BRIEF REPORT

REVISED Are adverse effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination? [version 5; peer review: 2 approved, 1 approved with reservations]

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Abstract

Cannabidiol (CBD)-containing products are widely marketed as over the counter products, mostly as food supplements. Adverse effects reported in anecdotal consumer reports or during clinical studies were first assumed to be due to hydrolytic conversion of CBD to psychotropic Δ^9-tetrahydrocannabinol (Δ^9-THC) in the stomach after oral consumption. However, research of pure CBD solutions stored in simulated gastric juice or subjected to various storage conditions such as heat and light with specific liquid chromatographic/tandem mass spectrometric (LC/MS/MS) and ultra-high pressure liquid chromatographic/quadrupole time-of-flight mass spectrometric (UPLC-QTOF) analyses was unable to confirm THC formation. Another hypothesis for the adverse effects of CBD products may be residual Δ^9-THC concentrations in the products as contamination, because most of them are based on hemp extracts containing the full spectrum of cannabinoids besides CBD. Analyses of 293 food products of the German market (mostly CBD oils) confirmed this hypothesis: 28 products (10%) contained Δ^9-THC above the lowest observed adverse effect level (2.5 mg/day). Hence, it may be assumed that the adverse effects of some commercial CBD products are based on a low-dose effect of Δ^9-THC, with the safety of CBD itself currently being unclear with significant uncertainties regarding possible liver and

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reproductive toxicity. The safety, efficacy and purity of commercial CBD products is highly questionable, and all of the products in our sample collection showed various non-conformities to European food law such as unsafe Δ^9-THC levels, hemp extracts or CBD isolates as non-approved novel food ingredients, non-approved health claims, and deficits in mandatory food labelling requirements. In view of the growing market for such lifestyle products, the effectiveness of the instrument of food business operators' own responsibility for product safety and regulatory compliance must obviously be challenged, and a strong regulatory framework for hemp products needs to be devised.

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Tetrahydrocannabinol, cannabidiol, Cannabis sativa, hemp, food supplements, risk assessment, drug effects

This article is included in the Agriculture, Food and Nutrition gateway.

REVISED **Amendments from Version 4**

Some further references on adverse effects of cannabidiol as well as on stability studies and surveys were included. The criticism regarding sample size of the original peer review was further addressed by including analytical results of 112 additional samples analyzed during 2021 into Table 2 (resulting in n=293). As Table 2 would have become extremely long, the table format was simplified to only include sample numbers per group per year. The full results are available in the updated dataset. Finally, the risk assessment of CBD was updated considering the recent EFSA statement on safety of cannabidiol as a novel food.

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Introduction

Since hemp has been re-approved for cultivation as an industrial crop in the form of low Δ^9-tetrahydrocannabinol (Δ^9-THC) hemp (*Cannabis sativa* L.) varieties in the European Union (EU), components of the hemp plant are increasingly used for the production of foods and other consumer products such as liquids for electronic cigarettes[1].

From all hemp constituents, cannabidiol (CBD) is currently the compound with highest interest. In contrast to Δ^9-THC, the major narcotic constituent of hemp, CBD is a non-psychotropic cannabinoid. It is currently being tested for its possible antispasmodic, anti-inflammatory, anxiolytic and antiemetic effects as a drug, e.g. for the treatment of epilepsy[2,3]. However, CBD products of all kinds can now also be purchased in organic shops, drug stores, specialised hemp and CBD stores, but also in supermarkets and via the Internet, often by advertising questionable "cure-all" properties including various unspecific health advantages. The marketing of CBD products is based on the current "hype" around medicinal hemp products, whereby the CBD products are offered as a supposedly safe alternative, promised as being free of psychotropic components or their adverse effects[4]. The awareness of recreational CBD use in Germany is high, with approximately half of the population being aware of them and 4.3% of the population having ever used them (1.1% current users)[5]. With the exception of the treatment of Dravet's syndrome, there is little clinical data on the efficacy and safety of CBD[6,7]. Cannabidiol is currently approved in the EU in a single medicinal product, namely Epidiolex® for the treatment of seizures in patients with two rare, severe forms of childhood-onset epilepsy. Apart from that, extemporaneous preparations in pharmacies are legally available on prescription in Germany and some other countries. However, most of the CBD products worldwide are available as food supplements or CBD-containing hemp extracts are used as ingredient in other foods.

Commercial CBD products are usually crude extracts from whole hemp plants (i.e., including flowers and stems). In other ways (e.g., in extracting the food-approved plant parts such as seeds), contents in the range of 1–10% CBD, which are typically advertised, cannot be achieved. Also, the limited available literature and manufacturer data confirm that CBD

products are usually extracted by supercritical CO_2 or with solvents such as ethanol or isopropanol from the entire hemp plant material, which typically has been decarboxylated before the process[7,8]. No further specific enrichment or purification of CBD is often conducted, so that the commercial extracts are regularly a cannabinoid mixture rather than pure CBD. Otherwise, extracts may be cleaned with different processes such as winterization, or partial fractionation using supercritical CO_2. These extracts, which are typically called "full spectrum extracts" in difference to chemically pure CBD (such as isolated or synthesized CBD), are then mixed into ordinary edible oils such as sunflower oil, olive oil or hemp seed oil to obtain the so-called CBD oil[7].

The strategy to market CBD products as food supplements within the framework of food regulations seems to be the most common approach of CBD sellers. The most prevalent food supplement products are CBD oils in liquid form or hemp extract containing capsules. Some other products, derived from hemp extracts, are CBD chewing gum, and cannabis resin, wax or pollen products, while so-called "CBD flowers" are typically sold as plant material to prepare a tea-like infusion or as an herbal product for smoking.

