RESEARCH NOTE

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

Dirk W. Lachenmeier, Stephanie Habel, Berit Fischer, Frauke Herbi, Yvonne Zerbe, Verena Bock, Tabata Rajcic de Rezende, Stephan G. Walch, Constanze Sproll
Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Karlsruhe, 76189, Germany

Abstract
Cannabidiol (CBD)-containing products are widely marketed as over the counter products, mostly as food supplements, to avoid the strict rules of medicinal products. Side-effects reported in anecdotal consumer reports or during clinical studies were first assumed to be due to hydrolytic conversion of CBD to psychoactive Δ9-tetrahydrocannabinol (THC). 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 side-effects of CBD products may be residual THC concentrations in the products as contamination, because most of them are based on crude hemp extracts containing the full spectrum of cannabinoids besides CBD. Analyses of 28 food products of the German market containing hemp extract as an ingredient (mostly CBD oils) confirmed this hypothesis: 10 products (36%) contained THC above the lowest observed adverse effects level (2.5 mg/day). Inversely, CBD was present in the products below the no observed adverse effect level. Hence, it may be assumed that the adverse effects of some commercial CBD products are based on a low-dose effect of THC and not due to effects of CBD itself. 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 THC levels, full-spectrum hemp extracts 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 must obviously be challenged.

Keywords
Tetrahydrocannabinol, cannabidiol, Cannabis sativa, hemp, food supplements, risk assessment, drug effects
Corresponding author: Dirk W. Lachenmeier (lachenmeier@web.de)

Author roles: Lachenmeier DW: Conceptualization, Formal Analysis, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Habel S: Data Curation, Writing – Review & Editing; Fischer B: Investigation, Writing – Review & Editing; Herbi F: Investigation, Writing – Review & Editing; Zerbe Y: Investigation, Writing – Review & Editing; Bock V: Formal Analysis, Writing – Review & Editing; Rajic de Rezende T: Formal Analysis, Writing – Review & Editing; Walch SG: Resources, Supervision, Writing – Review & Editing; Sroll C: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing – Review & Editing

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Introduction
Since hemp has again been approved for cultivation as an industrial crop in the form of low Δ⁹-tetrahydrocannabinol (THC) hemp varieties, components of the hemp plant are increasingly used for the production of foods and other consumer products such as liquids for electronic cigarettes. Some product groups (e.g., cosmetics, veterinary supplements, waxes or room fragrances) may be produced with intended off-label use, such as human consumption, in mind and therefore deliberately avoiding the strict safety requirements for medicinal or food products.

From all hemp constituents, cannabidiol (CBD) is currently the compound with highest interest. In contrast to THC, the major drug-constituent of hemp, CBD is a non-psychoactive cannabinoid. It is currently being tested for its possible antipsychotic, anti-inflammatory, anxiolytic and anti-epileptic effects as a drug, e.g. for the treatment of epilepsy. However, CBD products of all kinds can now also be purchased in organic shops, drug stores, supermarkets and via the Internet, mostly by advertising dubious “cure-all” properties including anti-carcinogenic effects or various unspecified 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 psychoactive components or their side-effects. With the exception of the treatment of Dravet’s syndrome, there is little clinical data on the efficacy and safety of CBD, particularly in the treatment of cancer.

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 CO₂ or with solvents such as ethanol or isopropanol from the entire hemp plant. Probably due to cost reasons, no further specific enrichment or cleanup of CBD is conducted, so that the commercial extracts are a cannabinoid mixture rather than pure CBD. These extracts are then mixed into ordinary edible oils such as sunflower oil, olive oil or hemp seed oil to obtain the so-called CBD oil.

The strategy to market CBD oil products as food supplements within the framework of food regulations seems to be the most common approach of food operators. Some other products, derived from hemp extracts, are CBD chewing gum, “CBD flowers” (plant material sold as tea), and cannabis resin, wax or pollen products.

However, no significant food consumption of full-spectrum hemp extracts or hemp flowers containing CBD 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 July 2019), no approved application is recorded. Basically, all available CBD products based on hemp extract marketed as food or food supplement within the EU are therefore illegally sold, but still widely available in all trade channels (retail, wholesale and e-commerce) due to an apparent lack of enforcement.

Anecdotal cases ranging from malaise to THC-like effects have become known to the food control authorities in consumer complaint cases regarding CBD products. Additionally, some pediatric 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 THC rather than of CBD. Currently there are three hypotheses for the cause of the side effects: (i) a direct pharmacological effect of CBD, (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 by-product due to co-extraction and enrichment or contamination. In this article, the hypotheses are investigated including new evidence from original data.

