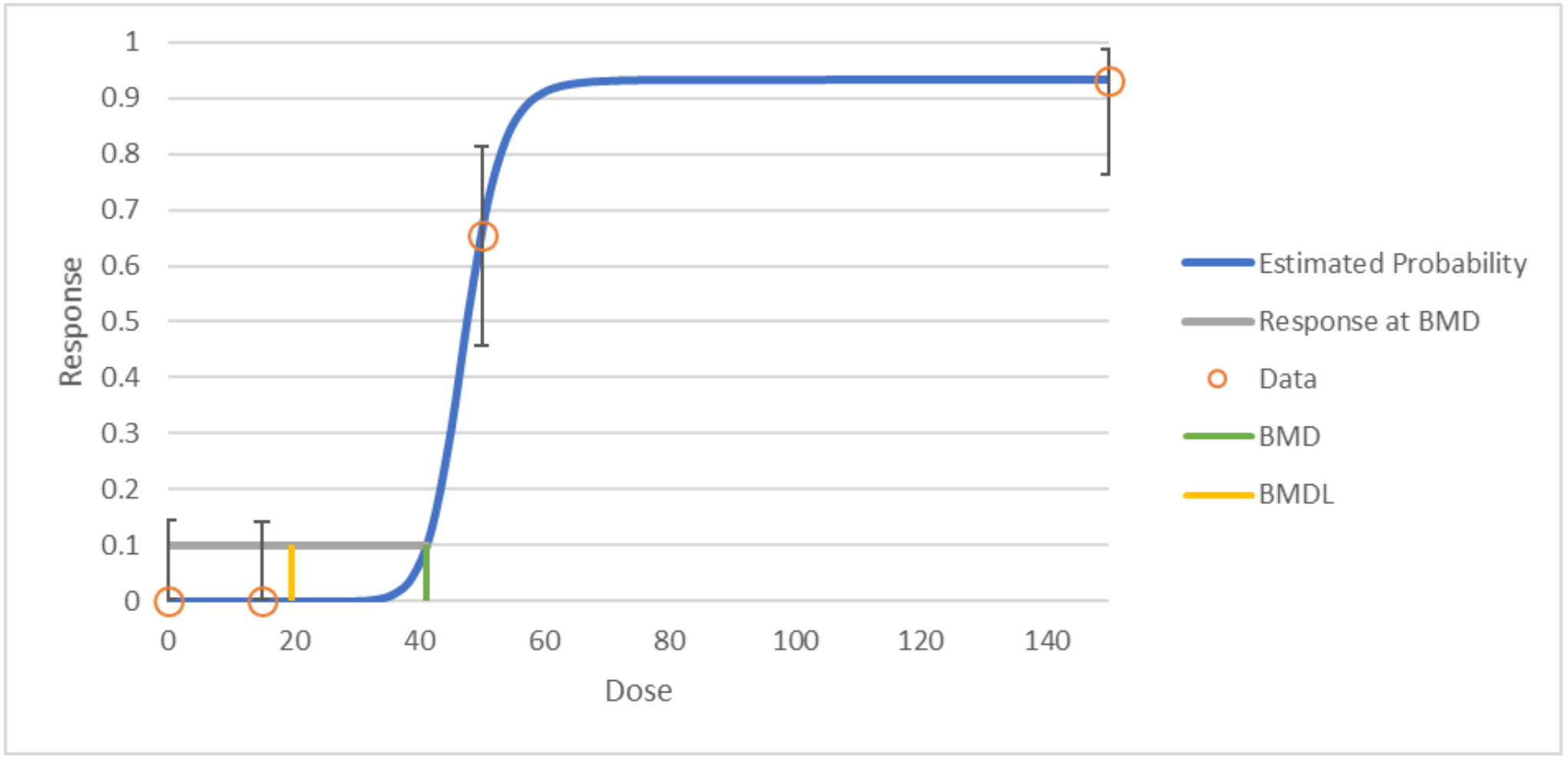

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Reference doses (RfD) for cannabidiol (CBD) based on animal and human data

