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Article

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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Abstract: At present, foods containing cannabidiol (CBD) and other cannabinoids are internationally being widely advertised and sold in increasing quantities. In the European Union (EU), these products require pre-marketing authorisation under the novel food regulation, so that all available CBD oils and CBD-containing food supplements in the EU are currently placed on the market with an infringement of the food laws. Currently, 19 CBD applications are under assessment at the European Food Safety Authority (EFSA). During the initial assessment of the application files, EFSA located several knowledge gaps that need to be addressed before the safety evaluation of CBD can be concluded. Namely, the effect of CBD on the liver, gastrointestinal tract, endocrine system, nervous system, psychological function, and reproductive system needs to be clarified. Nevertheless, the available literature allows a benchmark dose (BMD)-response modelling of several bioassays, resulting in a BMD lower confidence limit (BMDL) of 20 mg/kg bw/day for liver toxicity in rats. Human data in healthy volunteers found increases in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in a study at 4.3 mg/kg bw/day, which was defined by EFSA as a lowest observed adverse effect level (LOAEL). The EFSA panel currently concluded that the safety of CBD as a novel food cannot be evaluated, leading to a so-called clock stop of the applications until the applicants provide the required data. Meanwhile, the authors suggest that CBD products still available on the EU market despite the lack of authorisation must be considered as "unsafe". Products exceeding a reference dose of 10 mg/day must be considered as being "unfit for consumption" (Article 14(1) and (2) (b) of Regulation No 178/2002), while the ones in exceedance of the human LOAEL must be considered "injurious to health" (Article 14(1) and (2) (a) of Regulation No 178/2002).

Keywords: food safety; risk assessment; *Cannabis sativa*; tetrahydrocannabinol; food supplements; cannabidiol; benchmark dose; reference dose; liver toxicity

1. Introduction

In the European Union (EU), foods and food ingredients evaluated as novel need a pre-marketing approval in the form of an implementing regulation issued by the European Commission (EC) [1]. Before that, the European Food Safety Authority (EFSA) is asked to provide a risk assessment for the novel food, on which the EC decision is based. The novelty of a food is determined by a lack of significant history of consumption prior to 15 May 1997 [2]. Regarding the hemp plant *Cannabis sativa* L., only the seeds and seed-derived products have a history of consumption and are treated as "not novel". In contrast, extracts and derived products containing cannabinoids, such as cannabidiol (CBD), but also synthetic cannabinoids are considered novel foods [3]. Hence, CBD products to be marketed as foods or food supplements in the EU, need prior authorisation. Despite being widely advertised and sold in increasing quantities, all available CBD oils and CBD-

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containing food supplements in the EU are, therefore, currently placed on the market with an infringement of the food laws [4]. This is not a niche anymore as the total EU CBD market was valued at EUR 1.6 billion in 2020 [5]. Apparently, it is a worldwide phenomenon that illegality is not a deterrent for producers, as CBD food products may be readily available in jurisdictions where they are illegal because jurisdictional enforcement is lenient [6].

As of mid-March 2022, the industry has so far provided more than 150 novel food applications for CBD products and 19 are currently under assessment by EFSA. Most of the applications are for CBD extracted from hemp plants, but there are also several applications with chemically synthesised CBD [7].

During the initial assessment of the application files, EFSA located several knowledge gaps that need to be addressed before the safety evaluation of CBD can be concluded. Namely, the effect of CBD on the liver, gastrointestinal tract, endocrine system, nervous system, psychological function, and reproductive system needs to be clarified [7]. One of the major adverse effects of CBD at therapeutic dosages appears to be liver injury, which may lead to symptoms of hepatitis even in healthy adults [8]. Literature was searched and reviewed by EFSA, but no observed adverse effect level (NOAEL) could not be identified in both animal and human studies [7]. The EFSA panel currently concluded that the safety of CBD as a novel food cannot be evaluated, leading to a so-called clock stop of the applications until the applicants provide the required data [7].

This article aims to provide an in-depth look into the available data about CBD and provide an interim judgement about the risk of products currently on the market. As NOAEL were not available or uninformative, benchmark dose-response modelling of the data highlighted by EFSA was conducted to provide an alternative point of departure (POD) for toxicological risk assessment.