However, no significant food consumption of CBD products has been documented before 15 May 1997. These products are therefore classified as "novel" in the Novel Food catalogue of the European Commission under the entry "cannabinoids" and therefore require approval according to the Novel Food Regulation. Up to date (as of October 2022), no approved application is documented. Basically, all available CBD products based on hemp extract but also those based on isolated or synthesized CBD, which are marketed as food or food supplement within the EU, are therefore illegally sold[2]. To circumvent the strict safety requirements for medicinal or food products, some CBD products may be sold as other product categories (e.g., cosmetics, veterinary supplements, waxes, flavourings, air fresheners or room fragrances), but the off-label use, human consumption, is clearly intended.

Despite the enforcement efforts of the food and medicinal product control authorities (e.g. the EU's rapid alert system for food and feed (RASFF) lists over 180 alerts for CBD since 2018), a multitude of CBD products is available on the internet and in some retail stores, so that CBD is currently easily available to consumers.

Despite the lack of mandatory nutrivigilance in the EU, anecdotal cases ranging from indisposition to Δ^9-THC-like effects have been reported to our institute from food control authorities in the German Federal State of Baden-Württemberg in the context of consumer complaint cases regarding CBD products. Several case reports of adverse effects of CBD products have also been published[9–12], and a survey of 135 CBD users in the USA detected a high prevalence of adverse effects (30% dry mouth, 22% feeling high, 20% change in appetite, 19% fatigue)[13]. Additionally, some paediatric studies in epilepsy patients with orally administered CBD also reported

adverse effects such as drowsiness and fatigue that could be explained by pharmacological properties of Δ^9-THC rather than of CBD[14–16]. Respiratory depression was reported in a case of CBD overdose in a paediatric patient[17]. Clinical trials with doses of 300 mg/day and above have shown elevated liver enzymes consistent with liver injury[18,19]. Concerns also include negative effects on the male reproductive system[20].

Diarrhoea was an adverse outcome associated with CBD treatment in a meta-analysis of randomized clinical trials, after excluding studies of childhood epilepsy[21]. Post marketing safety surveillance of a full spectrum hemp extract reported gastrointestinal symptoms as most common adverse effect, however, they were infrequent (0.03%)[22]. More recently, the epidemiology of CBD-related cases in the national poison data system of the USA was assessed. Cannabidiol cases increased from 0% in 2009–2018 to 17% of all cases in 2019[23]. Among the exposures in which CBD was the only reported substance (n=1275), the most common symptoms were mild central nervous system depression (10%), tachycardia (6%), dizziness/vertigo (5%), vomiting (5%), nausea (5%) and agitation (4%)[24]. The European food safety authority (EFSA) has recently summarised the state of knowledge on the safety of CBD consumption in the context of the novel food approval procedures. The EFSA determined that the effect of CBD on liver, gastrointestinal tract, endocrine system, nervous system and on psychological function needs to be clarified, and that studies in animals show significant reproductive toxicity[25].

Currently there are three hypotheses for the cause of the adverse effects: (i) a direct pharmacological effect of CBD, (ii) the degradation of CBD to Δ^9-THC due to acidic hydrolysis in the stomach following oral consumption, and (iii) Δ^9-THC directly contained in the products as by-product due to co-extraction and enrichment or contamination such as formation from CBD degradation during storage. In this article, the hypotheses are investigated including new evidence from original data.

Methods
CBD degradation
To investigate CBD degradation into Δ^9-THC under acidic conditions, differently concentrated CBD in methanolic solutions was used in a range corresponding to typical amounts consumed with supplements based on commercial CBD (Supelco Cerilliant, certified reference material, #C-045, 1.0 mg/mL in methanol) supplied by Merck (Darmstadt, Germany). These solutions were exposed to an artificial gastric juice as well as different incubation times and stress factors such as storage under light and heat (see Table 1 for full experimental design). The solutions were stored either in standard freezer (-18°C) or refrigerator (8°C) or at room temperature (20°C). Increased temperatures were achieved using a thermostatically controlled laboratory drying oven type "UT6120" (Heraeus, Langenselbold, Germany) set to either 37°C or 60°C. The daylight condition was achieved by storage at a window (south side). For ultraviolet light exposure, six 25 W ultraviolet (UV) fluorescent tubes type

"excellent E" (99.1% UVA) built into a facial tanner type "NT 446 U" (Dr. Kern GmbH, Mademühlen, Germany) were placed 15 cm from the surface of the solutions (open sample vials). In deviation of an experimental protocol of Merrick et al.[26], a gastric juice without addition of surfactants was used, which was strictly produced according to the European pharmacopoeia[27] (0.020 g NaCl + 0.032 g pepsin + 0.8 mL HCl (1 mol/L), filled up to 10 mL with water). As pure CBD was available only in methanolic solution, the final experimental setups contained 0.08 mol/L HCl and 1% methanol due to dilution (methanol residues in this order of magnitude are not interfering with the analysis).