Methods
CBD degradation
To investigate CBD degradation, differently concentrated CBD in methanolic solutions was used in a range corresponding to typical amounts consumed with supplements based on commercial CBD (Supelco Cerilliant #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 “NT 446 U” (Dr. Kern GmbH, Mademühlen, Germany) were placed 15 cm from the surface of the solutions. In deviation of an experimental protocol of Merrick et al., a gastric juice without addition of surfactants was used, which was strictly produced according to the European pharmacopoeia (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.

The samples were measured 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 separation column (Luna Omega Polar C18, 150 x 2.1 mm, 1.6 µm, 100 Å, Phenomenex, Aschaffenburg, Germany). The separation was...
isocratic with 25 % formic acid (0.1 %) and 75 % formic acid (0.1 % in acetonitrile) and a flow of 0.3 mL/min. In case of QTOF with 35 % formic acid (0.1 %) and 65 % formic acid (0.1 % in acetonitrile) 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 $\Delta^9$-THC, $\Delta^8$-THC and CBD, the mass transition m/z 315 to 193 was used, for cannabinol (CBN) m/z 311 to 223, and for tetrahydrocannabinolic acid (THCA) m/z 359 to 341. For $\Delta^9$-THC and $\Delta^8$-THC, baseline separation was achieved. 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 $\Delta^9$-THC and $\Delta^8$-THC.

As internal standards $\Delta^9$-THC-D$_3$ (Supelco Cerilliant #T-011, 1.0 mg/mL in methanol), THCA (Supelco Cerilliant #T-093, 1.0 mg/mL in acetonitrile) and CBN (Supelco Cerilliant #C-046, 1.0 mg/mL in methanol), and cannabinol-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.

### THC contamination of commercial products
To study the possible influence of natively contained THC in hemp products as a cause for side effects, a sampling of all 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

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Temperature (°C)</th>
<th>Light exposure</th>
<th>Storage time</th>
<th>Storage medium</th>
<th>CDB concentration in medium (µg/L)</th>
<th>$\Delta^9$-THC formation$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative control</td>
<td>-18</td>
<td>None</td>
<td>14 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td>Light</td>
<td>20</td>
<td>None</td>
<td>3 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>None</td>
<td>14 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Daylight</td>
<td>3 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Daylight</td>
<td>14 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>UVA</td>
<td>1 h</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>UVA</td>
<td>3 h</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td>Temperature</td>
<td>20</td>
<td>None</td>
<td>5 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>None</td>
<td>14 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>None</td>
<td>5 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>None</td>
<td>14 days</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>None</td>
<td>3 h</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>None</td>
<td>1 h</td>
<td>Methanol</td>
<td>1000</td>
<td>0%</td>
</tr>
<tr>
<td>Simulated gastric juice</td>
<td>37</td>
<td>None</td>
<td>1 h</td>
<td>Simulated gastric juice</td>
<td>200</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>None</td>
<td>2 h</td>
<td>Simulated gastric juice</td>
<td>200</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>None</td>
<td>3 h</td>
<td>Simulated gastric juice</td>
<td>200</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>None</td>
<td>1 h</td>
<td>Simulated gastric juice</td>
<td>400</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>None</td>
<td>2 h</td>
<td>Simulated gastric juice</td>
<td>400</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>None</td>
<td>3 h</td>
<td>Simulated gastric juice</td>
<td>400</td>
<td>0%</td>
</tr>
<tr>
<td>Positive control</td>
<td>20</td>
<td>None</td>
<td>14 days</td>
<td>Methanol / 1 mol/L HCl (50:50)</td>
<td>500</td>
<td>27%</td>
</tr>
</tbody>
</table>

$^1$ Average of LC-MS/MS and UPLC-QTOF measurements (n=2) (for raw results see dataset13, table sheet 1). THC formation calculated as % in relation to original CBD content.

Abbreviations: CBD: cannabidiol; THC: $\Delta^9$-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
chromatographic method with tandem mass spectrometry (LC-MS/MS) for THC content. For toxicological evaluation of the results, the lowest observed adverse effect level (LOAEL) of

A total of 28 samples (see Table 2 for product designations) were analyzed using the above described liquid chromatographic/tandem mass spectrometric analysis method. The results are summarized in Table 2.

Table 2. Results of THC analysis in commercial products based on hemp extracts from the German market (2018–2019).