2. Materials and Methods

The data analysed in this study were obtained from the EFSA statement [7]. No additional searches for data were conducted. The data were checked for the suitability of benchmark dose-response modelling according to the criteria of Hindelang et al. [9]: (i) a study considered for inclusion in this research had to have administered at least 3 different doses and a control group receiving vehicle. Dose spacing was not considered relevant, (ii) applied doses had to be administered in mg/kg of body weight, (iii) the number of animals per dose group had to be declared. (iv) studies reporting concomitant treatment with other medications were not included.

The eligible studies were then assessed using the benchmark dose (BMD) approach according to the United States (US) Environmental Protection Agency (EPA) [10]. The BMD and its respective lower confidence interval, the BMDL, were calculated by fitting multiple statistical models using the EPA benchmark dose v. 3.2.0.1 (rel. 2022-03-15) software (BMDS) [11], which performs automated fitting of selected models to dose-response data retrieved from toxicological studies. The most suitable model was determined based on the Akaike information criteria generated in the output. All settings of BMDS were at default.

3. Results

From the studies assessed by EFSA [7], only 3 animal studies were identified with suitable dose-response data for benchmark dose modelling. Two of the studies (GWTX1412 and GWTX1413) were published in the context of the approval process of the CBD medicinal product Epidiolex as part of the application review files on the US Food and Drug Administration (FDA) website [12]. Another study, by Marx et al. [13], was published in the peer-reviewed literature, but the test object was a hemp extract and not isolated CBD. As the extract was of a comparably high purity of CBD, the authors decided

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to still include the study for comparative reasons. The results of the dose-response modelling are presented in Table 1. An example for the BMD modelling of the GWTX1412 study, which was judged as being the most informative, is shown in Figure 1. The full BMD modelling reports of all studies included in Table 1 are provided as supplementary materials (documents S1-S4).

Table 1. Dose-response modelling results for cannabidiol (CBD) in different animal experiments.

Study, animal model	Study design, CBD doses	Endpoint	Sex	Model [a]	*p*-value [b]	BMD [c] (mg/kg bw/day)	BMDL [d] (mg/kg bw/day)
GWTX1412 [12], rats	26-week oral at doses of 0, 15, 50, and 150 mg/kg bw/day (n=15/sex/group)	Liver, centrilobular hypertrophy [e]	Males + females combined [f]	Dichotomous Hill	0.9989	41	20
GWTX1413 [12], dogs	39-week oral at doses of 0, 10, 50, and 100 mg/kg bw/day (n=4/sex/group)	Liver, hepatocyte hypertrophy [e]	Males + females combined [f]	Log-Probit	0.5771	(3) [g]	(2) [g]
Marx et al. 2018 [13], rats	90-day oral at doses of 0, 25, 90, and 180 mg/kg bw/day (n=10/sex/group) [h]	Liver weight	Males [i]	Exponential 2	0.5235	52	43
			Females [i]	Polynomial 3	0.9771	52	34

[a] Data of the viable recommended model selected with BMDS 3.2.0.1 (rel. 2022-03-15) software are presented. [b] A *p*-value greater than 0.1 indicated that the model fits the data (*p*-value 1.0 = perfect fit). [c] BMD: benchmark dose for a benchmark response of 1 standard deviation (continuous models) or 10% extra risk (dichotomous data). [d] BMDL: 95% lower one-sided confidence limit of the BMD. [e] The sum of incidences for all grades of liver effects was evaluated. [f] A single curve is fitted to both sexes as the analysis revealed no significant differences in dose-response between the sexes. [g] BMD and BMDL are both 3x lower than the lowest non-zero dose and the model must be cautiously interpreted. [h] The study of Marx et al. [13] was conducted with a hemp extract containing 26% of cannabinoids of which 96% is CBD. The dose levels were adjusted to reflect pure CBD. [i] Due to lack of raw data, the sexes could not be combined in this case, despite no obvious differences between the sexes in this study as well.