To ensure the utmost analytical validity, all samples were independently measured on two different instruments, using a triple quadrupole mass spectrometer (TSQ Vantage, Thermo Fisher Scientific, San Jose, CA, USA) coupled with an LC system (1100 series, Agilent, Waldbronn, Germany) and also using a quadrupole time-of-flight (QTOF) mass spectrometer (X500, Sciex, Darmstadt, Germany) coupled with an UPLC system (1290 series, Agilent, Waldbronn, Germany). Both systems used the same type of separation column (Luna Omega Polar C18, 150 × 2.1 mm, 1.6 µm, 100 Å, Phenomenex, Aschaffenburg, Germany). The separation was isocratic with 25 % water (0.1 % formic acid) and 75 % acetonitrile (0.1 % formic acid) and a flow of 0.3 mL/min. In case of QTOF with 35 % water (0.1 % formic acid) and 65 % acetonitrile (0.1 % formic acid) and a flow of 0.45 mL/min. The evaluation took place after fragmentation of the mother ion into three mass traces for each compound. As quantifier for Δ^9-THC and CBD, the mass transition m/z 315 to 193 was used. In case of QTOF, quantification was conducted over accurate mass and control of fragmentation pattern. CBD eluted as one of the first cannabinoids, a few minutes before Δ^9-THC. As internal standards Δ^9-THC-d$_3$ (Supelco Cerilliant #T-011, 1.0 mg/mL in methanol) was used for the quantification of Δ^9-THC (Supelco Cerilliant #T-005, 1.0 mg/mL in methanol), and cannabidiol-d$_3$ (Supelco Cerilliant #C-084, 100 µg/mL in methanol) for quantification of CBD (Supelco Cerilliant #C-045, 1.0 mg/mL in methanol). The certified reference materials were obtained as solutions in ampoules of 1 mL, all supplied by Merck (Darmstadt, Germany). A limit of detection (LOD) of 5 ng/mL was determined. For both procedures, relative standard deviations better than 5% were achieved. Both methods are able to chromatographically separate Δ^9-THC and CBD from their acids. Specificity was ensured using a certified reference material as a reference standard of THCA (Supelco Cerilliant #T-093, 1.0 mg/mL in acetonitrile). Baseline separation was achieved between Δ^9-THC, Δ^8-THC and THCA. Therefore, the reported values in this study are specific for Δ^9-THC and CBD. In contrast to some previous studies based on gas chromatography, we do not report "total THC" or "total CBD", which would be a sum of the free form and its acid.

Δ^9-THC contamination of commercial products
To study the possible influence of natively contained Δ^9-THC in hemp products as a cause for adverse effects, a sampling

Table 1. Cannabidiol (CBD) stability experiments under various storage conditions.

Experiment	Temperature (°C)	Light exposure	Storage time	Storage medium	CBD concentration in medium (µg/L)	Δ⁹-THC formation[1]
Negative control	-18	None	14 days	Methanol	1000	0%
Light	20	None	3 days	Methanol	1000	0%
	20	None	14 days	Methanol	1000	0%
	20	Daylight	3 days	Methanol	1000	0%
	20	Daylight	14 days	Methanol	1000	0%
	20	UVA	1 h	Methanol	1000	0%
	20	UVA	3 h	Methanol	1000	0%
Temperature	20	None	5 days	Methanol	1000	0%
	20	None	14 days	Methanol	1000	0%
	8	None	5 days	Methanol	1000	0%
	8	None	14 days	Methanol	1000	0%
	37	None	3 h	Methanol	1000	0%
	60	None	1 h	Methanol	1000	0%
Simulated gastric juice	37	None	1 h	Simulated gastric juice	200	0%
	37	None	2 h	Simulated gastric juice	200	0%
	37	None	3 h	Simulated gastric juice	200	0%
	37	None	1 h	Simulated gastric juice	400	0%
	37	None	2 h	Simulated gastric juice	400	0%
	37	None	3 h	Simulated gastric juice	400	0%
Positive control	20	None	14 days	Methanol / 1 mol/L HCl (50:50)	500	27%

[1] Average of LC-MS/MS and UPLC-QTOF measurements (n=2) (for raw results see dataset[28], table sheet 1). Δ⁹-THC formation calculated as % in relation to original CBD content.

Abbreviations: CBD: cannabidiol; Δ⁹-THC: Δ⁹-tetrahydrocannabinol; UVA: ultraviolet A; LC-MS/MS: liquid chromatography/tandem mass spectrometry; UPLC-QTOF: ultra-high pressure liquid chromatography/quadrupole time-of-flight mass spectrometry

of available CBD products registered as food supplement in the German State Baden-Württemberg, other available hemp extract products in retail, as well as all products available at the warehouse of a large internet retailer were sampled between December 2018 and December 2021. A total of 293 samples (see Table 2) were analysed using the above-described liquid chromatographic method with tandem mass spectrometric detection (LC-MS/MS) for Δ⁹-THC content. For 2020-2021 samples, the following parameters of the method were changed: separation column (Raptor, ARC-18, 150 × 2.1 mm, 2.7 µm, Restek, Bad Homburg, Germany). The separation was a gradient starting with 20% eluent A (0.1 % formic acid in water) and 80% eluent B (0.1 % formic acid in methanol) for 18 min, followed by 5% A and 95% B for 5 min, and back to 20% A and 80% B for 7 min. All methods were validated and externally accredited according to ISO 17025 standard. Recently, the method reported satisfactory results for Δ⁹-THC during the international government chemist CBD food and cosmetic ring trial[29].

For toxicological evaluation of the results, the lowest observed adverse effect level (LOAEL) of 2.5 mg Δ⁹-THC per day published by the EFSA based on human data (central nervous system effects and pulse increase) was used[30]. Taking uncertainty factors (factor 3 for extrapolation from LOAEL to no observed adverse effect level (NOAEL) and factor 10 for interindividual differences, total factor 30) into account, an acute reference dose (ARfD) of 1 µg Δ⁹-THC per kg body weight was derived[30]. In their assessment, the Panel on Contaminants in the Food Chain of EFSA also considered interaction between Δ⁹-THC and CBD, but found the information controversial and not consistently antagonistic[30]. This is consistent with more recent research of Solowij et al.[31] that the effects of Δ⁹-THC may even be enhanced by low-dose CBD (e.g., as found in food supplements) and may be particular prominent in infrequent cannabis users. However, the current scientific evidence does not allow for considering cumulative effects. The applicability of the acute

Table 2. Results[1] of THC analysis in commercial hemp-based products from the German market (2018–2021).