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Product</th>
<th>CBD [mg/day] (labelling)</th>
<th>CBD [mg/day] (analysis)</th>
<th>THC [mg/day] (analysis)</th>
<th>Toxicity assessment according to Ref. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>180630663</td>
<td>CBD oil supplement</td>
<td>200</td>
<td></td>
<td>9</td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>180776480</td>
<td>CBD oil supplement</td>
<td>74</td>
<td>51</td>
<td>4</td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>190203194</td>
<td>CBD pollen</td>
<td>-</td>
<td></td>
<td>2.6</td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>190267605</td>
<td>CBD oil</td>
<td>2000</td>
<td>3140</td>
<td>30</td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>180198245</td>
<td>CBD buds (hemp flowers &amp; leaves)</td>
<td>-</td>
<td></td>
<td>(1.3)</td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>180198246</td>
<td>CBD buds (hemp flowers &amp; leaves)</td>
<td>-</td>
<td></td>
<td>(1.3)</td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>180598182</td>
<td>CBD hemp flower supplement</td>
<td>500</td>
<td></td>
<td></td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>180598187</td>
<td>CBD hemp flower supplement</td>
<td>250</td>
<td></td>
<td></td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>180781746</td>
<td>CBD chewing gum</td>
<td>15</td>
<td>30</td>
<td>(1.5)</td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>190203193</td>
<td>CBD wax</td>
<td>660</td>
<td>860</td>
<td>(1.7)</td>
<td>THC &gt; LOAEL</td>
</tr>
<tr>
<td>180565755</td>
<td>CBD oil supplement</td>
<td>24</td>
<td>18</td>
<td>0.2</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>180565756</td>
<td>CBD oil supplement</td>
<td>12</td>
<td>9</td>
<td>0.2</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190080916</td>
<td>Supplement with hemp extract</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190080917</td>
<td>Supplement with hemp extract</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190141197</td>
<td>CBD oil supplement</td>
<td>22.32</td>
<td></td>
<td>1.6</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190199739</td>
<td>Supplement with hemp extract</td>
<td>-</td>
<td>34</td>
<td>0.5</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190203189</td>
<td>Supplement with hemp extract</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190203191</td>
<td>Supplement with hemp extract</td>
<td>-</td>
<td>-</td>
<td>0.7</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190207787</td>
<td>CBD oil supplement</td>
<td>67.5</td>
<td>95</td>
<td>0.4</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190332551</td>
<td>CBD oil supplement</td>
<td>42</td>
<td></td>
<td>0.3</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190332552</td>
<td>CBD oil supplement</td>
<td>84</td>
<td></td>
<td>0.3</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190332553</td>
<td>CBD oil supplement</td>
<td>166</td>
<td></td>
<td>0.3</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190303096</td>
<td>CBD chewing gum</td>
<td>5</td>
<td></td>
<td>0.1</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190304229</td>
<td>CBD chewing gum</td>
<td>5</td>
<td></td>
<td>0.1</td>
<td>ARfD &lt; THC &lt; LOAEL</td>
</tr>
<tr>
<td>190304228</td>
<td>CBD supplement</td>
<td>20</td>
<td></td>
<td>0.05</td>
<td>THC &gt; German guideline&lt; THC &lt; ARfD</td>
</tr>
<tr>
<td>190203192</td>
<td>Supplement with hemp extract</td>
<td>-</td>
<td>-</td>
<td>0.07</td>
<td>THC &gt; German guideline&lt; THC &lt; ARfD</td>
</tr>
<tr>
<td>190272024</td>
<td>CBD oil</td>
<td>27</td>
<td>38</td>
<td>0.01</td>
<td>THC &gt; German guideline&lt; THC &lt; ARfD</td>
</tr>
<tr>
<td>190203186</td>
<td>Supplement with hemp extract</td>
<td>-</td>
<td>-</td>
<td>Not detectable</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Average of 1–6 replicates measured with LC-MS/MS reported (for raw results see dataset13, table sheet 2).
2 Not analyzed or outside calibration.
3 No labelling provided by manufacturer.
4 THC (mg/day) calculated on the basis of 1 portion according to the manufacturer’s labelling. The LOAEL may be exceeded with a probable intake of 2 portions/day.
5 The German guideline value for THC content in food products is 150 µg/kg14.

Abbreviations: CBD: cannabidiol; THC: Δ9-tetrahydrocannabinol; ARfD: acute reference dose (ARfD) of 1 µg THC per kg body weight15; LOAEL: lowest observed adverse effect level of 2.5 mg THC per day15; LC-MS/MS: liquid chromatographic/tandem mass spectrometric analysis method.
2.5 mg THC per day published by the European food safety authority (EFSA) based on human data (central nervous system effects and pulse increase) was used\textsuperscript{15}. Taking safety 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 THC per kg body weight was derived\textsuperscript{15}. 

Results and discussion

Direct pharmacological effect of CBD as explanation of side effects

There is not much evidence to assume that chemically pure CBD may exhibit THC-like side-effects. The World Health Organization (WHO) judged the compound as being well tolerated with a good safety profile\textsuperscript{2} and the CBD doses in the food supplements on the market are typically much lower than the ones tested in clinical studies. Additionally, there is a 90-day experiment in rats with a hemp extract (consisting of 26% cannabinoids, 96% CBD and <1% THC) from which a NOAEL of 100 mg bw/day could be derived\textsuperscript{16}. For CBD this would be about 25 mg/kg bw/day (or 1750 mg/day for a person with a body weight of 70 kg). This NOAEL would not be reached by the CBD dosages in food supplements.