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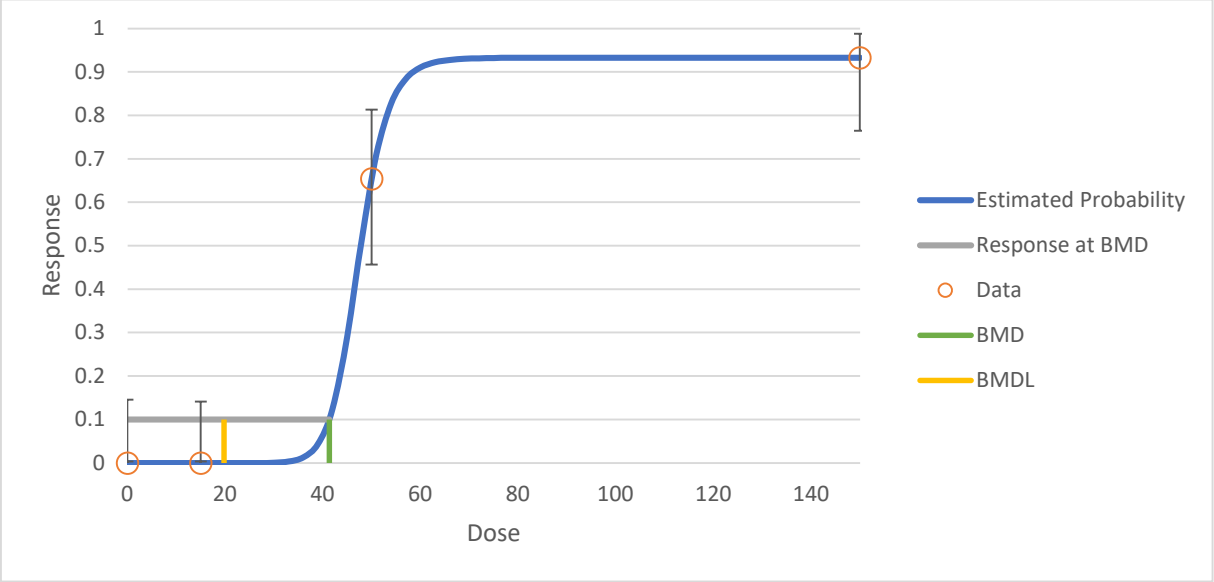

Figure 1. Benchmark dose (BMD) modelling of cannabidiol (CBD) for centrilobular hypertrophy of the liver in a 26-week oral study in rats (GWTX1412, see Table 1): frequentist dichotomous Hill model with benchmark response (BMR) of 10% extra risk for the BMD and 95% lower confidence limit (BMDL).

From the animal study modelling results, the authors suggest to use the BMDL of 20 mg/kg bw/day from the GWTX1412 study in rats as POD, as this is the lowest, i.e., most conservative, value from the informative studies. The authors do not believe that the BMDL of the GWTX1413 study is meaningful because the dose-response model led to considerable extrapolation beyond the lowest non-zero dose.

None of the human studies reported by EFSA was sufficient for dose-response modelling. Therefore, the lowest LOAEL of 4.3 mg/kg bw/day, specifically highlighted by EFSA in their presentation [14], was used as POD. The original study from which EFSA derived this LOAEL was a randomized clinical trial in 120 healthy male and female healthcare professionals receiving 300 mg of CBD for 28 days. Four participants (6.8%) had elevated levels of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (1 critical and 3 mild) [15].

The PODs from animal and human data were then used to estimate reference doses (RfD) using suitable uncertainty factors (Table 2). Overall, the authors suggest to use the human RfD of 0.14 mg/kg bw/day for preliminary risk assessment, as it is more conservative than the animal RfD and human data should be preferred in any case. Nevertheless, as both animal and human RfD are in excellent agreement, the animal data provide independent validation of the correct magnitude of the human RfD.

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Table 2. Calculation of reference doses (RfD) for cannabidiol (CBD) based on animal and human data.

CBD	Animal data	Human data
Type of point of departure (POD)	BMDL, see Table 1	LOAEL [7,15]
Value of point of departure (POD)	20 mg/kg bw/day (1,400 mg/day [a])	4.3 mg/kg bw/day (300 mg/day [a])
Uncertainty factor (UF)	100 [b]	30 [c]
Reference dose (RfD)	0.20 mg/kg bw/day (14 mg/day [a])	0.14 mg/kg bw/day (10 mg/day [a])

[a] Calculation for a 70-kg human standard weight [16]. [b] Default UF of 100 (10 for inter-species variability x 10 for intra-human variability [16]). [c] Overall UF of 30 (3 for extrapolation from the LOAEL to a NOAEL x 10 for intra-human variability, as previously suggested by EFSA for tetrahydrocannabinol (THC) [17].

4. Discussion

Despite the lack of data on CBD safety, correctly specified by EFSA [7] and also in a recent review by Nyland and Moyer [6], the authors believe that the available data allow to make at least a preliminary risk assessment if the dose-response information contained in the available data is appropriately considered. The authors also believe that the principle of precautionary public health protection demands the use of that data. The authors have previously commented regarding THC contamination of CBD products that it is short of a "scandal" because unapproved and potentially unsafe products are placed on the food market within the EU [18]. Other authors similarly characterised the CBD market as containing "black sheep" disregarding regulations trying to make a quick profit with the hype surrounding cannabis legalisation [19].