Year	Samples with Δ^9-THC content exceeding LOAEL	Samples with Δ^9-THC content between ARfD and LOAEL	Sample with Δ^9-THC content below ARfD	Samples (total)
2018	7 (78%)	2 (22%)	0 (0%)	9
2019	10 (16%)	30 (47%)	24 (38%)	64
2020	4 (4%)	49 (46%)	54 (50%)	107
2021	7 (6%)	50 (44%)	56 (50%)	113
2018–2021 (total)	28 (10%)	131 (45%)	134 (46%)	293

[1] For raw results see dataset[28], table sheet 2.

Abbreviations: Δ^9-THC: Δ^9-tetrahydrocannabinol; ARfD: acute reference dose of 1 µg THC per kg body weight[30]; LOAEL: lowest observed adverse effect level of 2.5 mg Δ^9-THC per day[30]

reference dose (ARfD) of 1 µg Δ^9-THC per kg body weight was re-confirmed by EFSA in 2020[32] and by the German Federal Institute for Risk Assessment (BfR) in 2021[33]. The BfR has also concluded that the previously suggested German guidance values, which had been considered in versions 1–3 of this article, no longer correspond to current scientific knowledge[33]. For this reason, the guidance values were removed from our assessment, which is now exclusively based on EFSA's suggestions. For further details on interpretation of results and toxicity assessment, see Lachenmeier *et al.*[2]. A detailed rationale for the estimation of the daily dose of products to be applied for the risk assessment has been provided in a correspondence article[34].

Results and discussion
Direct pharmacological effect of CBD as explanation of adverse effects
There is not much evidence to assume that chemically pure CBD may exhibit acute Δ^9-THC-like adverse effects. The World Health Organization (WHO) judged the compound as being well tolerated with a good safety profile[3]. Similar conclusions were made in a recent systematic review of CBD human trials[35].

CBD doses in the food supplements on the market are typically much lower than the ones tested in clinical studies. Nevertheless, the EFSA judged in their review of available human and animal studies that a NOAEL could not be identified[25], and that there might be a possible risk of long-term effects in humans from chronic consumption of CBD as food. To exclude such chronic effect, based on the LOAEL for CBD of 4.3 mg/kg bw/day (or 300 mg/day for a person with a body weight of 70 kg) for liver effects in humans[25,36], a health-based guidance value (HBGV) of 10 mg/day might be assumed using the uncertainty factor of 30 similar to the evaluation of THC[36]. This HBGV could be exceeded by the CBD dosages in some of the food supplements.

Additionally, there are still many uncertainties and contradictions remaining regarding cannabinoid safety studies[37]. The metabolism of CBD is very complex. The main human metabolite

is 7-carboxy-cannabidiol (7-COOH-CBD; ~90 % of all drug-related substances measured in the plasma), which may form a reactive acyl-glucuronide[38–40]. Similar to CBD itself, the toxicological profile of its metabolites has not been systematically investigated[37].

CBD conversion into THC as explanation of adverse effects
Some, partly older, *in vitro* studies put up hypotheses about the conversion of CBD to Δ^9-THC under acidic conditions such as in artificial gastric juice[26,41–43]. If these proposals could be confirmed with *in vivo* data, consumers taking CBD orally could be exposed to such high Δ^9-THC levels that the threshold for pharmacological action could be exceeded[44]. However, taking a closer look at these *in vitro* studies raises some doubts. If CBD was to be converted to Δ^9-THC *in vivo*, typical Δ^9-THC metabolites should be detectable in blood and urine, but this has not been observed in oral or inhalatory CBD studies[45–47]. Due to the contradicting results, a replication of the *in vitro* study of Merrick *et al.*[26] was conducted using an extended experimental design. A more selective LC-MS/MS method and also an ultra-high pressure liquid chromatographic method with quadrupole time-of-flight mass spectrometry (UPLC-QTOF) were used to investigate the CBD degradation.

Under these conditions in contrast to Merrick *et al.*[26], no conversion of CBD to Δ^9-THC was observed in any of the samples. Only in case of the positive control (2 week storage in 0.5 mol/L HCl and 50% methanol), a complete degradation of CBD into 27% Δ^9-THC and other not identified products (with fragments similar to the ones found in cannabinol and Δ^9-THC fragmentations but with other retention times) was observed (Table 1, underlying data[28]). From an analytical viewpoint, the use of less selective and specific analytical methods, especially from the point of chromatographic separation, could result in a situation in which certain CBD degradation products might easily be confused with Δ^9-THC due to structural similarities. Thus, similar fragmentation patterns and potentially overlapping peaks under certain chromatographic conditions might have led to false positive results in the previous studies. In conclusion of our degradation

experiments, we agree with more recent literature[48–51] that CBD would not likely react to Δ^9-THC under *in vivo* conditions. The only detectable influence leading to degradation is strong acidity, which should be avoided in CBD formulations to ensure stability of products[52]. Similar observations were recently provided by Yangsud *et al.* determining CBD as stabile under stress conditions, other than acidic or alkaline conditions[53]. Transformation of CBD may also occur in acidified plasma samples or during pyrolysis gas chromatography[54,55], but not during vaping or smoking of low-THC cannabis products[56].