CBD conversion into THC as explanation of side effects

Some, partly older, in vitro studies put up hypotheses about the conversion of CBD to THC under acidic conditions such as in artificial gastric juice\textsuperscript{13,17-19}. If these proposals could be confirmed with in vivo data, consumers taking CBD orally could be exposed to such high THC levels that the threshold for pharmacological action could be exceeded\textsuperscript{20}. However, taking a closer look at these in vitro studies raises some doubts. If CBD was to be converted to THC in the stomach, typical THC metabolites should be detectable in blood and urine, but this has not been observed in oral CBD studies\textsuperscript{21,22}. Due to the contradicting results, a replication of the in vitro study of Merrick et al.\textsuperscript{13} 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.\textsuperscript{13}, no conversion of CBD to 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% THC and other not identified products (with fragments similar to the ones found in CBN and THC fragmentations but with other retention times) was observed (Table 1, underlying data\textsuperscript{15}). 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 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\textsuperscript{23,24} that CBD would not likely react to 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.

THC contamination as cause of side effects

Out of 28 samples, 10 samples (36% of the collective) were exceeding the THC LOAEL and were assessed as harmful to health. 14 samples (50% of the collective) were classified as unsuitable for human consumption due to exceeding the ARfD (see Table 2, underlying data\textsuperscript{15}). Furthermore, all samples (100%) 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\textsuperscript{25} and therefore being unauthorized novel foods. The labelling of 28 samples (100%) 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\textsuperscript{26}, 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\textsuperscript{27}. In summary, none of the products in our survey was found as being fully compliant with European food regulations.

The THC dose leading to intoxication is considered to be 10 to 20 mg (very high dose up to 60 mg) for inhalatory intake\textsuperscript{28}. The resorption of orally ingested THC varies greatly inter-individually with respect to both total amount and resorption rate\textsuperscript{29}. This might be one of the reasons for the individually very different 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 in five adults, a single dose of 5 mg already showed corresponding symptoms\textsuperscript{30}.

Some of the CBD oil supplements contained THC in doses up to 30 mg, which can easily explain the adverse effects observed by some consumers. Most of the CBD oils with dosage of around 1 mg offer the possibility to achieve intoxicating dosages of THC if the products are used off-label (i.e. increase the actual contents in the products). In summary, none of the products in our survey was found as being fully compliant with European food regulations.

Hence our results provide compelling evidence that THC natively contained in CBD products by contamination may be a direct cause for side effects of these products. Obviously, there is an involuntary or deliberate lack of quality control of CBD products. Claims of “THC-free”, used by most manufacturers, even of the highly contaminated products, have to be treated as fraudulent or deceptive food information.
Conclusions
In light of the discussion about the three potential causative factors for side 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 or metabolization. The conclusions and findings of this study are further supported by the findings of Hazekamp reporting data from the Netherlands on cannabis oils according to which the labelling information for CBD and THC was often different from the actual contents. In 26 out of 46 products the THC content was >1%. Further corresponding results were reported in a study from the USA, in which the CBD content was correctly declared for only 26 of 84 CBD products and 18 of the products had THC contents.

CBD degradation products are currently unknown and need to be characterized and toxicologically assessed, e.g. within the context of the novel food registration 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.). Finally, the production hygiene also needs to be improved to minimize contamination. According to own observations some CBD oils are manufactured in back offices not suitable for food production.

In our opinion the high THC content of CBD products is almost a “small 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 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.

Data availability

Underlying data
Open Science Framework: Dataset for “Are side effects of cannabidiol (CBD) products caused by delta9-tetrahydrocannabinol (THC) contamination?” https://doi.org/10.17605/OSF.IO/F7ZXY

This project contains the following underlying data:

- Dataset for “Are side effects of cannabidiol (CBD) products caused by delta9-tetrahydrocannabinol (THC) contamination” F1000 Research.xlsx (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).

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgements

The authors would like to thank Sylvia Ullrich, Jutta Neumeister and Ingrid Kübel for their excellent technical support, sample preparation and measurements using LC-MS.

References

13. Lachenmeier DW: Dataset for “Are side effects of cannabidiol (CBD) products caused by delta9-tetrahydrocannabinol (THC) contamination?” F1000 Research.xlsx (Excel spreadsheet with data underlying Table 1 and Table 2, missing data/empty cells correspond to values outside calibration (CBD) or not measured)

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgements

The authors would like to thank Sylvia Ullrich, Jutta Neumeister and Ingrid Kübel for their excellent technical support, sample preparation and measurements using LC-MS.


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.

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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

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Reviewer Report 19 August 2019

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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.
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&Keyword), 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).


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
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