This preliminary risk assessment of available bioassays and human data on CBD toxicity strengthens this assessment, as many products on the market would be exceeding the estimated reference dose of 10 mg/day. For example, there are several CBD oil products on the market containing 10% of CBD, which means that the reference dose would be contained in an amount of 0.1 g, which is typically contained in only 3–4 drops of the product. The usually recommended dosage of several drops per day may, therefore, exceed the reference dose. For some products, which may contain even higher concentrations of CBD, the possible intake can even exceed the LOAEL of about 300 mg/day.

The reference dose of 10 mg/day proposed in this article is very similar to another approach for risk assessment by the Swiss Federal Food Safety and Veterinary Office (FSVO) determining an oral daily dose of 12 mg CBD/adult, which should not be exceeded [20]. The FSVO based its recommendation on a healthy volunteer phase I study, in which 5 out of 12 healthy subjects developed ALT elevations above the normal range at 5 mg/kg/day during the three-week treatment period [21]. The FSVO has used an uncertainty factor of 30, similar to the proposal in this study (Table 2), to calculate the guidance value.

The liver effects that are consistently observed in all tested species, including humans, are clearly a major cause for concern. It must be considered that this risk assessment concerns foods, for which safety must be generally guaranteed, unlike medicinal products for which risk-benefit considerations must be included. For CBD-containing foods, it must also be considered that they may be consumed daily a life-long without medical supervision or any form of nutrivigilance, which is not mandatory in the EU.

Meanwhile, the authors suggest that CBD products still available on the EU food market despite the lack of authorisation must be assessed if they might be "unsafe" in the sense of Article 14 (1) of the Basic Food Regulation No 178/2002 [22]. If they exceed the

reference dose, they would be "unfit for consumption" (Article 14(1) and 14 (2) (b) of the Basic Regulation [22] or corresponding national regulations such as §12 of the German food and feed law). Products in exceedance of the human LOAEL of 4.3 mg/kg bw/day should be considered as being "injurious to health" (Article 14(1) and (2) (a) of the Basic Regulation [22]) 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), similar to the practice for THC risk assessment [23].

5. Conclusions

There is clearly a growing consumer demand for CBD and other cannabinoid products, which has not been adequately followed up by policy leading to a huge market of unregulated CBD products, often marketed in the supposed legal loopholes as cosmetic mouth sprays, non-food flavours or even phantasy products for mythical animals [24,25]. This situation is completely unsatisfactory for consumers, industry and control authorities alike. The unregulated market also leads to safety problems beyond cannabinoids, e.g., contamination with pesticides, heavy metals, or microbiological risks, or even the addition of synthetic cannabinoids [6]. Apart from that, quality control is lacking leading to inconsistent labelling making dosing unpredictable [26].

As the EFSA has convincingly highlighted the lack of data necessary for final risk assessment, novel food approval could still take years, including the time required to conduct the chronic toxicity studies for the missing endpoints in the low-dose range expected in foods. The authors would now expect a response by the risk management of the European Commission and national authorities, how to go forward during the years until the completion of the novel food applications. Continuation of the complete prohibition of CBD products is obviously not a considerate policy, as this has not worked in the past 5 years and consumers are still ingesting CBD in considerable amounts. The authors currently can envision at least 3 pathways to proceed: (i) low-dose CBD products (up to 10 mg/day and less than 300 mg/package) could be approved as foods in an intermediary basis including warning labels about the potential toxic effects (see the post-brexit UK approach), (ii) regulation of low-dose CBD products as over-the-counter medicinal products only available in pharmacies, as an additional category to the already available prescription-based high-dose CBD medicinal products (see suggestion by Health Canada [27]), or (iii) regulation of CBD products outside the scope of foods or medicines inside a separate framework, e.g., within the currently planned controlled distribution of cannabis to adults for recreational use in licensed stores in Germany. This is now a political decision to be made and the authors hope that the legislator does not again turn a blind eye to the problem as in the past.

Supplementary Materials: BMDS 3.0 analysis reports S1: GWTX1412; S2: GWTX1413; S3: Marx et al. 2018 (males); S4: Marx et al. 2018 (females).

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