Δ^9-THC contamination as cause of adverse effects

Out of 293 samples, 28 samples (10% of the collective) have the potential to exceed the Δ^9-THC LOAEL and were assessed as harmful to health. 131 samples (45% of the collective) were classified as unsuitable for human consumption due to exceeding the ARfD (see Table 2, underlying data[28]). Furthermore, all food samples (i.e., all samples except CBD liquids intended to refill electronic cigarettes) have been classified as non-compliant to Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods[57] and therefore being unauthorized novel foods[58]. The labelling of all food samples was also non-compliant to Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers[59], e.g. due to lack of mandatory food information such as ingredients list or use of unapproved health claims in accordance to Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods[60]. In summary, none of the food products in our survey was found as being fully compliant with European food regulations.

The Δ^9-THC dose leading to intoxication is considered to be in the range of 10 to 20 mg (very high dose in heavy episodic cannabis users up to 60 mg) for cannabis smoking[61]. The resorption of orally ingested Δ^9-THC varies greatly inter-individually with respect to both total amount and resorption rate[62]. This might be one of the reasons for the individually very different observed psychotropic effects. A single oral dose of 20 mg THC resulted in symptoms such as tachycardia, conjunctival irritation, "high sensation" or dysphoria in adults within one to four hours. In one out of five adults, a single dose of 5 mg already showed corresponding symptoms[63].

Some of the CBD oil supplements contained Δ^9-THC in doses up to 30 mg (in this case in the whole bottle of 10 ml), which can easily explain the adverse effects observed by some consumers. Interestingly, it was observed that the symptoms reported with cannabidiol exposures in the so far largest epidemiological study[24] were Δ^9-THC-like symptoms[64].

Most of the CBD oils with dosage of around 1 mg Δ^9-THC per serving offer the possibility to achieve intoxicating and psychotropic effects due to this compound if the products are used off-label (i.e. increase of the labelled maximum recommended daily dose by factors of 3–5, which is probably not an unlikely scenario. Some manufacturers even suggest an increase of daily dosage over time). Generally, these products pose a risk to human health considering EFSA's ARfD that is considerably exceeded, even without consideration of THCA.

Hence our results provide compelling evidence that THC natively contained in CBD products may be a direct cause for adverse effects of these products. Obviously, there seems to be an involuntary or deliberate lack of quality control of CBD products. Claims of "THC-free", used by most manufacturers, even on highly contaminated products – sometimes based on the use of unsuitable analytical methodologies with limits of detection in the percentage range –, have to be treated as fraudulent or deceptive food information.

Conclusions

In light of the discussion about the three potential causative factors for adverse effects of CBD products, the described effects can be explained most probably by the presence of native THC as contaminant in the products rather than by direct action of CBD or its chemical transformation. The conclusions and findings of this study are further supported by several other surveys from the Netherlands and the USA showing inconsistent labelling and THC contents[7,65–67].

CBD degradation products are currently unknown and need to be characterized and toxicologically assessed, e.g. within the context of the novel food authorisation process. Until then, the safety of the products remains questionable. Furthermore, standardization and purification of the extracts need to be improved and stability of commercial products during shelf life should be checked (e.g. to prevent CBD degradation by avoiding acidity in ingredients etc.).

In our opinion the systematically high Δ^9-THC content of CBD products is clearly a "scandal" on the food market. Obviously, the manufacturers have – deliberately or in complete ignorance of the legal situation – placed unsafe and unapproved products on the market and thus exposed the consumer to an actually avoidable health risk. In view of the growing market for such lifestyle food supplements, the effectiveness of the instrument of food business operators' own responsibility for food safety must obviously be challenged.

It has been claimed by C. Hillard that "many CBD products would be delivering enough THC along with it to provide a bit of a high and that's more likely where the relief is coming from"[68]. Our results have partially corroborated this opinion for a substantial number of products on the German market. Similarly, a recent survey reported that 22% out of 135 users of CBD products reported "feeling high" as common adverse effect[13].

Currently we still observe a CBD market in the EU, where obviously considerable numbers of unsafe and misleadingly labelled products are available. Due to consistent deficits

in mandatory labelling including a lack of maximum recommended daily dose, dosages up to psychotropic levels (for THC) or pharmacological levels (for CBD) cannot be excluded with certainty. The risk also includes positive cannabis urine tests for several days, which may be expected from daily oral doses of more than 1 mg Δ^9-THC[1,2,69]. Therefore, about 16% of products in our study would probably lead to false-positive urine tests, which could have grave consequences for persons occupationally or otherwise required to prove absence of drug use or of doping in professional sports[70–72]. Possible long-term risks encompass liver toxicity and reproductive toxicity[25].

Obviously, the current regulatory framework is insufficient to adequately regulate products in the grey area between medicines and food supplements. For cannabis-derived products, such as CBD, the problem is aggravated by conflicting regulations in the narcotic, medicinal, and food law areas. For example, hemp extract-based products of similar composition were suggested to be treated as illegal narcotics, prescription-based medicinal products, or novel foods. Only recently, the EU commission clarified its position to not further consider cannabidiol as narcotic, but to advance the novel food approval procedure[73]. Clearly for CBD products alongside other cannabis products, a regulated legalization (see e.g. Anderson *et al.*[74]) would be preferable, introducing stricter regulations, such as mandatory labelling requirements, safety assessment, testing, pre-marketing approval and post-marketing surveillance (also see 46,75).