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CBD	Animal data	Human data
Type of point of departure (POD)	BMDL	LOAEL
Value of point of departure (POD)	20 mg/kg bw/day (1,400 mg/day)	4.3 mg/kg bw/day (300 mg/day)
Uncertainty factor (UF)	100	30
Reference dose (RfD)	0.20 mg/kg bw/day (14 mg/day)	0.14 mg/kg bw/day (10 mg/day)

Suggestion for Preliminary Risik assessment

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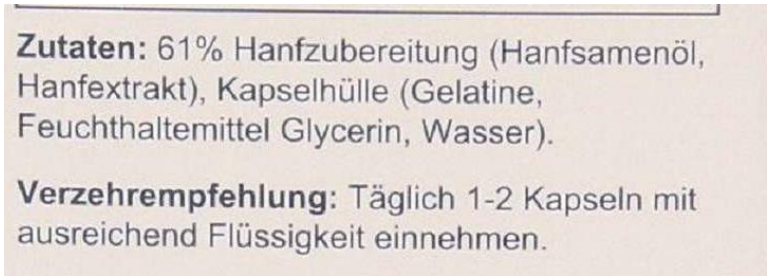
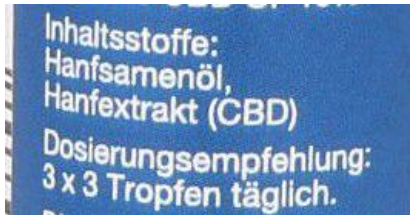
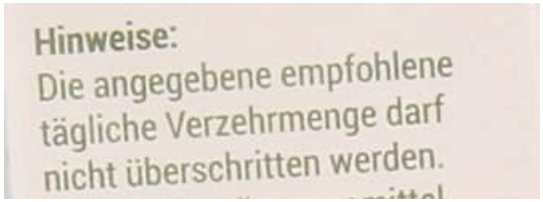
- Available data on liver toxicity:
  - Lowest-observed adverse effect level (LOAEL): 4.3 mg CBD/kg bw/day (300 mg CBD/day)
  - Reference dose (RfD): 0.14 mg CBD/kg bw/day (10 mg CBD/day)
- Case by case decision for every single product considering typical consumption amounts
- Products in exceedance of the human LOAEL should be considered as being “injurious to health” (Article 14(1) and (2) (a) of Regulation No 178/2002) and they should also be considered as being a serious risk to health in the sense of the criteria for the EU Rapid Alert System for Food and Feed (RASFF)







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Conclusions

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- CBD- and hemp extract-based products (if sold as food or supplement) typically in infringement of various food laws (THC, novel food, health and disease claims, misleading food information, labelling issues)
- Since EFSA CBD statement: safety of CBD itself must be included in risk assessments
- Current legal situation of CBD as food in the EU is highly unsatisfactory: we have a billion EUR market despite lack of approval
- Interim risk management decisions necessary till finalization of novel food evaluations: how are we dealing with products already on the market?
- Suggestion: Regulation of low-THC cannabis products alongside legalized lifestyle and recreational cannabis products in separate policy framework

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Thank you for your interest

References:

Conference proceedings paper with detailed BMD calculations

EFSA NDA Panel. Statement on safety of cannabidiol as a novel food: data gaps and uncertainties. EFSA Journal 2022; 20(6):7322. doi:10.2903/j.efsa.2022.7322

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Marx et al. An assessment of the genotoxicity and subchronic toxicity of a supercritical fluid extract of the aerial parts of hemp. J. Toxicol. 2018, 2018, 8143582. doi:10.1155/2018/8143582

Picture sources: own pictures if not otherwise stated; p.1: AI-generated using the phrase “a bottle of cannabidiol oil and a hemp leaf in front of a stop sign” using DALL-E 2 on OpenAI.com.

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