Data availability

Underlying data

Open Science Framework: Dataset for "Are adverse effects of cannabidiol (CBD) products caused by delta9-tetrahydrocannabinol (THC) contamination?" (Version 4) https://doi.org/10.17605/OSF.IO/F7ZXY[28]

This project contains the following underlying data:

- Dataset for 'Are adverse effects of cannabidiol (CBD) products caused by delta9-tetrahydrocannabinol (THC) contamination' F1000 Research.xlsx (Version 4) (Excel spreadsheet with data underlying Table 1 and Table 2, missing data/empty cells correspond to values outside calibration (CBD) or not measured)

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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Open Peer Review

Current Peer Review Status: ✓ ✓ ?

Version 5

Reviewer Report 11 November 2022

https://doi.org/10.5256/f1000research.140541.r155511

✓ **Arno Hazekamp** ⓘD

Hazekamp Herbal Consulting BV, Leiden, The Netherlands

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Analytical science, cannabis, cannabinoids, quality control

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 3

Reviewer Report 24 August 2020

https://doi.org/10.5256/f1000research.28743.r69794

✓ **Arno Hazekamp** ⓘD

Hazekamp Herbal Consulting BV, Leiden, The Netherlands

Great job done by the authors. This manuscript is ready for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: medicinal cannabis cultivation, quality control, development of administration

forms, clinical trials, patient surveys.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

- -

Version 2

Reviewer Report 06 July 2020

https://doi.org/10.5256/f1000research.24583.r59941

?

Volker Auwärter (iD)
Institute of Forensic Medicine, Forensic Toxicology, Medical Center - University of Freiburg, Freiburg, Germany

With respect to the two previous reviews I will refrain from summarizing the article once more.

Although the article addresses an important issue and the hypothesis of THC residues being responsible for some of the adverse effects of CBD preparations is plausible and supported by the data, I miss the discussion of two relevant points:

1. No details are given regarding the extraction of the products. Was the 'total THC content' measured by heat-induced decarboxylation of THC acid A? That would be close to the procedure used by most forensic laboratories in Germany. The author's response to reviewer 2 (page 4, comments #3 and #8) suggests, however, that THC acid A was determined separately. If the 'total THC content' was given as the sum of THC and THC acid A after correction for the molecular weight the dose would be overestimated (maximum conversion rates of smoked, 'vaped' or baked cannabis were usually reported to be below 70%). The available THC doses after oral ingestion without heating the material would be even lower (depending on the THC acid A content).

2. Regarding the THC dose required to produce psychotropic effects the authors did not discuss the 'inverse agonist' like properties of CBD at the CB1 receptor (McPartland *et al.*, 2015[1]) which have been shown to reduce the intoxicating effects of THC (e.g. Solowij *et al.*, 2019[2]). This might affect the LOAEL and the ARfD of THC when contained in CBD rich products as these values were not yet assessed for such cannabinoid preparations.

Page 8: The German guidance value seems to be several orders of magnitude (up to 4) lower than the CBD contents in the products.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Forensic Toxicology, Metabolism, NPS, Cannabinoids

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Jul 2020
Dirk W. Lachenmeier, Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Karlsruhe, Germany

Thank you for your comments!
1. Regarding the extraction and measurement of the products, no heat was applied during the whole procedure. The samples were extracted and/or diluted using solvents at room temperature and then subjected to LC-MS/MS as described in the methods section. By this method, tetrahydrocannabinolic acid (THCA) can be distinguished from both Δ^9-THC and Δ^8-THC (the methods section in version 1 of the paper is more detailed in this regard). As THCA is not psychotropic, we believe that the use of "total THC content", which has been historically based on gas chromatographic determination always leading to decarboxylation in the injection port, is not informative for meaningful risk assessment of cannabis products (for

details on risk assessment see[1]). Hence, we only report the specific content of Δ^9-THC in Table 2 of our article (in our article THC is used as abbreviation for Δ^9-tetrahydrocannabinol but not for "total THC", see introduction line 2). The many samples that exceed the German guideline value (which – as footnote 6 in table 2 correctly states – indeed refers to total THC), exceed it already for Δ^9-THC alone. Therefore, we have disregarded THCA for this assessment and refrained from calculating sums of THC and THCA. This means that the assumption of the reviewer that we might have overestimated the risk by including THCA is unfounded. Considering the German guideline values, our approach purely based on Δ^9-THC is even for the benefit of the manufacturer, as we believe it is over-conservative to include precursors of Δ^9-THC formation in risk assessment of products for which there is not typically a hazard of decarboxylation (e.g., when the foods are intended for baking). It should be also considered that the more recent EFSA ARfD value is also based on Δ^9-THC and not on total THC.

2. The reviewer is correct that risk assessment methods of mixtures are currently evolving and have not been applied to mixtures of cannabinoids. Typically, to provide such a risk assessment would be the responsibility of the food business operator and not the responsibility of the authority. Hopefully, such a risk assessment will be provided during the toxicological assessments necessary during the novel food application procedure, which several companies have initiated. In light of the currently available evidence, we do not believe a change in our risk assessment based on EFSA ARfD would be justified. For example, Solowij et al.[2] state that the effects of THC may even be enhanced by low-dose CBD (most food supplements would fall in the low CBD dose range) and may be particular prominent in infrequent cannabis users. Furthermore, Haney et al.[3] found that oral CBD does not reduce the reinforcing, physiological, or positive subjective effects of smoked cannabis. Niemsink and van Laar[4] acknowledge that CBD may counteract the negative effects of THC, but warned that the question remains how laboratory results translate to the real world. Furthermore, a recent survey reported a high prevalence of side effects in 74 out of 135 young adult cannabidiol users (55%), with dry mouth, feeling high, change in appetite and fatigue most commonly reported.[5] All in all, we strongly believe that the current evidence does not allow to negate side effects of THC in commercial cannabidiol products despite the potential antagonistic effect of CBD.

3. We agree with the reviewer that the German guidance value is typically one to several orders of magnitude lower than the THC contents in the products (please note that the guideline value is for THC. There is currently no guideline value for CBD available).

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Competing Interests: none

Reviewer Report 17 February 2020

https://doi.org/10.5256/f1000research.24583.r59880

✔

Arno Hazekamp iD

Hazekamp Herbal Consulting BV, Leiden, The Netherlands

The authors of this manuscript have addressed my questions and concerns in a satisfactory manner. I see no more objection for indexing of this very welcome manuscript.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: medicinal cannabis cultivation, quality control, development of administration

forms, clinical trials, patient surveys.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

✔ **Linda A. Parker**
Department of Psychology, Neuroscience Graduate Program, University of Guelph, Guelph, ON, Canada

Commercial CBD products are usually crude extracts from whole hemp plant material, that are available for purchase in several venues. These extracts have been reported to contain cannabinoid mixtures rather than pure CBD, and are then mixed into edible oils to obtain CBD oil. They are marketed as being free of psychoactive component, i.e. THC. Anecdotal reports of THC-like side effects from these mixtures have been reported. Three hypotheses for these side effects are posed: i) direct pharmacological effect of CBD-for which there is little evidence, ii) the degradation of CBD to THC due to acidic hydrolysis in the stomach following oral consumption, and iii) THC directly contained in the products as a by-product due to co-extraction and enrichment or contamination. The article investigated the latter two of these hypotheses.

CBD degradation: Differently concentrated CBD in methanolic solutions was evaluated in a range corresponding to typical amounts consumed in supplements based on commercial CBD supplied by Merck. These solutions were exposed to an artificial gastric juice at different incubation times and under different environmental conditions. In no case was there any conversion of CBD to THC in any of the samples. Indeed, if CBD is converted to THC in the stomach, among consumers taking CBD it would be expected that THC metabolites would be detectable in the blood and urine, but this has not been shown in oral CBD studies.

THC contamination as a cause of side effects: A sampling of all available CBD products registered as food supplement in the German State Baden-Württemberg, other hemp extract products in retail, as well as products available at the warehouse of a large internet retailer were evaluated for THC content between December 2018 and July 2019. Of the 28 samples described in Table 2, none of the products was compliant with European food regulations and most of the samples contained THC, some at a dose that would be expected to lead to intoxication. Therefore, the results provided evidence that THC contamination in the CBD products is the most likely cause for the anecdotal THC-like side effects reported. Although it would have been even more informative to

have a clear indication of the CBD content of each of the samples, the data clearly present evidence that the products are mislabeled and that THC-like side effects reported by patients is likely the result of contamination of the product with THC, which was the purpose of the study.

This is an important manuscript that will clear up the misconception that CBD is converted to THC in gastric juices of users.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cannabinoids, nausea, CBD, rat models, addiction, learning

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

> Author Response 31 Jan 2020
>
> **Dirk W. Lachenmeier**, Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Karlsruhe, Germany
>
> Thank you for your assessment of our article.
>
> *Competing Interests:* none

Reviewer Report 19 August 2019

https://doi.org/10.5256/f1000research.21875.r52382

? Arno Hazekamp 🆔

Hazekamp Herbal Consulting BV, Leiden, The Netherlands

The manuscript focuses on the quality of CBD oils, which is a meaningful and contemporary issue. Table 2 is the core of the study, because it compares the **claimed** composition of CBD oil, with **lab results** obtained by the authors. The conclusion is that the currently available products in Germany are often not what they claim to be.

Unfortunately, the authors did not analyze the actual CBD content of many of the products, and they assume that their own lab analyses are fully accurate, without proving or showing why. The authors use two different methods of analysis without explaining why one method is not sufficient. Also, in many parts of the text, they explain the current situation concerning CBD product without realizing that many readers may not have enough background information to follow their line of reasoning. The manuscript should be rewritten to explain basic concepts better.

Also, more data should be added to table 2, particularly about CBD content of the products analyzed. Right now, CBD analysis data is missing for more than half of the samples. It is not clear why so many of the products have not been studied for CBD content, and this undermines the strength of the paper. In general, the idea behind the study is very good, but the execution is relatively poor because it only focuses on the THC content of the product analyzed.

Please see my annotated copy of the article here for additional comments.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: medicinal cannabis cultivation, quality control, development of administration forms, clinical trials, patient surveys.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 31 Jan 2020

Dirk W. Lachenmeier, Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Karlsruhe, Germany

Thank you for your detailed comments and annotations in the copy. As requested, we have revised the background information to clarify the basic concepts.

Regarding the criticism of lack of CBD analysis, it must be remarked that the aim of our paper was to investigate the side effects of the products due to THC contamination. Hence, the main purpose of our analytical efforts was to accurately determine the content of THC for health risk assessment. See also the title of the paper, which is regarding THC and not CBD. The analysis of CBD is more or less a secondary addition to the aim of our study, which was THC analysis. It is therefore true that CBD quantification is missing for many samples for the pure reason that CBD and THC contents are so different and CBD was outside the linearity of our calibration. For cost reasons, we have refrained from determining CBD using a second method or dilution (it is of note that we had not specific funding for this study and have to generally work economically as tax-payer funded institute). In the legal evaluation of the products, the CBD content is more or less unimportant as long as the content is below the level of pharmacological action (for food products). As all products had to be objected for various reasons (lack of novel food authorisation, THC contents outside of acceptable levels, mandatory labelling etc.), the CBD quantification was not relevant as well because the issue of consumer deception by mislabelling of CBD is secondary to the safety aspects posed by THC or the use of non-approved, potentially unsafe novel food ingredients.

Regarding the question on analytical methods, we actually have confidence in our analytical methods and they are fully validated and our institute is externally accredited according to ISO 17025. Nevertheless, as there is no official method for CBD analysis available, we have confirmed our results with a second procedure to even further improve confidence and validity. As of now, we believe that both methods perform similarly and could both be used in instances of laboratories without access to two different instruments.

To improve the strength of the paper, as requested by the reviewer, we have added the results of 39 samples measured in the meantime (new total 67 samples). In many of these samples it was also possible to quantify CBD. The measurement of these additional samples corroborates our previous results and interpretation, and we hope that the sample collective now appears as sufficient for publication.

Regarding the comments in the annotated copy, we have revised the text considering all

suggested changes, except for the following comments for which we provide a detailed response (comment numbering according to Adobe Acrobat comment numbering in annotated copy of reviewer):

- Page 3, comment #2 "Not yet. The European Food Safety Authority (EFSA) has advised that CBD should be classified as a novel food. But now it is up to individual EU member states to implement that advise into national legislation. Some countries may decide to not follow the advise."

We disagree with this comment. The classification of CBD and hemp extracts (which was published in the novel food catalogue of the European commission and not by EFSA, see: https://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm?ascii=Cannabinoids) is a consensus decision of all EU member states. EU regulations such as the novel food regulation are binding in its entirety and directly applicable in all Member States. Therefore there appears to be no leverage for member states to act in infringement of the novel food regulation. If you check the Rapid Alert System for Food and Feed (RASFF) portal for CBD (https://webgate.ec.europa.eu/rasff-window/portal/?event=SearchByKeyword&NewSearch=1&Keywords=cbd), there are more than 80 notifications of CBD products as „unauthorised novel food ingredient" from various countries including Spain, Belgium, Denmark, Germany, Austria, Switzerland, Slovenia, Lithuania, Italy, Sweden. In Germany, there are currently at least 7 court rulings that confirmed the status of CBD as novel food and confirmed the actions of the authorities (typically removal of products from the market).

For details on novel food status and German court rulings, please refer to: Lachenmeier DW, Rajcic de Rezende T, Habel S, et al.: Recent jurisdiction confirms novel food status of hemp extracts and cannabidiol in foods – Classification of cannabis foods under narcotic law is still ambiguous. Deut Lebensm Rundsch. 2020;116: 111-119. DOI: https://doi.org/10.5281/zenodo.3631608

The following court rulings confirmed the novel food status of cannabidiol and hemp extracts:
VG Cottbus 08.01.2020 Az. 3 L 230/19
OVG Lüneburg 12.12.2019 Az. 13 ME 320/19
VG Hannover 18.11.2019 Az. 15 B 3035/19
VG Gießen 11.11.2019 Az. 4 L 3254/19.GI
VGH Baden-Württemberg 16.10.2019 Az. 9 S 535/19
VG Düsseldorf 27.09.2019 Az. 16 L 2333/19
VG Stade 05.09.2019 Az. 6 B 735/19

- Page 5, comment #5: "Based on your table, this product seems to be the most reliable. But in fact this sample may not contain any cannabinoids at all."

Some cannabinoids could be qualitatively detected in this sample around the detection limit of the method.

- Page 4, comment #1: "It is not common to use two methods and use the average. Does that mean you do not trust your own methods?"

In our line of work in providing expert opinions that may be used in court cases, it is often common to use two methods, especially in cases where a reference procedure is not established or when there may be grave consequences in application of the results, such as

taking products from the market. We currently cannot see the reason why doing more than perhaps absolutely necessary might hinder publication of such results.
Furthermore, as there was a discrepancy between our results and some previous studies regarding *in vitro* formation of THC from CBD, we found it prudent to confirm our results using a second methodology.
  ○ Page 4, comments #3 and #8 regarding THCA, CBDA and CBN

Basically, we can accurately quantify all these other cannabinoids using the same method. However, as the results of these are not presented and unnecessary for the current paper, we have deleted all mentions of these compounds in the method section to avoid confusion.
  ○ Page 5, comment #7: "Why are some samples measured 1 time, and others up to 6 times?"
The number of replicates depended on several factors, sometimes restricted by the very low sample volume we have received. Typically in the cases with highest THC content leading to a judgment of "non-safe food product" we aimed for at least 3 if possible 5 replicates. In certain cases, more replicates were made, for example when several dilutions were within the linearity range.

Competing Interests: none

Comments on this article

Version 2

Author Response 09 Jul 2020

Dirk W. Lachenmeier, Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Karlsruhe, Germany

Thank you for the comment. We did not observe Δ^8-THC in our degradation experiments (please note that Δ^8-THC was included in the spectrum of our analytes, see methods sections of article version 1). Otherwise, the conversion of CBD to Δ^8-THC was reported under certain acidic conditions. See our recent review on conversion of cannabidiol[1].

References
1. Golombek P, Müller M, Barthlott I, Sproll C, Lachenmeier DW. Conversion of Cannabidiol (CBD) into Psychotropic Cannabinoids Including Tetrahydrocannabinol (THC): A Controversy in the Scientific Literature. *Toxics*. 2020; 8(2):41. https://doi.org/10.3390/toxics8020041

Competing Interests: none

Reader Comment 24 Jun 2020

Istvan Ujvary, iKem BT, Hungary

I could have missed it but did not find data on the delta-8-THC content. This THC isomer, which is thermodinamically more stable than the delta-9 isomer thus its formation from CBD is plausible under acidic conditions, is also 'psychotropic' so may contribute to the overall psychoactivity of such hemp preparations.

Competing Interests: none

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